Medical Oncology Syllabus

Session 1: Breast Cancer, Lung Cancer, and Neuro-Oncology

Session 2: GU, GYN and GI Tumors

Session 3: GI, Sarcoma, and Palliative Care

Course Organizers:

THE GEORGE WASHINGTON UNIVERSITY

WASHINGTON, DC

47

Familial Cancer Syndromes

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August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

47 - Hereditary Cancer Syndromes

Elizabeth Stark, MS, LCGC

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: Color Genomics**

Learning objectives

1. Recognize key features of common hereditary cancer syndromes

2. Evaluate your patient population for appropriate genetic counseling and testing referrals

3. Identify patients who may benefit from therapeutic agents linked to genetic markers

4. Determine when PRS and RNA testing can add clinical utility

Why is this important

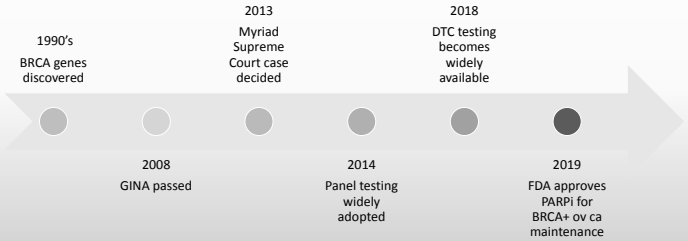
- Targeted Therapeutics
  - Treatment decisions can and should be influenced by genetic testing results
- Prevention
  - Secondary malignancies
  - Cancers in family members

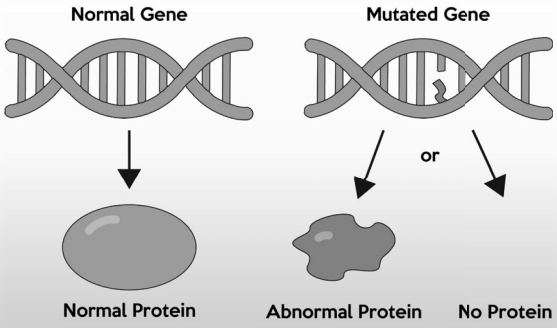
Every breast or ovarian cancer patient with a *BRCA1* or *BRCA2* mutation detected after diagnosis is a missed opportunity to prevent cancer.

No woman with a mutation in *BRCA1* or *BRCA2* should die of breast or ovarian cancer.

-Dr. Mary-Claire King

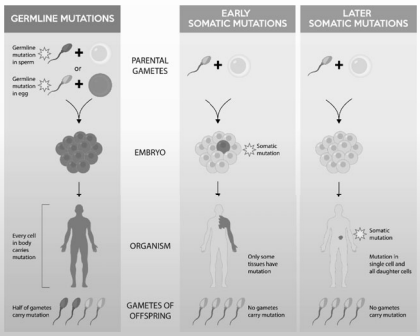
Timeline





Kintalk, UCSF

Germline vs. somatic mutations



Kintalk, UCSF

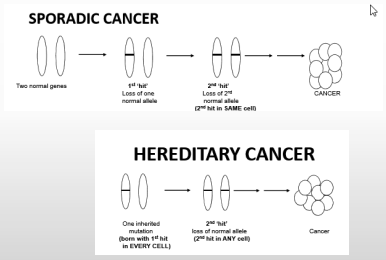
Different types of genetic testing

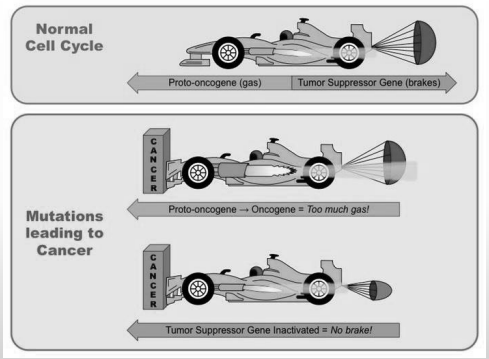
Somatic
- Looks at tumor genetics only
- All tumors have genetic changes
- Primarily used to identify therapeutic targets, recurrence risk
- Most somatic mutations identified are not germline, BUT
- May suggest a higher risk of having a germline mutation

Germline
- Present and constant from the time of conception
- Determines risk of developing a cancer (or a NEW primary)
- Now being used to identify therapeutic targets

SNVs
- Single nucleotide variants (formerly polymorphism)
- Germline differences – the spice of life!
- Can have large impacts cumulatively
- Some are common (SNPs, >1% of population) and some are more rare

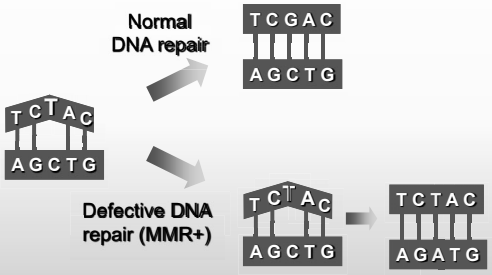
Knudson Two Hit Hypothesis





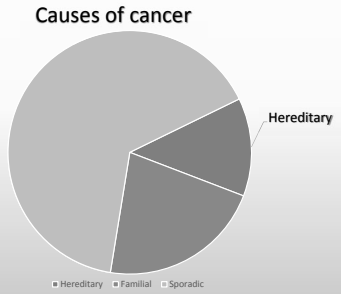
https://lb.bioninja.com.au/standard-level/topic-1-cell-biology/16-cell-division/cancer-development.html

DNA Mismatch Repair (MMR) Genes



Basic principles of hereditary cancer

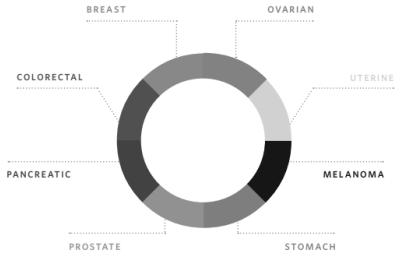
- About 15% of cancer is hereditary (higher for rare cancers)
- Autosomal dominant or autosomal recessive inheritance
- Men and women have the same chance to inherit a mutation
- Each child is at risk to inherit the altered gene
- Mutations can be inherited from either parent
- Risk factor – not a diagnosis
- Testing of affected family members is the most informative



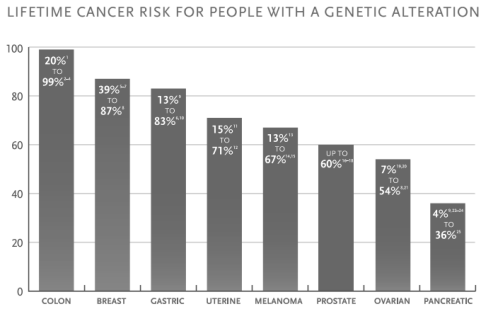
When to suspect a hereditary cancer syndrome

- Cancer in 2 or more family members (same side of family)
- Cancer diagnosis at early age
- Multiple primary tumors in the same individual
- Bilateral or multiple rare cancers
- Constellation of tumors consistent with hereditary cancer syndrome (eg, Lynch)
- Multiple affected generations
- Specific tumor histologies

What Types of Cancer Can Be Hereditary*?



GENES	BREAST & GYN	ENDOCRINE	GASTROINTESTINAL	GENITOURINARY	HEMATOLOGIC	NERVOUS SYSTEM/BRAIN	PROSTATE	SARCOMA	SKIN
ATM	■		■		○		○		
BRCA1	■		○	○			○		
BRCA2	■		○	○			○		■
CDH1	■		○						
CHEK2	■	■	○	○			○		
PALB2	■		○				○		
PTEN	■	■	○	○		○			■
STK11	■		○						
TP53	■	■	○	○	○	○	○	■	■
NBN	■			○	○		○	■	
NF1	■	■	○		○	○		■	
APC		■	○			○		■	
AXIN2			○						
BARD1	■								
BMPR1A			○						
BRIP1	■								
CDK4									■
CDKN2A			○						■
CTNNA1			○						
DICER1	■	■		○		○		■	
EPCAM	■		○	○	○	○	○	■	
GREM1			○						
HOXB13							○		
KIT			○					■	
MEN1		■	○			○			
MLH1	■		○	○	○	○	○	■	
MSH2	■		○	○	○	○	○	■	
MSH3			○						
MSH6	■		○	○	○	○	○	■	
MUTYH			○						
NTHL1			○						
PDGFRA			○					■	
PMS2	■		○	○	○	○	○	■	
POLD1			○						
POLE			○						
RAD50	■								
RAD51C	■								
RAD51D	■						○		
SDHA		■	○					■	
SDHB		■	○	○				■	
SDHC		■	○	○				■	
SDHD		■	○					■	
SMAD4			○						
SMARCA4	■					○			
TSC1			○	○		○			
TSC2			○	○		○			
VHL		■	○	○		○			



Results

- Positive
  - Actionable
  - Some modifications for a particularly strong family history
  - Includes Pathogenic and Likely Pathogenic
  - **Follow NCCN guidelines**
- Negative
  - Does not always mean it's not genetic!
  - True negative vs. uninformative negative
  - Includes Benign and Likely Benign. Will not be reported on.
  - **Follow based on family history**
- Variant of Uncertain Significance
  - Vast majority are benign differences
  - Lab needs more time
  - **Follow based on family history**

VUS Follow-up

Ordering providers are notified as VUS are reclassified

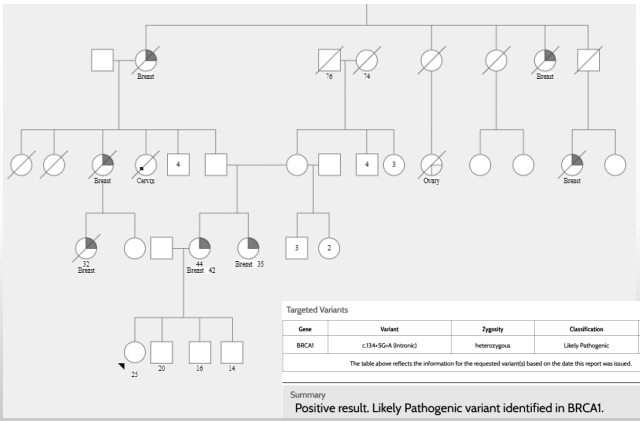
PROMPT

VUS Rates Falling

- Introduction of RNA testing is helping to reclassify VUS, especially splice site variants
  - RNA testing also helping to identify pathogenic intronic variants not typically captured by DNA alone
- Functional modeling harnesses machine learning to combine multiple lines of evidence for better predictions
- If a mutation is found or reclassified, implications are the same.
  - Just another way to identify an underlying familial cancer syndrome
  - Reclassification from pathogenic to VUS or Benign is VERY rare

Where we are now

- Testing is performed the same day
  - Saliva or Blood
- Majority of patients are getting multi-gene panel testing
- Insurance coverage is good, self-pay prices reasonable ($250)
- Results available in 2-3 weeks
  - 7-10 days for some genes
- Cancer genetics is about <u>prevention</u> and <u>targeted therapies</u>



<u>H</u>ereditary <u>B</u>reast and <u>O</u>varian <u>C</u>ancer

Study	Breast Cancer Risk (%) (95% CI)		Ovarian Cancer Risk (%) (95% CI)	
	BRCA1	*BRCA2*	*BRCA1*	*BRCA2*
Antoniou et al. (2003) [126]	65 (44–78)[a]	45 (31–56)[a]	39 (18–54)[a]	11 (2.4–19)[a]
Chen et al. (2007) [127]	55 (50–59)[a]	47 (42–51)[a]	39 (34–45)[a]	17 (13–21)[a]
Kuchenbaecker et al. (2017) [128]	72 (65–79)[b]	69 (61–77)[b]	44 (36–53)[b]	17 (11–25)[b]

CI = confidence interval.

[a]Risk estimate calculated up to age 70 years.

[b]Risk estimate calculated up to age 80 years.

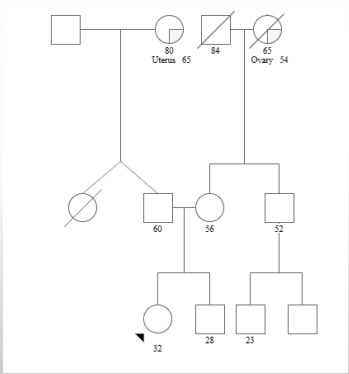
https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

Cancer Sites [6-8,12,62,169]	*BRCA1*		*BRCA2*	
	Strength of Evidence	Magnitude of Absolute Risk	Strength of Evidence	Magnitude of Absolute Risk
Breast (female)	+++	High	+++	High
Ovary, fallopian tube, peritoneum	+++	High	+++	Moderate
Breast (male)	+	Undefined	+++	Low
Pancreas	++	Very Low	+++	Low
Prostate[a]	+	Undefined	+++	High

https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

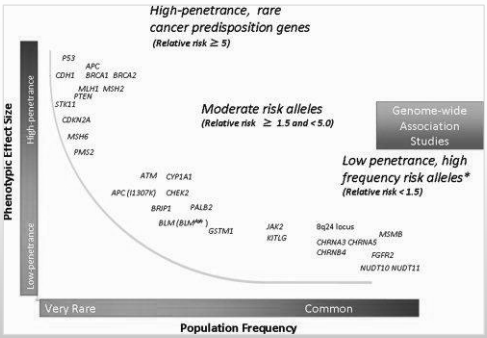
SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast awareness • Women should be familiar with their breasts and promptly report changes to their healthcare provider.	18 years old	Periodic and consistent
Clinical Breast Exam	25 years old	Every 6-12 months
Breast Screening* • Breast MRI with contrast • Mammography with consideration of tomosynthesis	25-29 years old	Individualized
	30-75 years old	Every 12 months
	>75 years old	Individualized
Discuss option of risk-reducing mastectomy	Individualized	N/A
Consider investigational imaging and screening studies, when available in context of a clinical trial	Individualized	Individualized
Consider options for risk reduction agents, such as chemoprevention (i.e. tamoxifen, raloxifene)	Individualized	Individualized
Ovarian Cancer		
Recommend risk-reducing salpingo-oophorectomy (RRSO)**	Typically 35 to 40 years old, and upon completion of child bearing	N/A
If RRSO not elected, transvaginal ultrasound combined with serum CA-125, although of uncertain benefit, may be considered	30-35 years old	Clinician's discretion
Consider investigational imaging and screening studies, when available in the context of a clinical trial	Individualized	Individualized
Consider options for risk reduction agents, such as chemoprevention (i.e. oral contraceptives)	Individualized	Individualized

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Male Breast Cancer		
Breast self-exam training and education	35 years old	Periodic and consistent
Clinical breast exam	35 years old	Every 12 months
Prostate Cancer		
Consider prostate cancer screening	40 years old	Clinician's discretion
Melanoma		
General risk management, such as annual full-body skin examination and minimizing UV exposure	Individualized	Annual, or shorter intervals if indicated
Pancreatic Cancer		
For individuals with exocrine pancreatic cancer in >1 first-or second-degree relative on the same side of the family as the identified pathogenic/likely pathogenic germline variant, consider pancreatic cancer screening.*	50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family)	Annually (with consideration of shorter intervals if worrisome abnormalities seen on screening)



High vs. Moderate Cancer Genes

- High Risk Breast
  - BRCA1
  - BRCA2
  - TP53
  - PALB2
  - CDH1
  - STK11
  - PTEN
- Moderate Risk Breast
  - ATM
  - CHEK2
  - NBN



Breast Cancer Risk Genes

Gene	Estimated RR(95%CI)	Other Associated Cancers
BRCA1	11.4	Ovary, Pancreas, Prostate
BRCA2	11.7	Ovary, Pancreas, Prostate, Sarcoma?
TP53	105 (62-165)	Sarcoma, ACC, CNS, other
PTEN	No reliable estimates	Thyroid, Endometrium, Renal, CRC
CDH1	6.6 (2.2 – 19.9)	Diffuse gastric
STK11	No reliable estimates	Colon, Pancreas, Ovarian sex-cord
PALB2	5.3 (3.0 – 9.4)	Pancreas, ?Ovary
NF1	2.6 (2.1 – 3.2)	Peripheral nerve sheath, CNS
ATM	2.8 (2.2 – 3.7)	Pancreas
CHEK2	3.0 (2.6 – 3.5)	CRC, Prostate
NBN	2.7 (1.9 – 3.7)	Unknown

Easton DF et al. N Engl J Med 2015;372:2243-57

Fanconi Anemia Genes and Breast Cancer Risk

- **High-Risk Genes**
  - BRCA1 (FANCS)
  - BRCA2 (FANCD1)
  - PALB2 (FANCN)
- **Moderate-Risk Genes**
  - BRIP1 (FANCJ)
  - FANCD2
  - RAD51C (FANCO)

- 16 genes associated with FA
- 6 have breast cancer risk implications
- Each of these accounts for 3% or less of all pathogenic variants

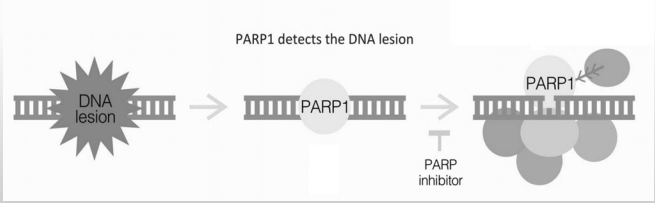
https://www.cancer.gov/types/breast/hp/breast-ovarian-genetics-pdq

Targeted Therapeutics

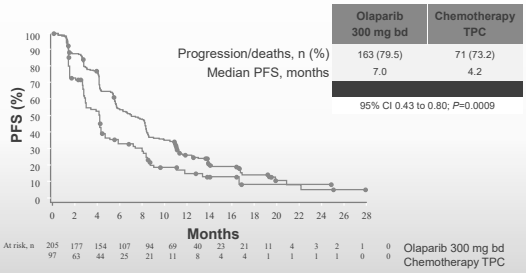
- PARP Inhibitors for BRCA+ (OlympiAD)
  - Metastatic HER2 negative breast cancer
  - Triple negative breast cancer
- Carbo for BRCA+ (TNT Trial)
  - Significant benefit
- Currently under investigation for efficacy with other genetic mutations including PALB2, ATM and the MMR genes

PARP Inhibitors

- PARP inhibitors work in part by blocking the ability of PARP proteins to repair damaged DNA, which includes recruiting other DNA repair proteins

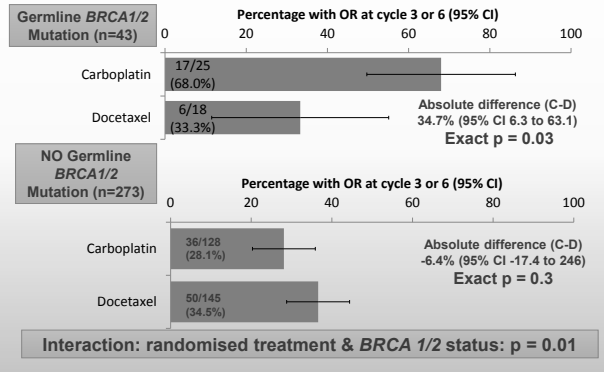


OlympiAD Trial: Progression free survival



Robson M et al. NEJM 2017

TNT Trial: Objective response



Ovarian

- One of the most heritable cancers, 18% due to a mutation (Norquist, 2016)
  - BRCA1, BRCA2, BRIP1, Lynch syndrome, RAD51C, RAD51D
    - PALB2 under investigation
- BRCA carriers receive greatest benefit from PARPi
  - Don't forget somatic mutation carriers!
- All ovarian cancer patients are candidates for genetic testing regardless of age or family history
- WISP trial available for carriers

Negative Germline?

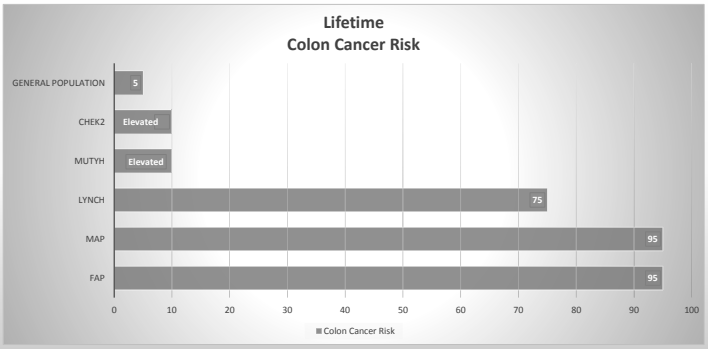
- It's not over yet…
  - 3% of breast cancers harbor BRCA somatic mutations
  - 7-8% of ovarian cancers harbor BRCA somatic mutations

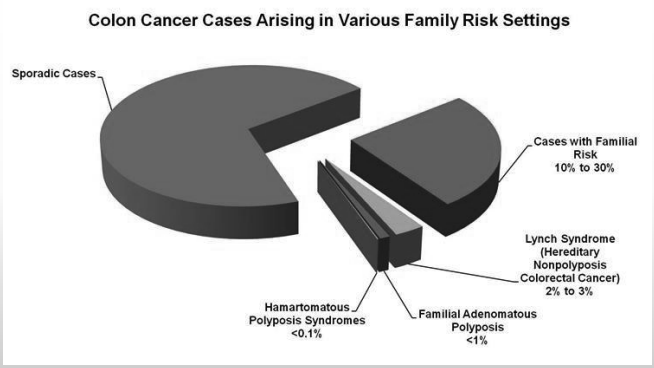
Colorectal Syndromes- Tumor Suppressor Genes

Gene	Syndrome	Inheritance	Predominant Cancer
APC	Familial Adenomatous Polyposis	AD	Colon, Intestinal
TP53	Li-Fraumeni	AD	Multiple (Including colon)
STK11	Peutz-Jeghers	AD	Multiple (Including intestinal)
PTEN	Cowden	AD	Multiple (including intestinal)
BMPR1A	JPS	AD	Gastrointestinal
SMAD4	JPS	AD	Gastrointestinal

Colorectal Cancer Syndromes- MMR Genes

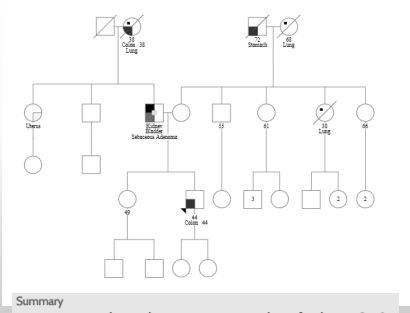
Gene	Syndrome	Inheritance	Predominant Cancer
MLH1, MSH2, MSH6, PMS2	Lynch	AD	Multiple (Including colon, uterine and others)
EPCAM	Lynch	AD	Multiple (including colon, uterine, and others)
MUTYH	MUTYH Associated Polyposis (MAP)	AR	Colon
POLE/POLD1	Oligopolyposis	AD	Colon, endometrial





Gastroenterology, Vol. 119, No. 3, Randall W. Burt, Colon Cancer Screening

Lynch Syndrome

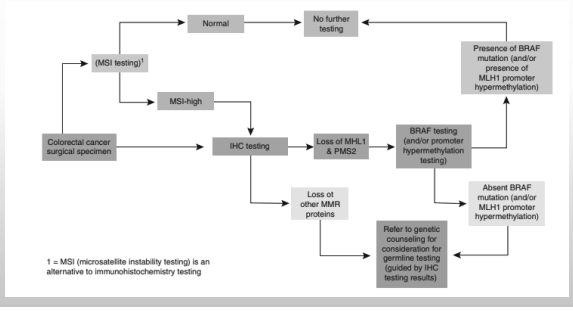


Lynch Syndrome

- AKA: HNPCC
  - Primarily a colon and uterine cancer syndrome
- Genes associated with Lynch Syndrome:
  - MLH1, MSH2, MSH6, PMS2, EPCAM
- Most common form of hereditary colon cancer
- Autosomal Dominant inheritance
  - AR inheritance leads to CMMRD
- Standard of care to screen all colon/uterine cancers by MSI or IHC

Dr. Henry Lynch
1928-2019

Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer



Lynch Syndrome Cancer Risks Vary By Gene

Cumulative Risk for Diagnosis Through Age 80y

	MLH1	MSH2/EPCAM	MSH6	PMS2
Colorectal	46-61%	33-52%	10-44%	8.7-20%
Endometrial	34-54%	21-57%	16-49%	13-26%
Breast	No data	1.5-12.8%	11.1-12.8%	8.1-12.8%
Ovary	4-20%	8-38%	1-13%	3%
Gastric	5-7%	.2-9%	1-7.9%	Inadequate data
Pancreas	No data	.5-1.6	1.4-1.6%	1-1.6%
Bladder	2-7%	4.4-12.8%	1-8.2%	1-2.4%
Biliary Tract	1.9-3.7%	.02-1.7%	NE	.2-1%
Renal pelvis/ureter	.2-5%	2.2-28%	.7-5.5%	1-3.7%
Small Bowel	.4-11%	1.1-10%	1-4%	.1-.3%
Prostate	04.4-11.6%	3.9-15.9%	2.5-11.6%	4.6-11.6%

NCCN 1.2020 Hereditary Colon Cancer

Variable Lynch syndrome recommendations

	MLH1	MSH2/EPCAM	MSH6	PMS2
Age to start colonoscopy	20-25	20-25	30-35	30-35
Frequency of colonoscopy	1-2 years	1-2 years	1-2 years	1-2 years
RRSO	Consider RRSO	Consider RRSO	Insufficient evidence	Insufficient evidence

CMMRD

- Constitutional Mismatch Repair Deficiency
  - When an individual has biallelic mutations in an MMR gene (AR Inheritance)
- Childhood cancer syndrome
  - 16 fold increased risk in developing cancer
- Heme, CNS, Colon cancers with risks starting at age 1
- Derm features overlapping with NF

Polyposis Syndromes

Familial Adenomatous Polyposis (FAP): APC

- AD inheritance
- Classic: 100s-1000s of polyps
- Attenuated (AFAP): 10-100 polyps (Avg 30)
- 30% de novo rate for classic
- Upper GI, CHRPE, desmoids, osteomas, thyroid, brain
- APC I1307K = low risk mutation (AJ)

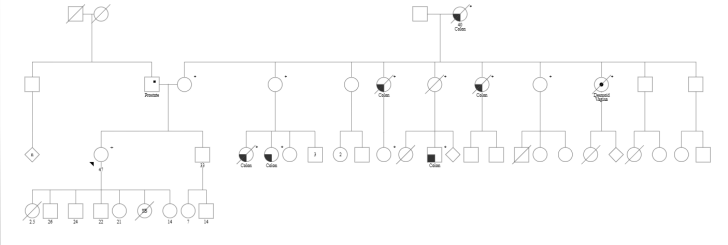
MUTYH Associated Polyposis (MAP): MUTYH

- AR inheritance
- A single mutation slightly increases risk

POLE/POLD1

- AD Inheritance

Familial Adenomatous Polyposis



Summary

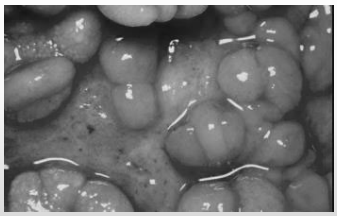
Positive result. Pathogenic variant identified in APC.

Risks for Extraintestinal Malignancies in FAP

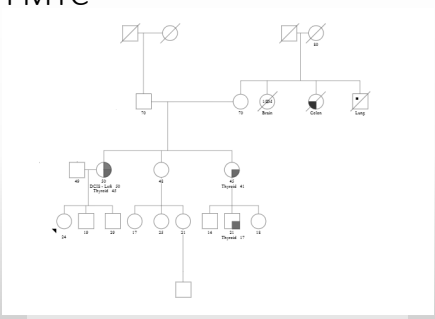
Type of Malignancy	Lifetime Risk
Small bowel: duodenum or periampulla	4-12%
Thyroid: Papillary thyroid cancer	1-2% (higher in women)
CNS: Medulloblastoma	<1%
Liver: Hepatoblastoma	1-2%
Pancreatic Adenocarcinoma	1%
Bile Duct Adenocarcinoma	<1%
Gastric Adenocarcinoma	<1% in Western cultures

FAP Management

- TAC/IRA is recommended for AFAP and TPC/IPAA is recommended for FAP
- If surgery is declined or deferred, yearly c'scope starting at age 10-15.



MEN2/FMTC



Summary

Positive result. Pathogenic variant identified in RET.
Variant of Uncertain Significance identified in MSH3.

MEN2 Clinical Features

Medullary thyroid cancer

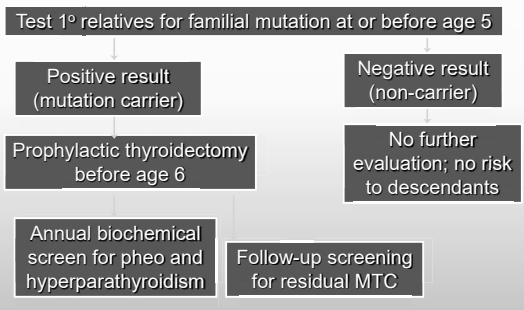
<u>MEN2A</u>

- Pheochromocytoma, PC (50%)
- Parathyroid hyperplasia, HPT (15-30%)

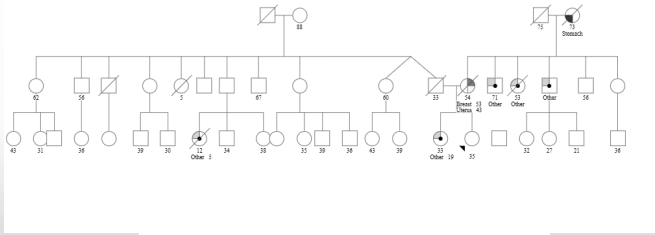
<u>MEN 2B</u>

- Pheochromocytoma (50%)
- Developmental Abnormalities: Ganglioneuromatosis, Mucosal Neuromas, Marfanoid Phenotype

Genetic Testing in MEN 2A or FMTC Families With Known *RET* Mutations



Cowden Syndrome

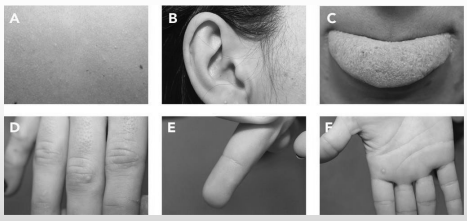


CancerNext-Expanded: ***Analyses of 49 Genes Associated with Hereditary Cancer***

PANEL RESULTS		
PTEN	Pathogenic Mutation:	p.R233*
ATM	Variant, Unknown Significance:	p.P1354T
MSH2	Variants, Unknown Significance:	p.I691T p.N835D

PTEN Clinical Features

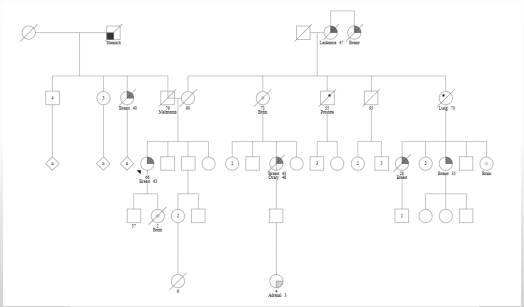
- Macrocephaly (58cm women, 60cm men)
- Thyroid cancer (papillary or follicular)
- Breast cancer
- Uterine cancer
- GI Polyps (hamartomas)
- Multiple cutaneous lesions
- Oral papillomas
- Autism
- Kidney cancer



SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast awareness • Women should be familiar with their breasts and promptly report changes to their healthcare provider	18 years old	Periodic and consistent
Clinical Breast Exam	25 years old, or 5-10 years before the earliest known breast cancer in the family (whichever is first)	Every 6-12 months
Breast Screening • Mammography with consideration of tomosynthesis • Breast MRI with contrast	30-35 years old, or 5-10 years before the earliest known breast cancer in the family (whichever is first) Women treated for breast cancer: MRI and mammogram of remaining breast tissue	Every 12 months
	>75 years old: individualized management	Individualized
Discuss option of risk-reducing mastectomy	Individualized	N/A
Endometrial Cancer		
Encourage prompt response to symptoms (e.g., abnormal bleeding)	Individualized	Individualized
Consider random endometrial biopsies and/or ultrasound	30-35 years old	Every 12 months
Discuss option of hysterectomy upon completion of childbearing	Individualized	N/A
Thyroid Cancer		
Comprehensive physical exam, with particular attention to thyroid exam	18 years old, or 5 years before the youngest age of diagnosis of *PTEN* hamartoma tumor syndrome-related cancer in the family (whichever is first)	Every 12 months
Thyroid ultrasound	Time of *PTEN* hamartoma tumor syndrome diagnosis	Every 12 months
Colorectal Cancer		
Colonoscopy	35 years old unless symptomatic, or if close relative with colorectal cancer before age 40, then start 5-10 years before the earliest known colorectal cancer in the family	Every 5 years, or more frequently if patient is symptomatic or polyps found
Kidney Cancer		
Renal ultrasound	40 years old	Every 1-2 years
Melanoma		
Dermatologic management	Individualized	Clinician's discretion
Other Cancers		
Psychomotor assessment in children and brain MRI if there are symptoms	In childhood (at diagnosis)	Clinician's discretion

1. NCCN Clinical Practice Guidelines in Oncology®. Genetic/Familial High-Risk Assessment: Breast and Ovarian. V 1.2018. Available at nccn.org.

Li-Fraumeni Syndrome



Summary

Positive result. Likely Pathogenic variant identified in TP53.
Variant of Uncertain Significance identified in FH.

TP53 Associated Cancers

Primary Cancers

- Breast cancer
- ACC
- Osteosarcoma
- Brain/CNS
- Leukemia

Also seen

- Lung
- Melanoma
- Thyroid cancer
- GI Tumors
- Kidney
- Gonadal germ cell

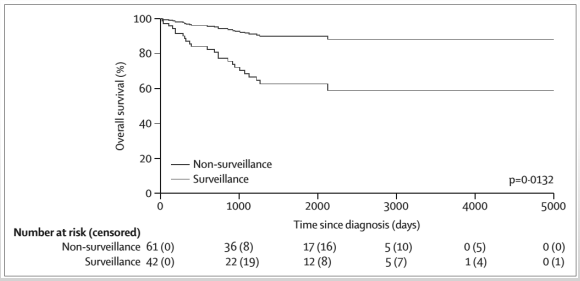
Risk is appx 50% by age 30, 90% by age 60

Confirmation of Result

- Becoming standard practice to confirm germline presence of TP53 through confirmatory testing of a second cell line
  - Can be confirmed on punch biopsy or eyebrow pluck
  - Allele fraction can give a clue (looking for about 50%)
  - Especially important if the case/fam hx doesn't look typical for TP53
  - High de novo rate for TP53
  - Other possibilities include CHIP, chemo effect, or mosaicism
- LiFT UP Study through DFCI and COH
- Important implications for care of patient and family members

SCREENING/SURGICAL CONSIDERATIONS[1]	AGE TO START	FREQUENCY
Female Breast Cancer		
Breast Awareness • Women should be familiar with their breasts and promptly report changes to their healthcare provider	18 years old	Periodic and consistent
Clinical Breast Exam	20 years old (or at the age of earilest diagnosed breast cancer in the family)	Every 6-12 months
Breast Screening	20-29 years old, or the age of earliest diagnosed breast cancer in the family (if below age 20): MRI or mammogram (MRI preferred over mammogram) 30 -75 years old: MRI and mammogram Women treated for breast cancer: MRI and mammogram of remaining breast tissue	Every 12 months
	>75 years old: individualized management	Individualized
Discuss option of risk-reducing mastectomy	Individualized	N/A
Brain Tumors		
Brain MRI as part of whole body MRI (see below, Other Cancers), or a separate exam	Individualized	Every 12 months
Neurologic exam	Individualized	Every 6-12 months
Colorectal and Intestinal Cancer		
Colonoscopy and upper endoscopy	25 years old, or 5 years before earliest known colon cancer in the family (whichever comes first)	Every 2-5 years
Melanoma		
Dermatologic exam	18 years old	Every 12 months

Overall Survival of TP53 Mutation Carriers in Surveillance and Non-Surveillance Groups



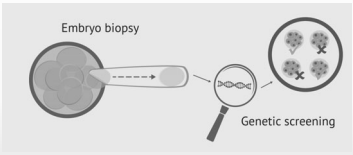
Villani A et al. Lancet Oncol 2016;17:1295-1305

LFS Considerations

- Testing children is appropriate
- Breast cancers are more likely to be triple positive
- Whole body MRI preferred, can do breast, brain separately otherwise
- Radiation sensitivity
  - With breast cancer, radiation therapy should be avoided if possible.
    - Treat the cancer in front of you, even if there is an increased risk of developing a second malignancy

Prenatal Testing: The Next Generation

- Amnio and CVS are options for couples considering termination for an affected fetus
- PGD is available for prevention
  - Screening for a specific genetic mutation(s)
  - Part of IVF cycle
  - Must be done on embryos
  - Only those embryos who have functional genes will be implanted
  - Currently being used for everything from LFS to BRCA



Prostate Cancer

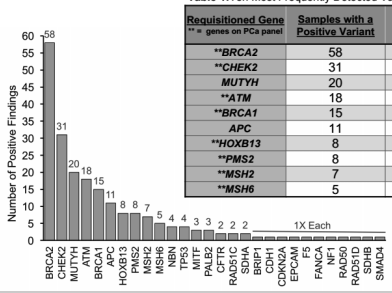
- Genetic mutation carriers tend to have:
  - Earlier age of diagnosis
  - More aggressive disease
  - Higher likelihood to metastasize
- New for 2020: FDA approval for use of PARPi
  - BRCA1, BRCA2, ATM metastatic castration-resistant prostate cancer
  - Phase III PROfound trial showed an OS benefit
  - TRITON2 trial showed nearly 45% of men with BRCA2 mutations showed a tumor response
    - In more than half of these men the response lasted at least 6 months

199 of 1158 (17.2%) Tulane prostate cancer patients had identifiable mutation in MGPT

ATM	*BRCA1*	*BRCA2*	*CHEK2*	*EPCAM*
HOXB13	*MLH1*	*MSH2*	*MSH6*	*NBN*
PMS2	*TP53*	*PALB2**	*RAD51D**	

Table 1: Ten Most Frequently Detected Variants in 1158 Patients with PCa

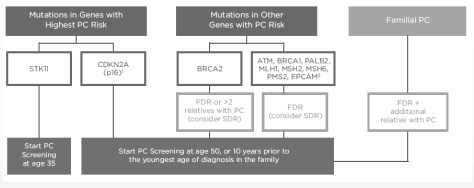
Requisitioned Gene (** = genes on PCa panel)	Samples with a Positive Variant	% of Total Positive Variants (N = 212)	% of Total Samples (N = 1158)
***BRCA2**	58	27.4	5.0
***CHEK2**	31	14.6	2.7
***MUTYH**	20	9.4	1.7
***ATM**	18	8.5	1.6
***BRCA1**	15	7.1	1.3
APC	11	5.2	1.0
***HOXB13**	8	3.8	0.7
***PMS2**	8	3.8	0.7
***MSH2**	7	3.3	0.6
***MSH6**	5	2.4	0.4



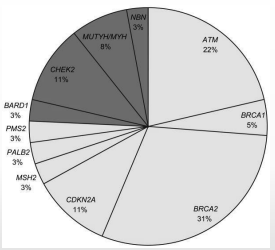
42.5% of mutations were in genes other than *BRCA2*

Piper LW et al. ASCO 2017

Pancreatic Cancer



Genes	Lifetime PC Risk
STK11	11-36%
CDKN2A	Up to 17%
BRCA2	7% (higher in some families)
MLH1, MSH2, EPCAM	Up to 6%
ATM, BRCA1, PALB2, MSH6, PMS2	Elevated



14% had a mutation identified, 9% did not meet criteria for FPC. Testing should be offered to all with PADC.

Chaffee KR et al. Genet Med 2018;20:119-127
Canto MI, et al. Gut 2013; 62:339-347.
Syngal S, et al. Am J Gastroenterol 2015; 110:223-262

NCCN Update for Screening

- MRCP and/or EUS can be considered for:
  - Carriers of ATM, BRCA1, BRCA2, CDKN2A, Lynch syndrome, PALB2, STK11, TP53 with a family history of pancreatic cancer
  - 2 or more first degree relatives with pancreatic cancer, even in absence of a mutation
  - 3 or more first or second degree relatives with pancreatic cancer, even in absence of a mutation

Syndromes with Melanoma Risk

Gene	Effect on Pigment	Effect on Nevi	Penetrance	Other cancer risks
CDKN2A	No	Yes	High	Panc, Breast, cervical, GI, lymphoma, lung, Wilm's
CDK4	No	Yes	High	Similar to CDKN2A
TERT	No	Yes	High	Renal, bladder, AML, myeloproliferative neoplasms
POT1	No	No	High	Glioma, brain, breast, lung, CLL, endometrial
ACD	No	No	High	Brast, brain, lung, ovarian, cervical, colorectal, prostate, myeloproliferative neoplasms
TERF2IP	No	No	High	Similar to ACD
BAP1	No	Yes	High	Uveal melanoma, mesothelioma, renal, meningioma, paraganglioma
PTEN	Yes	Yes	High	Breast, thyroid, endometrium, colorectal, kidney
MC1R	Yes	No	Medium	None reported
BRCA2	No	No	Medium	Breast, ovarian, prostate, pancreas
MITF	Yes	Yes	Medium	Pancreatic, Renal

RiskHawkes JE et al. Sem Oncol 2016;43:591-597

Genetic Testing Referral Criteria: Affected Patients

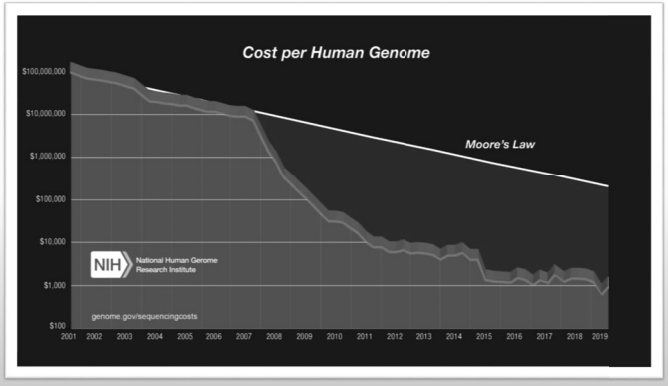
- All ovarian
- All pancreatic
- Colon or uterine under age 50
- All medullary thyroid
- All pheochromocytoma/ paraganglioma
- All adrenal cortical carcinoma
- Anyone Tested prior to 2014
- Metastatic prostate cancer
- PREMM, BRCAPro, Penn II or other validated model showing a 10% risk for having a mutation

Genetic Testing Referral Criteria: Breast Cancer Patients

- Breast cancer under age 45
- Breast cancer and AJ heritage
- Male breast cancer
- Triple neg breast cancer under age 60
- Bilateral breast cancer under age 50
- Metastatic, Her2- breast cancer
- Anyone Tested prior to 2014
- 2 or more family members with breast cancer at any age
- Family history of ovarian, pancreatic, or metastatic prostate cancer
- Dx <50 and limited or male dominated family structure

Genetic Testing Referral Criteria: Unaffected

- First or second degree relative that meets criteria
  - Per NCCN
  - Not necessarily per insurance!
- Anyone Tested prior to 2014

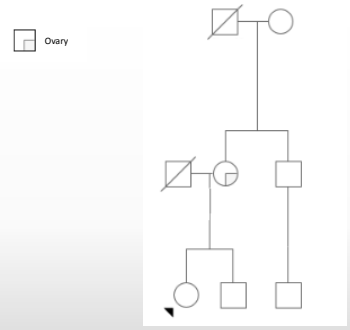


Evaluating genetic testing laboratories

- Methodology
- Depth of coverage
  - Minimum depth
- Interpretation of variants
- Technical accuracy
  - Ex: Bolland Inversion and PMS2 pseudogenes
- Reporting and reclassification of VUS
- <u>Classification matters</u>

Testing Options

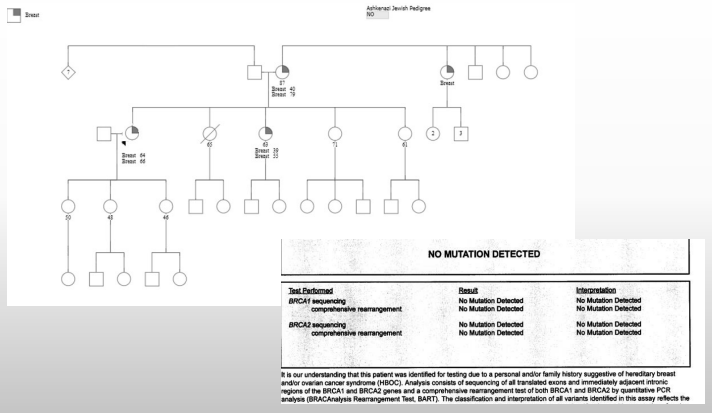
- Targeted
  - Known familial mutation
- Single Gene
  - Sequencing
  - Duplication/Deletion analysis
- Multi Gene Panel
  - 3-5% of mutation carriers have more than one mutation
  - Disease specific or pan cancer panels
  - Range from 5-90+ genes



Test Performed
Sequence analysis and deletion/duplication testing of the 42 genes listed in the results section below.
- Invitae Common Hereditary Cancers Panel (Breast, Gyn, GI)

Reason for Testing
Family history
Family variant testing

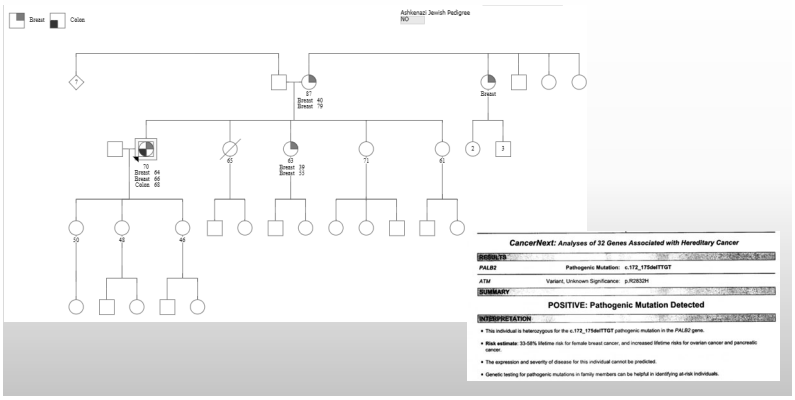
Summary
Positive result. Pathogenic variants identified in BRCA1 and CHEK2.



NO MUTATION DETECTED

Test Performed	Result	Interpretation
BRCA1 sequencing	No Mutation Detected	No Mutation Detected
comprehensive rearrangement	No Mutation Detected	No Mutation Detected
BRCA2 sequencing	No Mutation Detected	No Mutation Detected
comprehensive rearrangement	No Mutation Detected	No Mutation Detected

It is our understanding that this patient was identified for testing due to a personal and/or family history suggestive of hereditary breast and/or ovarian cancer syndrome (HBOC). Analysis consists of sequencing of all translated exons and immediately adjacent intronic regions of the BRCA1 and BRCA2 genes and a comprehensive rearrangement test of both BRCA1 and BRCA2 by quantitative PCR analysis (BRACAnalysis Rearrangement Test, BART). The classification and interpretation of all variants identified in this assay reflects the



***CancerNext*: Analyses of 32 Genes Associated with Hereditary Cancer**

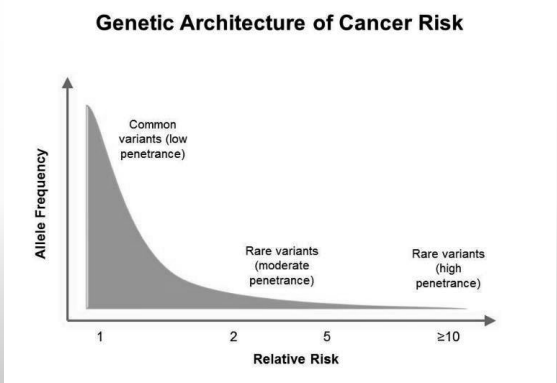
RESULTS		
PALB2	Pathogenic Mutation:	c.172_175delTTGT
ATM	Variant, Unknown Significance:	p.R2832H

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the c.172_175delTTGT pathogenic mutation in the *PALB2* gene.
- **Risk estimate:** 33-58% lifetime risk for female breast cancer, and increased lifetime risks for ovarian cancer and pancreatic cancer.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.



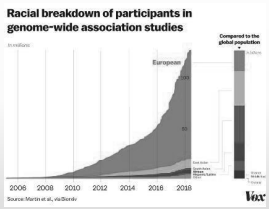
https://www.cancer.gov/about-cancer/causes-prevention/genetics/overview-pdq

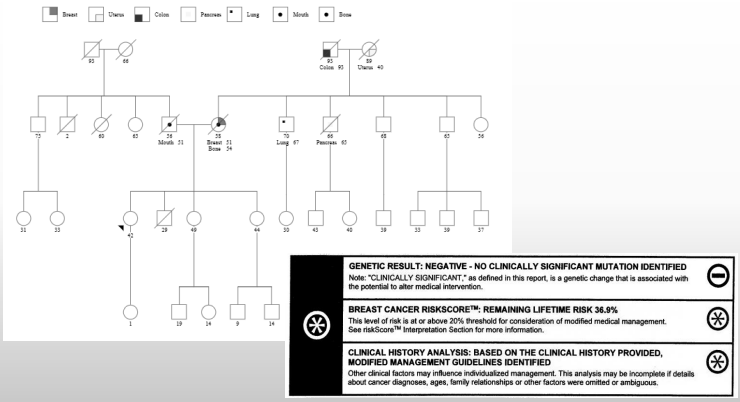
Polygenic Risk Scores

- Use data from GWAS (genome-wide association studies), large scale genetic analyses which focus on uncovering common DNA differences that influence disease and physical traits
- Each variant has modest effect on risk
- Combinations of variants can pose more substantial risk
- Predicts risk in unaffected individuals
- Currently clinically available for breast cancer and prostate cancer only for those of European ancestry

GWAS

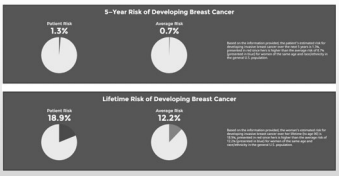
- Genome Wide Associate Studies scan the entire genome looking for differences between the control group and the experimental group
- Currently 80% of participants are of European (non Ashkenazi) ancestry
- Better than rate in 2008 (95%!), but really not okay
- Basis for many new advances
- Need information on underrepresented populations: Black, Hispanic, Asian to be truly informative and generalizable
- All of Us Study from NIH hoping to help address this issue



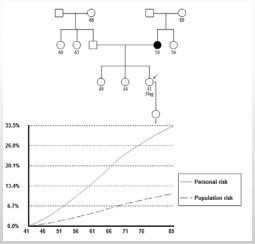


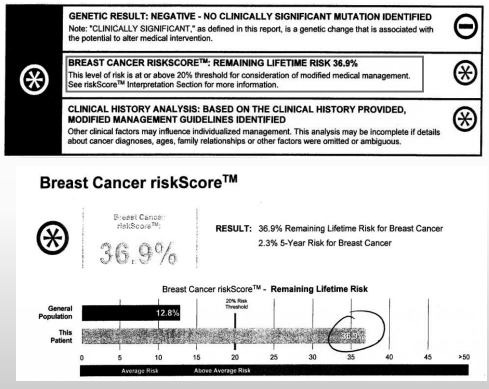
Prediction Models

Gail Model

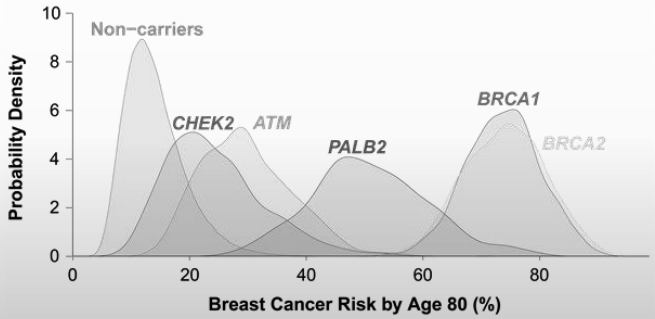


Tyrer-Cuzick



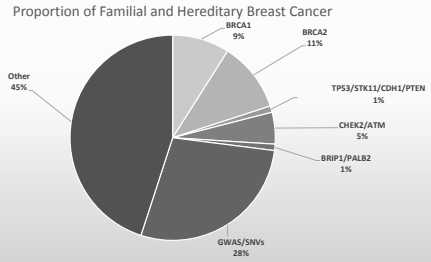


PRS on Mutation Carriers



JAMA Network Open. 2020;3(7):e208501. doi:10.1001/jamanetworkopen.2020.8501

The changing pie chart



Thank You!

Feel free to email me with any questions or comments.

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48

Head and Neck Cancer

David J. Adelstein, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

48 – Head and Neck Cancer

David J. Adelstein, MD, FACP, FASCO

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

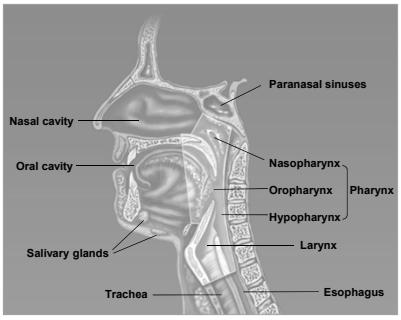
- **None**

Head and Neck Cancer

The Medical Oncologist's Viewpoint

1. Anatomic distinctions less important
2. Common risk factors / co-morbidity
3. Common pathology
4. Common natural history and staging
5. Common response to chemotherapy

Head and Neck Anatomy



Head and Neck Cancer

Pathology:

1. Squamous cell carcinoma
   Nasopharyngeal carcinoma
2. Salivary gland: adenocarcinoma, acinic cell, adenoid cystic, mucoepidermoid, benign mixed,…
3. Paranasal sinus: esthesioneuroblastoma, SNUC, primary neuroendocrine,…
4. Lymphoma, plasmacytoma
5. Thyroid cancers
6. Sarcoma, melanoma, metastatic cancers

Squamous Cell Head and Neck Cancer

Natural History

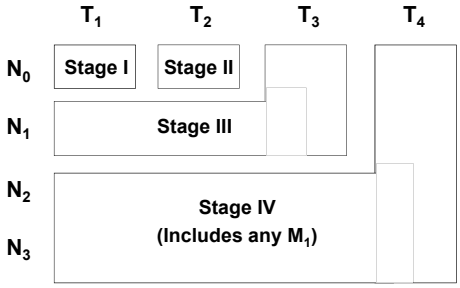
1. Late presentation
2. Local extension - major cause of morbidity
3. Nodal spread common
4. Multiple aerodigestive cancers (10-30%)
5. Distant metastases less common (10-20%)
   - lung, bone

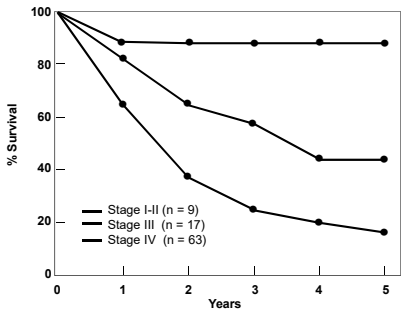
Squamous Cell Head and Neck Cancer

Staging

1. Careful clinical exam of head and neck
2. Examination under anesthesia: (laryngoscopy, esophagoscopy, bronchoscopy, nasopharyngoscopy)
3. Chest x-ray/CT
4. PET/CT Scan
5. MRI scan

Head & Neck Cancer Staging AJCC 1st-7th eds. (1977-2018)





Standard of Care

Newly diagnosed H & N Squamous Cell Cancer

1. In patients with loco-regionally confined disease, treatment is given with curative intent.
2. The definitive treatments are surgery and radiation therapy
3. Single modality treatment is preferred in early stage disease.
4. Choice of modality is based on functional expectations and expertise.

Standard of Care

Newly diagnosed H & N Squamous Cell Cancer

5. Both the primary site and the neck must be addressed.
6. Combined modality therapy is often required for advanced tumors
7. Systemic therapies are adjunctive, not definitive. They have no established role as single modality therapy in primary management.

Standard of Care

Recurrent or Metastatic HNSCC

1. If loco-regionally confined, treatment with surgery, radiation, chemoradiation or even re-irradiation has curative potential.
2. If further surgery or radiation is not possible, systemic treatments are considered palliative.

Squamous Cell Head and Neck Cancer

Chemotherapy for Recurrent or Metastatic Disease

1. There are many active cytotoxic agents:

Methotrexate	Carboplatin
Bleomycin	Paclitaxel
Cisplatin	Docetaxel
5-Fluorouracil	Gemcitabine

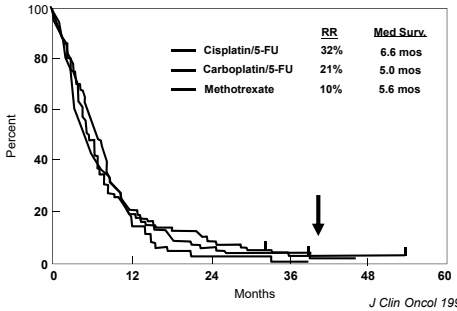
2. Many active drug combinations have been reported.

Squamous Cell Head and Neck Cancer

5-Fluorouracil and Cisplatin in Patients with Recurrent or Metastatic Disease

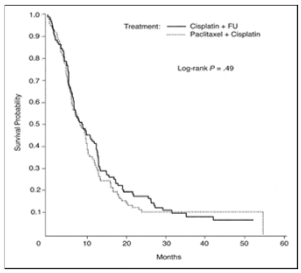
		No. Patients	Response (%)	Complete Response (%)	Median Survival (months)
Kish	1984	30	70	27	7
Kish	1985	18	72	22	6.8
Rowland	1986	30	60	17	9.1
Mercier	1987	20	35	5	6
Jacobs	1992	79	32	6	5.5
Forastiere	1992	87	32	6	6.6
Clavel	1994	116	33	2	N.S.

Overall Survival By Treatment Arm



J Clin Oncol 1992; 10:1245-51

Recurrent or Metastatic Disease:
Cisplatin/5FU vs. Cisplatin/Paclitaxel (E1395, N=218)



	CF	CP
Resp Rate	27%	21%
Med Surv	8.7 m	8.1 m

Q.O.L. Equivalent

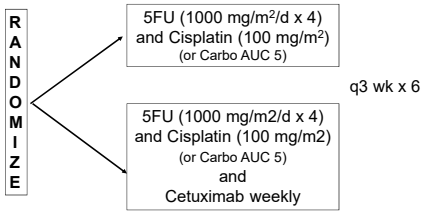
Gibson, MK et al. J Clin Oncol 23:3562-3567, 2005

Second-line EGFR inhibitors in recurrent/metastatic disease

		No.pts	Agent	CR/PR	CR/PR/NC	Med Surv
Trigo	2004	103	Cetux.	13%	46%	5.9 mos.
Baselga	2005	96	Cetux./P	10%	53%	6.1 mos.
Kies	2002	79	Cetux./P	10%	56%	5.2 mos.
Cohen	2003	52	Gefitinib	11%	53%	8.1 mos.
Stewart	2009	304	Gefitinib	5%	46%	5.8 mos.
Soulieres	2004	115	Erlotinib	4%	43%	6.0 mos.
Machiels	2015	322	Afatinib	10%	49%	6.8 mos.

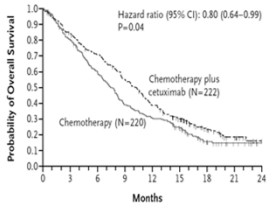
EXTREME Study

Randomized phase III trial in recurrent/metastatic disease



Vermorken et al. NEJM 2008; 359:1116-1127

First-line treatment in Recurrent/Metastatic Disease:
Overall Survival with Chemotherapy and Cetuximab

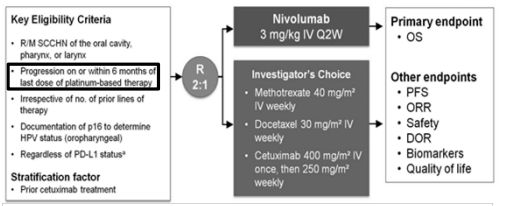


Response rate: 20% ⟶36%
Median survival: 7.4 ⟶ 10.1 mos.

Grade 3-4 Toxicity: 82%

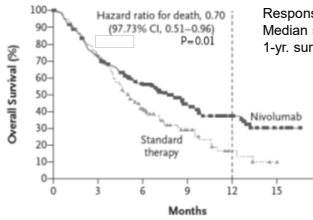
Vermorken et al. NEJM 2008; 359:1116-1127

Phase 3 CheckMate 141 Study Design
Nivolumab in R/M SCCHN After Platinum Therapy



Ferris et al. NEJM 2016; 375:1856-67

Overall Survival
Nivolumab vs. Investigator's Choice in 2nd line R/M HNSCC

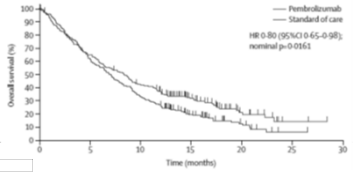


Response rate: 6% ⟶13%
Median survival: 5.1 ⟶7.5 mos.
1-yr. survival: 16.6%➔36%

Ferris et al. NEJM 2016; 375:1856-67

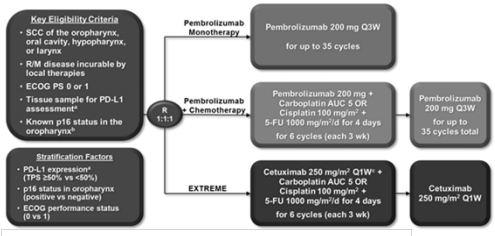
Overall Survival
Pembrolizumab vs. Investigator's Choice in 2nd line R/M HNSCC

Response rate: 10% ⟶15%
Median survival: 6.9 ⟶8.4 mos.
1-yr. survival: 26.5%➔37%



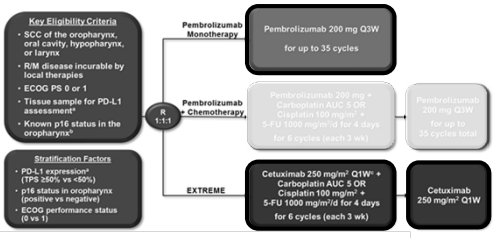
Cohen et al. Lancet 2019; 393:156-67

KEYNOTE-048 Study Design (NCT02358031)



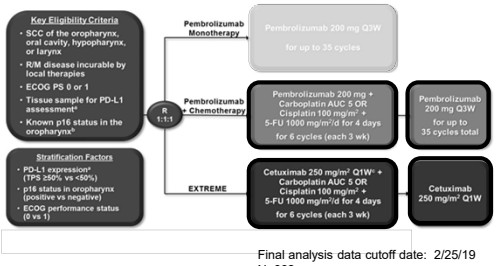
Final analysis data cutoff date: 2/25/19
N=882

KEYNOTE-048 Study Design (NCT02358031)



Final analysis data cutoff date: 2/25/19
N=882

KEYNOTE-048 Study Design (NCT02358031)



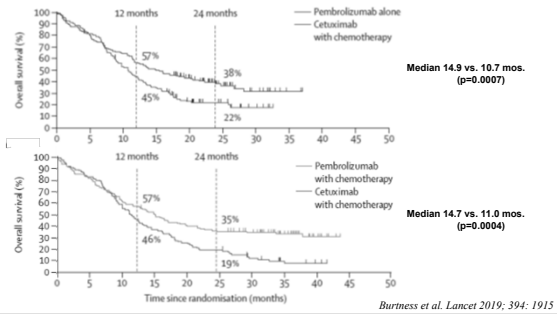
Final analysis data cutoff date: 2/25/19
N=882

KEYNOTE - 048: Analysis

Conclusions

1. When compared to the EXTREME regimen, overall survival was equivalent or better for the treatment arms containing pembrolizumab. This benefit was most apparent in patients with high PD-L1 expression (CPS), and these regimens are now FDA approved in these settings. (6/10/19).

Overall survival: CPS > 20 subgroup



Burtness et al. Lancet 2019; 394: 1915

KEYNOTE - 048: Analysis

Conclusions

1. When compared to the EXTREME regimen, overall survival was equivalent or better for the treatment arms containing pembrolizumab. This benefit was most apparent in patients with high PD-L1 expression, and these regimens are now FDA approved in these settings. (6/10/19).

2. When compared to pembrolizumab alone, the response rates were superior in patients receiving chemotherapy.

3. Toxicity was greater with chemotherapy

Squamous Cell Head and Neck Cancer

Systemic Therapy for Recurrent or Metastatic Disease

1. Treatment is given with palliative intent
2. Many "active" single agents and combinations.
3. Responses to cytotoxic chemotherapy are transient, and usually partial. Impact on survival is limited.
4. A role for immune checkpoint blockade as a component of first-line management has been defined. Durable benefit has been seen in a minority of patients.
5. Investigational therapies should be considered
6. Best supportive care may be the best choice for some patients.

Squamous Cell Head and Neck Cancer

Chemotherapy in Newly Diagnosed vs. Recurrent Disease Patients

	Response Rate	
Chemotherapy	New Diagnosis	Recurrence
DDP / Bleo	71%	33%
DDP / Bleo / Vinbl.	74%	45%
DDP / MTX / Bleo	88%	25%
Bleo / MTX / VCR	71%	43%

Squamous Cell Head and Neck Cancer

5-Fluorouracil / Cisplatin in Previously Untreated Patients

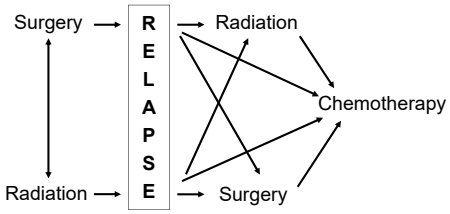
		No. Patients	Response (%)	Complete Response (%)
RTOG	'84	23	91	39
Rooney	'85	61	93	54
VALCSG	'91	166	85	31
Paccagnella	'94	118	80	31
Athanasiadis	'97	71	83	32

Squamous Cell Head and Neck Cancer

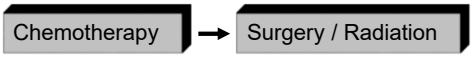
How do we optimally integrate systemic treatments into curative multimodality treatment strategies for locoregionally confined disease?

Squamous Cell Head and Neck Cancer

Multimodality Therapy



Induction Chemotherapy



Squamous Cell Head and Neck Cancer

Induction Chemotherapy: Rationale

The response rates to chemotherapy are better in previously untreated patients, suggesting that the optimal benefit will come from induction schedules.

Induction Chemotherapy: Phase II Experience

1. Many active agents and combinations
2. Response rates 60 - 100%; complete in 20 - 50%
3. Subsequent therapies are well tolerated
4. Responses are transient

There is no established role for chemotherapy as ***single*** modality treatment in the definitive management of squamous cell head and neck cancer.

Squamous Cell Head and Neck Cancer

Induction chemotherapy: Phase II Experience

Additional observations:

1. Response to chemotherapy predicts for a response to subsequent radiation

2. Chemotherapy responders live longer than nonresponders

Induction Chemotherapy

Chemotherapy → Surgery / Radiation

vs.

Surgery / Radiation

Squamous Cell Head and Neck Cancer

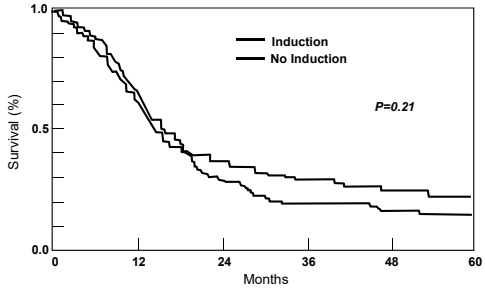
Induction Chemotherapy: Phase III Randomized Trials

		No. Patients	Chemotherapy	Surv. Benefit
Martin	1990	75	FP	No
Jortay	1990	187	VBM	No
Mazeron	1992	131	FPBM	No
Jaulerry	1992	100	PBVdMi	No
Jaulerry	1992	108	FPVd	No
Tejedor	1992	42	CpFt	No
Depondt	1993	324	FCp	No
DiBlasio	1994	69	FP	Advantage standard Rx
Hasegawa	1994	50	FP	No
Paccagnella	1994	237	FP	No*
Dalley	1995	280	FP	No
Volling	1996	97	FCp	No
Domenge	2000	318	FP	*Yes*

*Survival benefit only in unresectable patients only

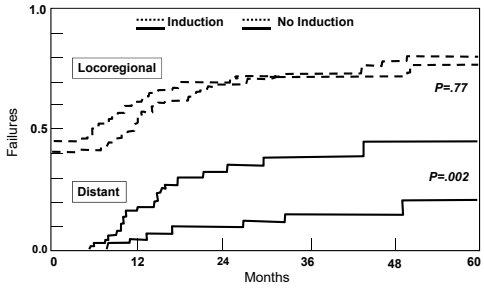
Overall Survival for all Patients

Paccagnella 1994



Time to Treatment Failure for all patients

Paccagnella 1994



Squamous Cell Head and Neck Cancer

Induction Chemotherapy: Phase III Experience

1. No consistent survival advantage
2. No improvement in locoregional control
3. Distant metastases reduced

Adjuvant Chemotherapy

Surgery / Radiation → Chemotherapy

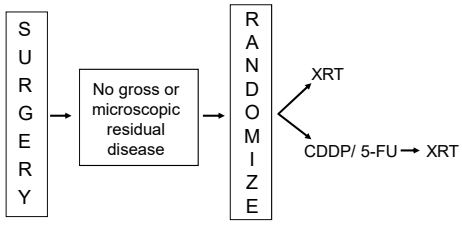
Adjuvant Chemotherapy

Surgery / Radiation → Chemotherapy

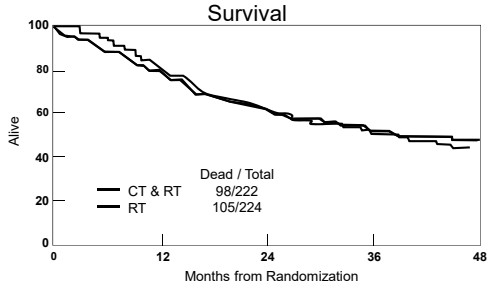
vs.

Surgery / Radiation

SCHEMA - INT 0034

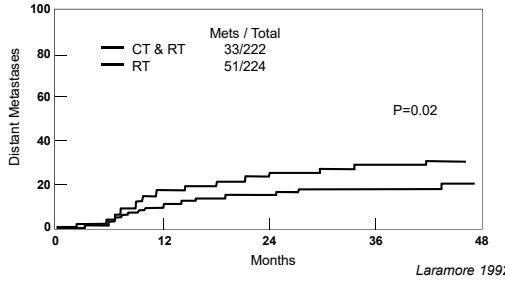


INT 0034
Survival



Laramore 1992

INT 0034
Time Until Distant Metastases



Laramore 1992

Squamous Cell Head and Neck Cancer

Adjuvant Chemotherapy

1. No survival benefit demonstrated
2. Reduction in distant metastases
3. Difficult clinical trials
   - Large number of patients required
   - Poor compliance

Concurrent Chemoradiotherapy

Chemotherapy
Radiation

Concurrent Chemoradiotherapy in Head and Neck Cancer: Advantages

1. Both chemotherapy and radiotherapy are independently active treatment modalities in this disease.

2. Chemotherapy may potentiate radiotherapy and improve local control.

3. Chemotherapy may decrease micrometastatic disease.

4. Concurrent treatment shortens overall treatment duration.

Concurrent Chemoradiotherapy in Head and Neck Cancer: Disadvantages

1. Concurrent use of two treatment modalities produces greater toxicity than either modality alone.

2. This may result in a compromise of dose intensity.
   - Single agent rather than combination chemotherapy
   - Split course radiotherapy
   - Chemotherapy dose reduction

Concurrent Chemoradiotherapy

Chemotherapy
Radiation

vs.

Radiation

Squamous Cell Head and Neck Cancer

Concurrent Single-Agent Chemoradiotherapy: Phase III Randomized Trials

		No. Pts.	Chemotherapy	RT (Gy)	Surv. Benefit
Lo	1976	136	F	60 - 70	*Yes*
Sanchiz	1990	859	F	60	*Yes*
Browman	1994	175	F	66	Marginal
Shanta	1980	157	B	55 - 60	*Yes*
Vermund	1985	222	B	65	No
Fu	1987	104	B	70	*Yes(RFS)*
Eschwege	1988	199	B	70	No
Haselow	1990	319	P	68 - 78	No
Gabriele	1996	130	Cp	70	*Yes*
Jeremic	1997	159	P/Cp	70	*Yes*
Jeremic	2000	130	P	77	*Yes*
Adelstein	2000	295	P	70	*Yes*

INT 0126: SCHEMA

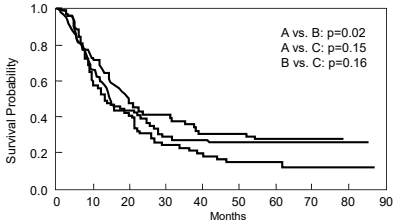
RANDOMIZE

Arm A: Radiotherapy Alone

Arm B: Radiotherapy plus Cisplatin

Arm C: Radiotherapy (split course) plus Cisplatin/5 FU

INT 0126: Overall Survival



Arm	1 yr	2 yrs	3 yrs	Median (months)
A	.52	.30	.20	12.6
B	.65	.41	.36	18.8
C	.60	.40	.28	14.0

Squamous Cell Head and Neck Cancer

Concurrent Multi-agent Chemoradiotherapy: Phase III Randomized Trials

		No. Patients	Chemo	Radiation (Gy)	Survival Benefit	Locoregional Control Benefit
Weissler	1992	32	FP	72 (bid/split)	*Yes**	-
Keane	1993	209	FMi	50 (split)	No	No
Smid	1995	49	MiB	66 - 70	*Yes**	-
Adelstein	1997	100	FP	66 - 72	*Yes**	*Yes*
Wendt	1998	270	FPLV	70.2 (bid/split)	*Yes*	*Yes*
Brizel	1998	116	FP	70 - 75 (bid)	*Yes*	*Yes*
Calais	1999	226	FCp	70	*Yes*	*Yes*
Staar	2001	240	FCp	69.9 (bid/CB)	*Yes**	*Yes**

Chemotherapy Meta-Analysis (MACH-NC) 1965-2000

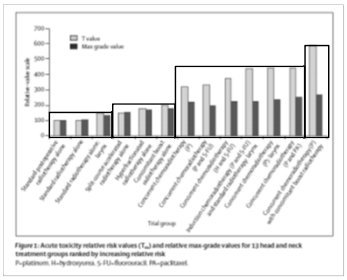
Survival:

Timing	No. trials	No. pts.	HR (95% CI)	P-value	5 yr. benefit
Induction	31	5311	0.96 (0.90 - 1.02)	NS	2.4%
Adjuvant	12	2567	1.06 (0.95 - 1.18)	NS	-1.0%
Concurrent	50	9615	0.81 (0.78 - 0.86)	<0.0001	6.5%

Concurrent chemoradiotherapy has become the standard of care for definitive, non-surgical management of HNSCC.

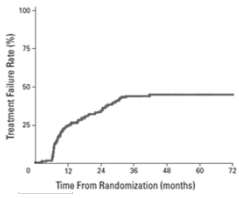
Pignon et al. Radiotherapy and Oncology 92:4-14, 2009

The Increasing Toxicity Burden of Current Multimodality Treatments



Trotti et al. Lancet Oncol 2007; 8: 613-24

Concurrent Chemoradiotherapy: Severe Late Toxicity
RTOG 91-11, 97-03, 99-14

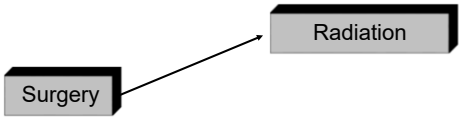


Severe Late Toxicity:
- ≥ Gr. 3 toxicity 6 mos. after treatment
- Feeding tube ≥ 2 yrs. after treatment
- Non-cancer death ≤ 3 yrs. after treatment

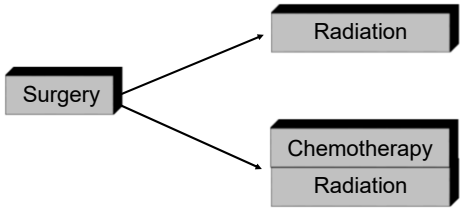
Severe late toxicity identified in 43%

Machtay et al. J Clin Oncol 2008; 26: 3582-89

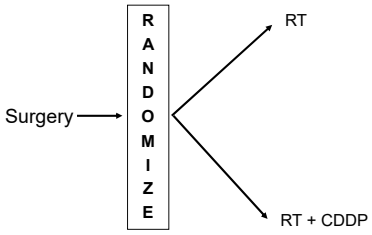
Adjuvant Radiotherapy



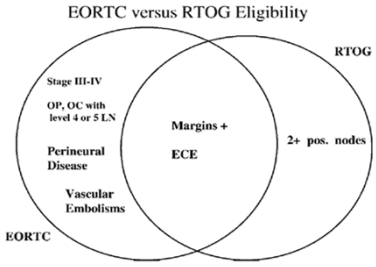
Adjuvant Chemoradiotherapy



Adjuvant Chemoradiotherapy: Schema
RTOG 9501, EORTC 22931

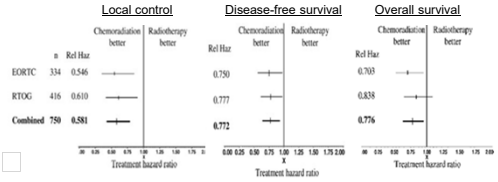


Post-op Adjuvant Chemoradiotherapy: Pooled data



Bernier et al. Head Neck 2005; 27:843-850

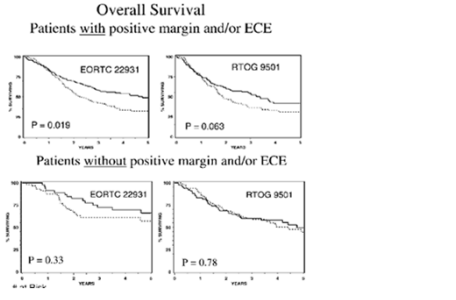
Post-op Adjuvant Chemoradiotherapy: Pooled data



Chemotherapy did not reduce the chance of distant metastases

Bernier et al. Head Neck 2005; 27:843-850

Post-op Adjuvant Chemoradiotherapy: Pooled data



Bernier et al. Head Neck 2005; 27:843-850

Squamous Cell Head and Neck Cancer

Post-operative Adjuvant Chemoradiotherapy

1. Survival benefit demonstrated

2. The benefit is greatest in, and is the standard of care for patients with positive surgical margins or extracapsular nodal spread.

EGFR inhibitors in newly diagnosed disease:

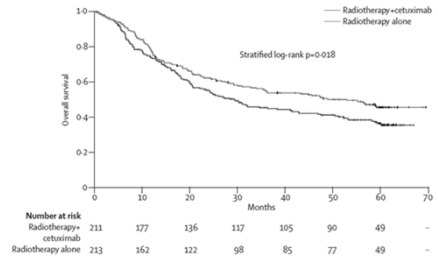
Cetuximab plus RT vs. RT alone

SCHNC Stage III/IV M_0

- Radiation Therapy
- Radiation Therapy plus Cetuximab (weekly)

Bonner, J. et al. N Engl J Med 2006;354:567-578

Kaplan-Meier Estimates of Overall Survival
Radiotherapy plus Cetuximab or Radiotherapy Alone



Bonner, J. et al. Lancet Oncol 2010; 11:21-28

RTOG 1016
Phase III Trial in HPV-Associated Oropharynx Cancer

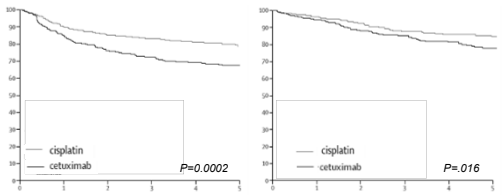
1. Oropharynx Cancer
2. Selected Stage III-IV
3. p16+ (HPV+)
4. Any smoking history

RANDOMIZE

- Accelerated IMRT + Cisplatin 100 mg/m^2 q3 wks x 2
- Accelerated IMRT + Cetuximab weekly x 8

RTOG 1016 Results (N=805)

Progression-free survival (%) | Overall survival (%)



Radiotherapy plus cetuximab did not meet the predefined non-inferiority criterion for overall survival (HR 1.45)
Late toxicity burden similar between treatment arms

Gillison et al. Lancet 2019; 393:40-50

Endpoints in Clinical Cancer Research

- Response
- Survival
- Quality of life
  - Organ (larynx) preservation

Squamous Cell Head and Neck Cancer

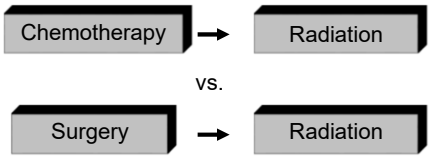
Organ Preservation Strategies

1. Although induction chemotherapy is very active, it does not alter survival or local control.

2. A response to induction chemotherapy will predict for a response to radiation therapy.

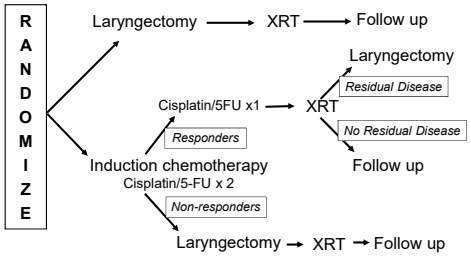
3. Chemotherapeutic downstaging may allow the substitution of definitive radiation for surgical resection or "organ preservation".

Organ Preservation



VALCSG: Stage III-IV Larynx Cancer

NEJM 1991;324:1685



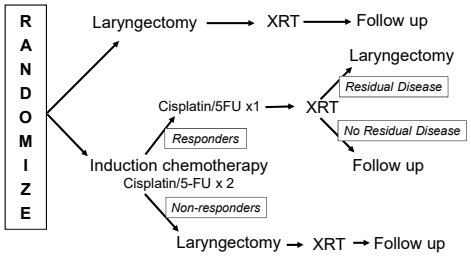
Squamous Cell Head and Neck Cancer

VALCSG - Laryngeal Preservation Trial

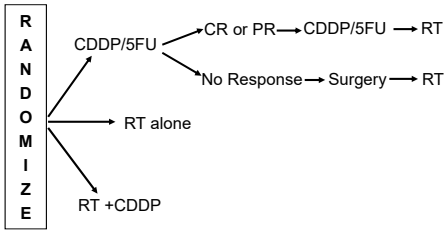
	Surg / RT	Chemo / RT
Response Rate (CR)		85%(31%)
Survival (3 years)	56%	53%
Laryngectomy	100%	38%

VALCSG: Stage III-IV Larynx Cancer

NEJM 1991;324:1685

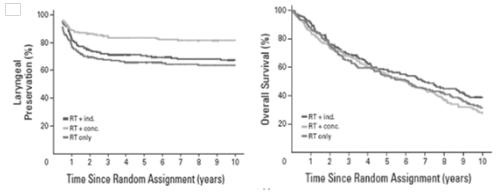


RTOG 91-11: Schema



RTOG 91-11: Outcomes

Median follow-up 10.8 years



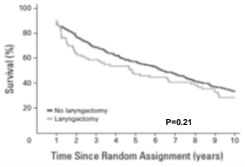
	RT v Ind.	RT v Con.	Ind. v Con.
Larynx Pres.	P=0.35	P<0.001	P=0.005

Forastiere et al. J Clin Oncol 2013; 31:845-852

RTOG 91 – 11: Surgical Salvage

	Induction	Concurrent	RT alone
No. Patients:	174	174	172
5 yr. Overall survival	58%	55%	54%
Salvage laryngectomy	55 (32%)	32 (18%)	61 (35%)
10 yr. Overall survival	39%	28%	32%

P=0.08



Forastiere et al. J Clin Oncol 2013; 31:845-852

Squamous Cell Head and Neck Cancer

Organ Preservation Strategies

Unresolved issues:

1. Are there better multimodality regimens?
2. Extension to non-laryngeal primary sites
3. Which patients are most likely to benefit from organ preservation strategies?
4. Quality of life and late toxicity issues must be addressed.

organ preservation ≠ organ function preservation

Standard of Care

Newly diagnosed Head and Neck Squamous Cell Ca

What is the role of systemic treatments in the definitive management of locoregionally confined disease?

Standard of Care

Newly diagnosed Head and Neck Squamous Cell Ca

1. Concurrent platin-based chemotherapy and radiation has been demonstrated to improve locoregional control and survival in:

   a. Patients with unresectable/unresected disease

   b. Patients with high-risk pathologic features after surgery.

Standard of Care

Newly diagnosed Head and Neck Squamous Cell Ca

2. Concurrent radiation and cetuximab can improve survival and locoregional control when compared to radiation therapy alone.

   a. Results after concurrent radiation and cetuximab are inferior to those achieved with concurrent radiation and cisplatin, and use of this combination is only recommended in patients ineligible for cisplatin.

3. The role of immune checkpoint inhibition in definitive management is under investigation but has not yet been defined.

Standard of Care

Newly diagnosed Head and Neck Squamous Cell Ca

4. Adjuvant chemotherapy alone does not improve survival and has no defined role in definitive treatment strategies.

5. Acceptable larynx preservation strategies include:

   a. Radiation with concurrent cisplatin.
   b. Induction chemotherapy followed by radiation.
   c. Radiation alone
   d. Larynx preservation surgery

Standard of Care

Newly diagnosed Head and Neck Squamous Cell Ca

6. Except in the organ preservation setting, induction chemotherapy has no role in definitive treatment strategies.

Squamous Cell Head and Neck Cancer

Is that really true?

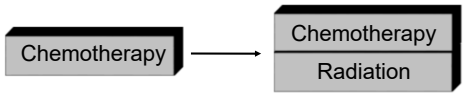
1. With better locoregional control, distant metastases are emerging as a more common cause of treatment failure. Perhaps induction chemotherapy can help.

2. Current three-drug taxane-containing induction chemotherapy regimens are better than the more commonly used fluorouracil/cisplatin doublet.

Induction Chemotherapy: Taxane/Cisplatin/5FU vs. Cisplatin/5FU

	N	Resp. rate
Paclitaxel/PF vs. PF Hitt (2005)	382	80% vs. 68% (*P< .001)*
Docetaxel/PF vs. PF Vermorken (2007)	358	68% vs. 54% (*P= .006)*
Docetaxel/PF vs. PF Posner (2007)	501	72% vs. 64% *(P=.07)*
Docetaxel/PF vs. PF Pointreau (2009)	213	80% vs. 59% (*P= .002)*

Induction followed by Concurrent "Sequential Therapy"



Sequential Therapy

Hypothesis:

Induction chemotherapy followed by concurrent chemoradiotherapy will:

a. achieve the same locoregional control as concurrent chemoradiotherapy alone

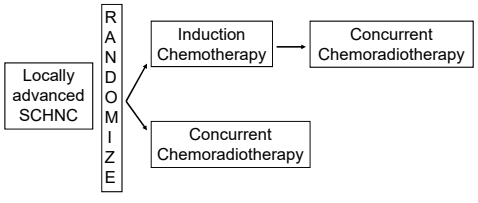
b. reduce distant metastases

c. improve survival.

Caveat:

Any benefit achieved will require treatment which is longer in duration, more toxic and more expensive.

Sequential Therapy
2nd Generation Randomized Trials of Induction Chemotherapy



Sequential Therapy

2nd Generation Randomized Trials of Induction Chemotherapy

1. Hitt (Spain)
   Induction: PF vs. DPF Concurrent: RT/DDP
   Sequential Rx: More toxic, no survival benefit. *Ann Oncol 2014*
2. U. Chicago (DeCIDE)
   Induction: DPF Concurrent: DFHX
   Sequential Rx: More toxic, no survival benefit. *J Clin Oncol 2014*
3. Dana Farber (PARADIGM)
   Induction: DPF Concurrent: Variable
   Sequential Rx: More toxic, no survival benefit. *Lancet Oncol 2013*

Standard of Care

Newly diagnosed Head and Neck Squamous Cell Ca

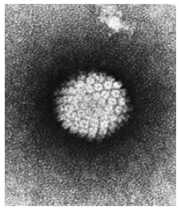
6. Except in the organ preservation setting, induction chemotherapy has no role in definitive treatment strategies.

Although "Sequential Therapy", (the use of induction chemotherapy followed by concurrent chemoradiotherapy), is theoretically attractive, it is more toxic, more expensive, requires more time to administer and does not improve survival.

It is not a current treatment standard.

Squamous Cell Head and Neck Cancer

The Human Papillomavirus (HPV)



Small DNA virus; epitheliotropic, 120 serotypes; esp. 16, 18

HPV-mediated Head and Neck Cancer

1. HPV DNA (esp. HPV-16) can be found in 25% of all HNSCC; and in >70% of oropharynx (tongue base and tonsil) cancers in the U.S.
2. Tumor p16 expression by IHC is an excellent surrogate for HPV-positivity in the oropharynx.
3. Tumor HPV-positivity is independent of tobacco and alcohol exposure.
4. Patients with HPV positive tumors are younger, and more often Caucasian.

HPV-mediated Head and Neck Cancer

5. HPV+ tumors are more often poorly differentiated (basaloid) and more advanced at presentation.
6. HPV+ tumors are associated with high-risk sexual behavior.
7. The incidence of HPV+ oropharynx cancer is increasing in the U.S.

Biologically: Two different diseases

HPV-positive head and neck cancer

- Viral oncoproteins E6 and E7 inactivate p53 and Rb tumor suppressors (with resultant p16 overexpression).
- EGFR often not overexpressed.

HPV-negative head and neck cancer:

- Carcinogen-mediated p53 mutations
- EGFR overexpression common

HPV-mediated Head and Neck Cancer

8. Both retrospective and prospective studies have identified a better prognosis for patients with HPV positive tumors.

9. This improved prognosis is independent of all of the other favorable prognostic features found in this patient population (age, performance status, smoking, etc.)

RTOG 0129: Schema

Eligible: Stage III-IV HNSCC (excluding all T_1, T_2N_1 and M_1)

Stratify

Tumor Site:
1. Larynx
2. Non-Larynx

Nodal Status:
1. N_0
2. N_1 or N_{2a-b}
3. N_{2c} or N_3

P.S.:
1. 0
2. 1

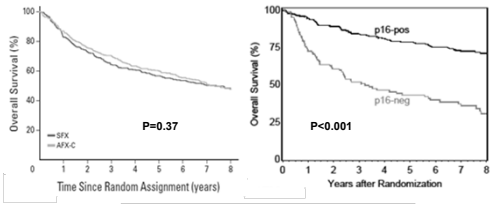
RANDOMIZE

- Standard Fractionation XRT (70 Gy/35 Fx/7 wks) + Cisplatin 100 mg/m^2 d1, 22, 43
- Accelerated Fractionation/ Concomitant Boost XRT (72 Gy/42 Fx/6 wks) + Cisplatin 100 mg/m^2 d1, 22

721 eligible/evaluable patients enrolled between 7/02 - 6/05
60% OP cancer; 64% of the OP patients were HPV+

RTOG 0129: Overall Survival

All patients | Oropharynx cancer patients



Median follow-up: 7.9 (range 0.3-10.1) years

Nguyen-Tan et al. J Clin Oncol 2014: 32: 3858-3867

RTOG 0129

Patient and tumor characteristics by HPV status

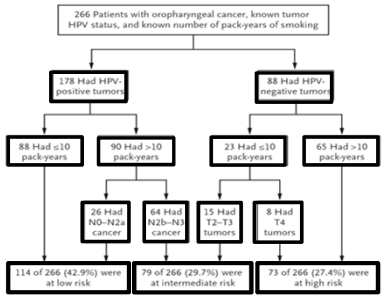
Variable	HPV-pos	HPV-neg	p-value
Age, years (median)	53.5	57.0	0.02
Race, white (%)	92.2	75.2	<0.001
Zubrod PS, 0 (%)	68.4	56.4	0.03
AJCC stage, IV (%)	87.9	83.8	0.30
T2-3 (%) (vs. T4)	75.2	60.7	0.008
N0-2a (%) (vs. N2b-3)	30.1	38.5	0.14
<20 Pack-yr smoker (%)	51.0	22.2	<0.001

RTOG 0129

Multivariable model for survival (OPC pts.)

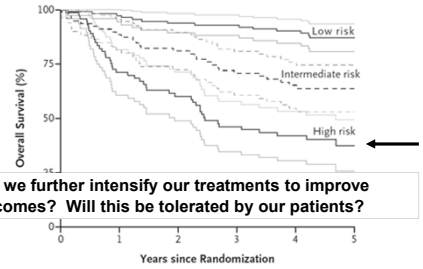
Variable	H.R.	95% CI	P-value
Age (≥50 vs.<50)	1.69	1.12 - 2.56	0.01
Race (non-white vs. white)	2.13	1.39 - 3.25	<0.001
T stage (T4 vs. T2-3)	2.00	1.43 - 2.80	<0.001
N stage (N2b-3 vs. N0-2a)	1.91	1.30 - 2.79	<0.001
Pack years (≥20 vs. < 20)	1.91	1.20 - 3.05	0.007
HPV status (neg vs. pos)	2.00	1.31 - 3.06	0.002

RTOG 0129: Overall Survival RPA



Ang et al. NEJM 2010; 363: 24-35

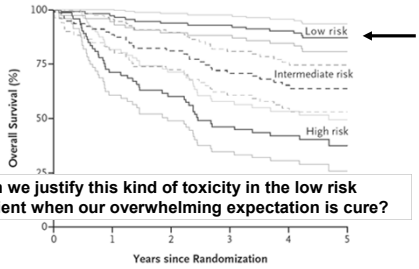
RTOG 0129: Overall Survival



Can we further intensify our treatments to improve outcomes? Will this be tolerated by our patients?

Ang et al. NEJM 2010; 363: 24-35

RTOG 0129: Overall Survival



Can we justify this kind of toxicity in the low risk patient when our overwhelming expectation is cure?

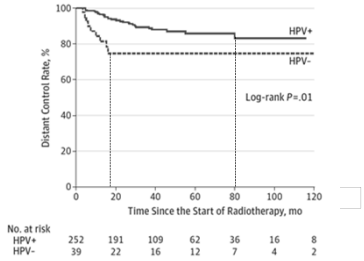
Ang et al. NEJM 2010; 363: 24-35

RTOG 0129: Three-year outcomes

Variable	HPV-pos (%)	HPV-neg (%)	p-value
Overall survival	82.4	57.1	<0.001
Progression-free survival	73.7	43.4	<0.001
Loco-regional control	86.4	64.9	<0.001
Second primary tumor	5.9	14.6	0.02
Aerodigestive 2nd 10	2.9	7.7	0.04
Distant metastases	8.7	14.6	0.23

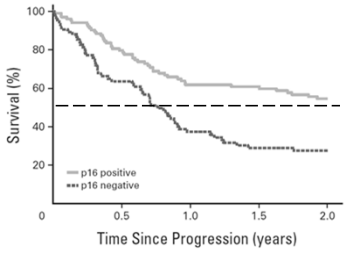
Is the distant metastatic failure pattern the same?

Cleveland Clinic Experience (1996-2013)
Distant Metastatic Control Rate

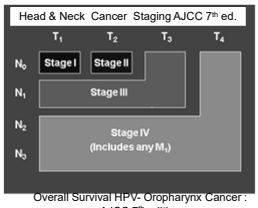


Trosman et al. JAMA Otolaryngol Head Neck Surg 2015; 141: 457-62

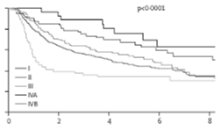
Oropharyngeal Cancer: Survival after Disease Progression
RTOG 0129 and 0522

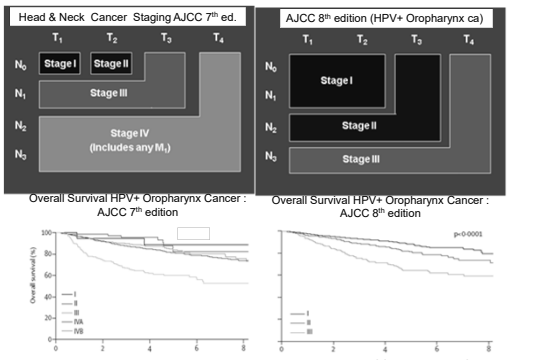


Fakhry et al. J Clin Oncol 2014; 32:3365-3373



Overall Survival HPV- Oropharynx Cancer : AJCC 7th edition





O'Sullivan et al. Lancet Oncol 2016; 17:440-51

Head and Neck Cancer

The Medical Oncologist's Viewpoint

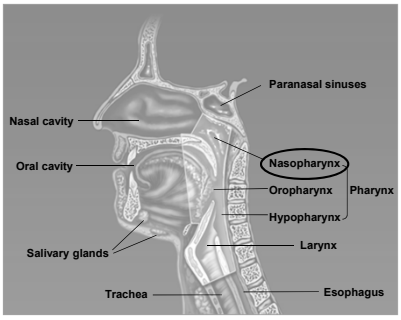
1. Anatomic distinctions less important
2. Common risk factors / co-morbidity
3. Common pathology
4. Common natural history and staging
5. Common response to chemotherapy

Summary:

1. HPV+ and HPV- oropharynx cancers are two distinct diseases:
   - different etiologies,
   - different demographics
   - different prognoses after treatment.

2. Separate approaches are required in their clinical investigation, and will likely be required in their management.

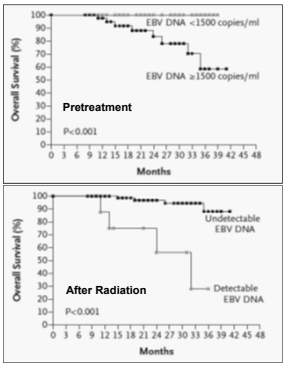
Head and Neck Anatomy



Nasopharynx cancer:

1. Etiology: Epstein-Barr Virus (EBV) vs. Human Papillomavirus (HPV)
2. Histopathology
   a. WHO Type I: Keratinizing squamous cell carcinoma
   b. WHO Type II: Differentiated Non-Keratinizing NPC
   c. WHO Type III: Undifferentiated Non-Keratinizing NPC
3. Often locoregionally advanced at presentation, and rarely amenable to surgery
4. Systemic failure more common than for the other HNSCCs
5. Definitive treatment for early disease is radiation therapy.
6. Chemotherapy sensitive
7. Plasma EBV DNA is highly prognostic

Prognostic value of plasma EBV DNA concentration



Lin et al. NEJM 2004; 350:2461

Nasopharyngeal Carcinoma

Chemotherapy is active in metastatic disease:

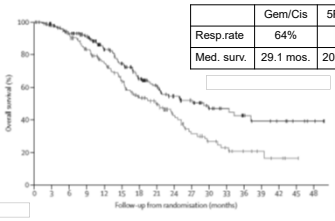
	No. pts.	Agents	CR	PR	LT PFS
Yeo (1996)	42	Carb/FU	17%	21%	2%
Fandi (1998)	165	Various(P)	19%	44%	10%
Siu (1998)	44	CAPMB	7%	73%	13%
Zhang (2016)	181	Gem/DDP	8%	56%	18.5%

Immunotherapy is active in the platinum-refractory:

Ma (2018)	44	Nivolumab	2%	18%	19%

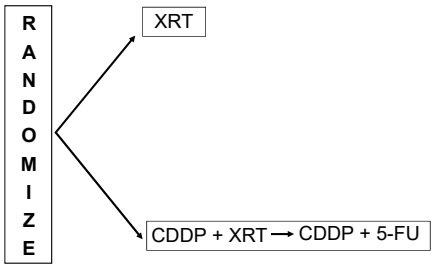
Recurrent/Metastatic Nasopharyngeal Cancer
Gemcitabine/Cisplatin vs. Fluorouracil/Cisplatin

	Gem/Cis	5FU/Cis	*p value*
Resp.rate	64%	42%	*<0.0001*
Med. surv.	29.1 mos.	20.9 mos.	*0.0025*



Zhang et al. Lancet 2016; 388:1883-92

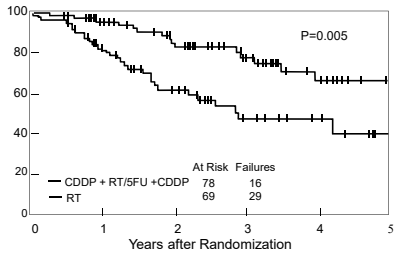
Locoregionally Advanced Nasopharyngeal Cancer
INT 0099: Treatment Schema



Al-Sarraf et al. J Clin Oncol 1998; 16:1310

INT 0099: Overall Survival for Patients on RT Only and Combined Therapy

Al-Sarraf et al. J Clin Oncol 1998; 16:1310



INT 0099: Limitations:

- Small North American trial – early closure
- Broad inclusion criteria
- Heterogeneous study population – 24% WHO I

But these results have been reproduced in a more homogeneous Asian population

- Concurrent vs. adjuvant components
- Only 55% received all adjuvant chemotherapy

Chemoradiotherapy in locoregionally advanced NPC
MAC-NPC Meta-analysis

Survival:

	No. trials	No. pts	HR (95% CI)	P-value
Overall	19	4806	0.79 (0.73-0.86)	<0.0001
Induction	6	1039	0.96 (0.80-1.16)	
Adjuvant	4	888	0.87 (0.68-1.12)	
Concurrent	7	1834	0.80 (0.70-0.93)	
Concurrent + Adj.	6	1267	0.65 (0.56-0.76)	

The additional benefit of adjuvant chemotherapy could not be determined, perhaps because it is so difficult to administer.

Blanchard et al. Lancet Oncol 2015; 16:645-55

What if we give the adjuvant chemotherapy first, i.e. induction/sequential therapy?

Can we improve compliance and results?

Trial Schema

UICC/AJCC 7th ed non-metastatic, stage III~IVB NPC , stratified by center and stage excluding T3-4N0

R 1:1

Induction Chemotherapy Group

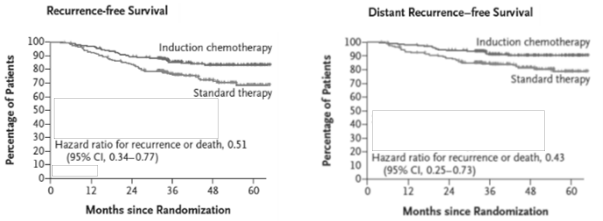
GP IC, q3w * 3 cycles
Gemcitabine 1g/m², d1 & 8
Cisplatin 80mg/m², d1
CCRT
Cisplatin 100mg/m², d1 q3w * 3 cycles
IMRT 68-70Gy in 30-33fr over 6.5w

Standard-Therapy Group

CCRT
Cisplatin 100mg/m², d1 q3w * 3 cycles
IMRT 68-70Gy in 30-33fr over 6.5w

Zhang et al. NEJM 2019; 381:1124-1135

Endpoints:



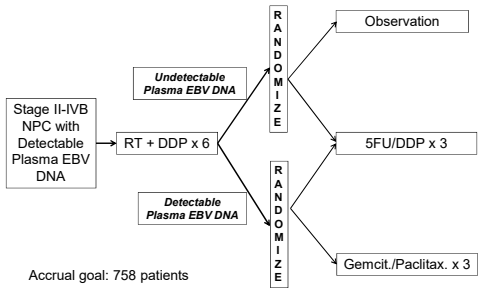
Zhang et al. NEJM 2019; 381:1124-1135

Cisplatin dosing during CCRT

	Induction	No Induction
2 doses	92%	98%

Zhang et al. NEJM 2019; 381:1124-1135

NRG HN001: Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Biomarker Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA)



Accrual goal: 758 patients

Standard of Care

Nasopharyngeal Cancer

1. Radiation therapy is often curative in early stage disease. Surgery rarely has a role.
2. Concurrent chemoradiotherapy, either preceded or followed by adjuvant chemotherapy is the standard of care for locoregionally advanced disease.
3. Patients with distant metastases can experience a significant palliative benefit (and occasionally long-term PFS) with systemic therapies.

Head and Neck Cancer
David Adelstein, MD

Tuesday, August 18, 2020

Cleveland Clinic Taussig Cancer Center

49

Non-Small Cell Lung Cancer

Bruce E. Johnson, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

49 – Non-Small Cell Lung Cancer

Bruce E. Johnson, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Post Marketing Royalties for EGFR mutation testing: DFCI**
- **Paid Consultant: Novartis, Checkpoint Therapeutics, Chugai, Daichi Sankyo, Foundation Medicine, G1 Therapeutics, GSK, Hengrui Therapeutics, Lilly**
- **Unpaid Member of a Steering Committee: Pfizer**
- **Research Support: Novartis, Cannon Medical Imaging**

- **Resolution - Reviewed and found to be unbiased**

Management of Untreated & Treated NSCLC

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- Relapsed Non-Small Cell Lung Cancer

NLST

Call now for more information . . . 1-800-4-CANCER

National Lung Screening Trial

August, 2002 – September, 2004
53,454 participants at Risk for Lung Cancer

Low-dose spiral CT

Smoked >1pack per day of cigarettes for 30 years Age 55-74

Randomize

Year 1 Year 2 Year 3

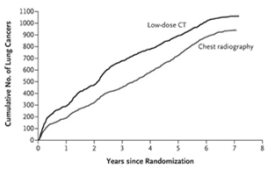
Chest X-Ray

Primary Endpoint: Mortality Due to Lung Cancer

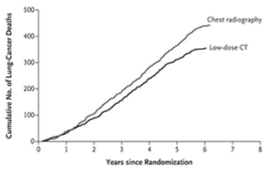
NLST Research Team. *Radiology* 2011; 258(1)

Screening for Lung Cancer

Lung Cancer



Death from Lung Cancer



Aberle et al. *NEJM*. 365:395, 2011
National Lung Screening Trial Research Team *NEJM*. 368:1980, 2013

Dutch-Belgian Screening Trial (Nelson)

December 2003 – June 2006
15,792 participants at Risk for Lung Cancer

Low-dose spiral CT

Smoked >10 cig per day for 30 years
>15 cig per day for 25 Years
Age 55-74

Randomize

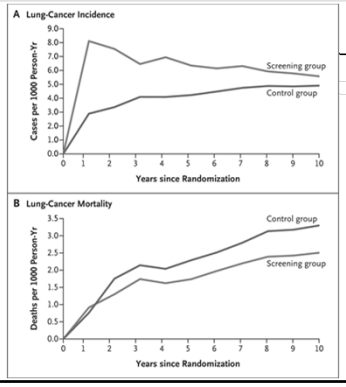
Year 1 Year 2 Year 3 Year 4 4

Usual Care

Primary Endpoint: Mortality Due to Lung Cancer

de Koning et al. *N Engl J Med*. 2020 382:503

Lung Cancer Mortality Rate Ratio



de Koning et al. *N Engl J Med.* 2020 382:503

Recommendations:

American College of Chest Physicians, ASCO, US Preventive Services Task Force

- USPSTF recommends annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years. *Grade B Recommendation*
- Centers for Medicare & Medicaid Services (CMS) issued a national coverage determination (NCD) for Medicare coverage of screening for lung cancer with low dose computed tomography (LDCT) if certain eligibility requirements are met, effective February 5, 2015.

  www.uspreventiveservicestaskforce.org/uspstf/uspslung.html

  www.cms.gov/Medicare/Medicare-General/Information/MedicareApprovedFacilities/Lung-Cancer-Screening-Registries.html

Management of Untreated & Treated NSCLC

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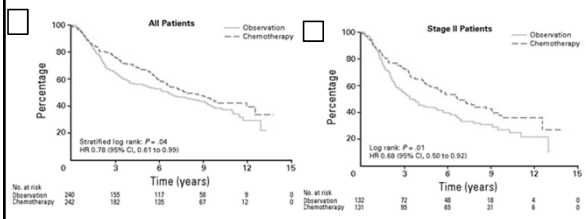
Management of Untreated Stage I & II NSCLC

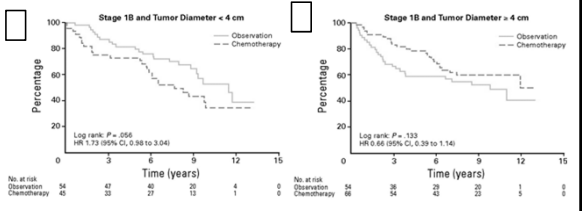
JBR.10: Adjuvant Cisplatin/Vinorelbine vs Placebo in Stages IB-II NSCLC



Butts CA, et al. *J Clin Oncol.* 2010;28(1):29-34

Management of Untreated Stage I & II NCSLC

JBR.10: Impact of Adjuvant Chemotherapy in Tumors ≥ 4 cm



Butts CA, et al. *J Clin Oncol* 2010; 28(1):29-34

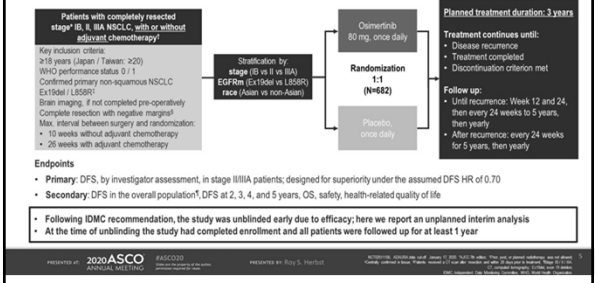
Management of Untreated Stage I & II NSCLC

Benefits of Adjuvant Chemotherapy for Surgically Resected NSCLC

	# Pts	↑ 5 yr (%)	HR	95% CI	*P*
	1209	3	0.96	0.81-1.13	.59
	1867	4	0.86	0.76-0.98	.03
	482	15	0.70	0.52-0.92	.01
	344	2	0.80	0.60-1.07	.10
	840	8	0.79	0.66-0.95	.01
Meta06	4584	4	0.89	0.82-0.96	.005

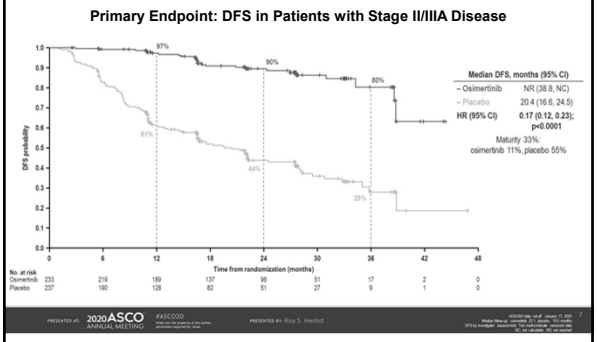
JNCI 03; *NEJM* 04; *NEJM* 05; *J Clin Oncol* 08; *Lancet Oncol* 06

ADAURA Phase III Double-Blind Study Design



Roy Herbst et al. ASCO 2020 LBA 1

7/3/20: FDA Grants Breakthrough Designation to Osimertinib in EGFR+ Lung Cancer



Roy Herbst et al. ASCO 2020 LBA 1

Management of Untreated Stage I & II NSCLC

Adjuvant Chemotherapy for Surgically Resected NSCLC

- Four cycles adjuvant cisplatin based therapy is standard of care for resected stage II and III NSCLC (ASCO guidelines)
  - Cisplatin/vinorelbine
  - Cisplatin/docetaxel
  - Cisplatin/gemcitabine
  - Cisplatin/pemetrexed
- Areas of controversy (not routine clinical use)
  - Stage IB—(maybe for larger tumors greater than 4 centimeters)
  - Role of carboplatin-based regimens—(OK if not cisplatin candidate)

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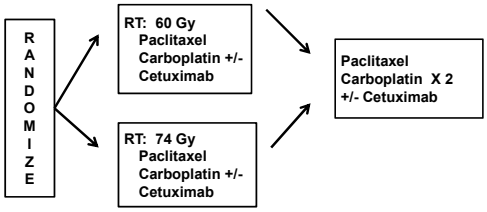
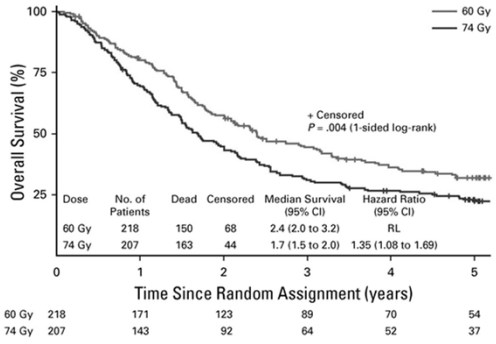
Management of Stage III NSCLC

RTOG 0617



Bradley JD. *Lancet Oncology* 2015; 6: 87

Management of Stage III NSCLC: 60 Versus 74 Gy in RTOG 0617



Bradley JD. *J Clin Oncol* 2020 Mar 1;38(7):706

Management of Stage III NSCLC: Durvalumab vs. Observation in Maintenance

Two Cycles of Platinum-Based Chemotherapy (Etoposide, Vinblastine, Vinorelbine, a Taxane, or Pemetrexed) Plus 5400-6600 Gy Chest RT Concurrently

Eligibility
- Nonsquamous NSCLC
  - Stage IIIA/IIIB
  - PS 0,1
  - Radiation plan ≤20 Gy to <35% Lung Vol
  - Randomized up to 6 Weeks after Chest RT

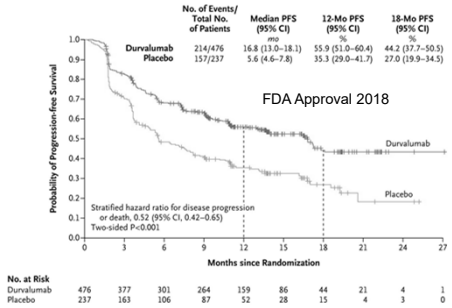
RANDOMIZE*

2 → **Durvalumab 10 mg/kg IV every 2 weeks for 1 Yr**

1 → **Observation**

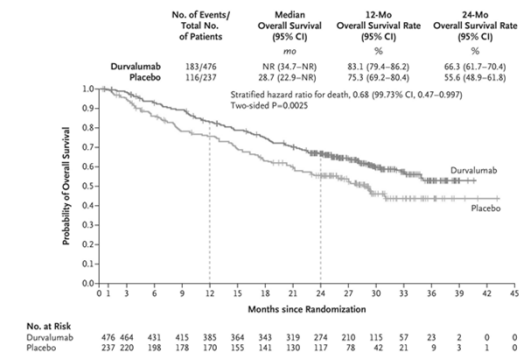
Antonia et al. *N Engl J Med* 2017; 377:1919

Management of Stage III NSCLC: Durvalumab vs. Observation in Maintenance



Antonia et al. *N Engl J Med* 2017; 377:1919

Management of Stage III NSCLC: Durvalumab vs. Observation in Maintenance - Survival



Antonia et al. *N Engl J Med*. 2018 Dec 13;379(24):2342

Management of Stage III NSCLC

Management of Patients With N2 Disease

- Patients should be treated with concurrent chest irradiation and platinum-based chemotherapy (etoposide,paclitaxel or pemetrexed are appropriate). Chest radiotherapy given to 60 Gy is an appropriate dose.
- Durvalumab should be administered to fit patients within two months of when the combined modality is completed

Management of Untreated & Treated NSCLC

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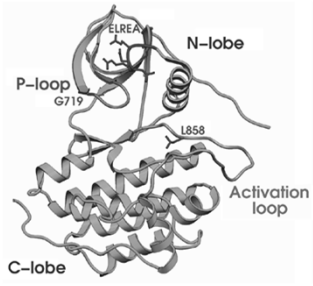
- Relapsed Non-Small Cell Lung Cancer

Epidermal Growth Factor Receptor Mutations

13 of 14 Patients with Response to Gefitinib Had EGFR Mutation



The NEW ENGLAND JOURNAL of MEDICINE
Lynch et al. 2004

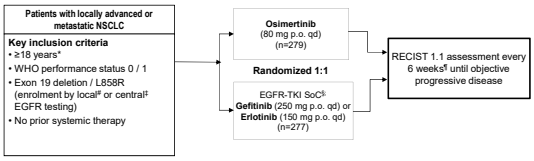
Science
Paez et al. 2004

Current Standards and Studies for Metastatic NSCLC
EGFR+

Study	Drugs	N (*EGFR* mutation)	RR	Median PFS (months)
IPASS	**Gefitinib** vs carboplatin/paclitaxel	261	**71.2%** vs 47.3%	**9.5** vs 6.3
WJTOG 3405	**Gefitinib** vs cisplatin/docetaxel	172	**62.1%** vs 32.2%	**9.2** vs 6.3
NEJGSG002	**Gefitinib** vs carboplatin/paclitaxel	224	**73.7%** vs 30.7%	**10.8** vs 5.4
EURTAC	**Erlotinib** vs cisplatin/docetaxel	173	**58.1%** vs 14.9%	**9.7** vs 5.2
OPTIMAL	**Erlotinib** vs gemcitabine/carboplatin	154	**83.0%** vs 36.0%	**13.7** vs 4.6
LUX-Lung 3	**Afatinib** vs cisplatin/pemetrexed	345	**56.0%** vs 23.0%	**11.1** vs 6.9
LUX-Lung 6	**Afatinib** vs gemcitabine/cisplatin	364	**66.9%** vs 23.0%	**11.0** vs 5.6

Gefitinib EU Summary of Product Characteristics;
Mitsudomi et al. *Lancet Oncol* 2010;11:121–1128; Maemondo et al. *NEJM* 2010;362:2380–2388;
Rosell et al. *Lancet Oncol* 2012;13:239–246; Zhou et al. *J Clin Oncol* 2012;30: Abs 7520;
Sequist et al. *J Clin Oncol* 2013;31:3327–3334; Wu et al. *Lancet Oncol* 2014;15:213–222

Third Generation EGFR-TKI
Osimertinib vs. Gefitinib or Erlotinib

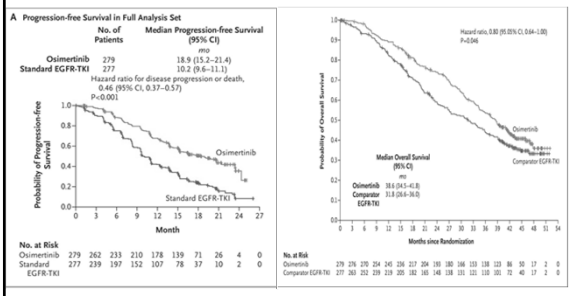


Endpoints
- **Primary endpoint:** PFS based on investigator assessment
- **Secondary endpoints:** objective response rate and survival, patient reported outcomes, safety

Soria et al. *N Engl J Med* 2018 Jan 11;378(2):113

Osimertinib vs. EGFR-TKI for Previously Untreated EGFR Mutant NSCLC

April 2018: FDA grants approval for use of osimertinib as first-line treatment for patients with EGFR+ NSCLC



Ramalingham et al. *NEJM* 2018; 378:113
Ramalingham *NEJM* 2020 382:41

Current Standards and Studies for Metastatic NSCLC
Crizotinib for First Line NSCLC

Randomized phase III trial of Crizotinib vs. chemotherapy in chemotherapy naïve EML4-ALK NSCLC

Key entry criteria
- Diagnosis of locally advanced/metastatic non-squamous NSCLC; ECOG 0-2
- Positive for *ALK*
- No prior treatment for advanced disease
- Brain metastases allowed

R A N D O M I Z E
N=320

Arm A: Crizotinib 250 mg BID administered on a continuous dosing schedule — N=160

Arm B: Pemetrexed/ cisplatin or pemetrexed/ carboplatin Day 1 of a 21-day cycle — N=160

Patients in Arm B who have RECIST-defined PD as determined by the independent radiology review will be allowed to cross over to Arm A

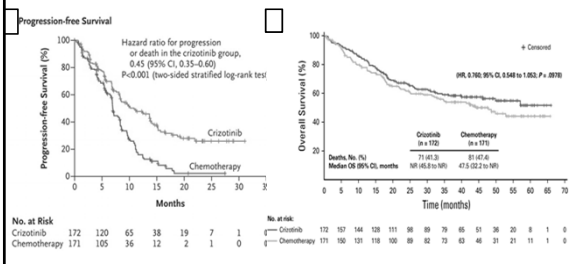
Primary end point: PFS

Secondary end point: ORR

www.clinicaltrials.gov (NCT01154140)

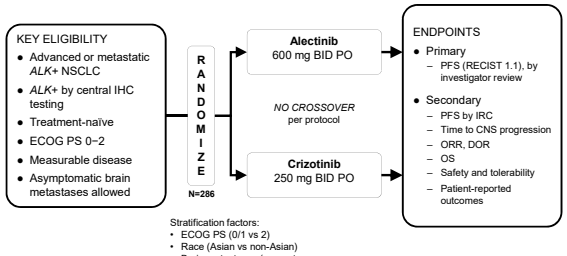
Current Standards and Studies for Metastatic NSCLC
Crizotinib for First Line NSCLC

Crizotinib | **2011 Accelerated Approval for ALK+ NSCLC**
2013 Full Approval



Solomon et al. *NEJM* 2014; 371:2167
Solomon et al. *J Clin Oncol* 2018;36:2251

Study Design

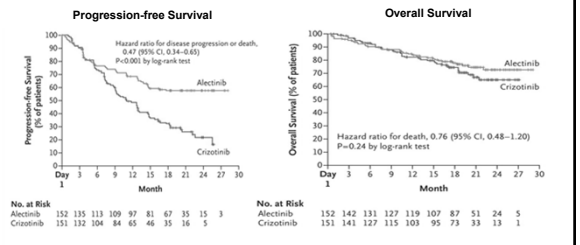


Stratification factors:
- ECOG PS (0/1 vs 2)
- Race (Asian vs non-Asian)
- Brain metastases (present vs absent)

Peters et al. *NEJM* 2017 Aug 31;377(9):829

Current Standards and Studies for Metastatic NSCLC
Alectinib for First Line NSCLC

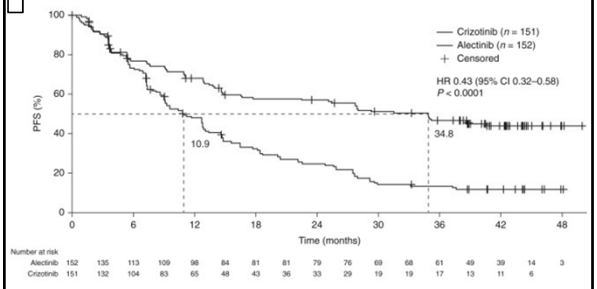
Alectinib | **2015 Accelerated Approval for Previously Rx ALK+ NSCLC**
2017 Approval for UnRx ALK+ NSclc



Peters et al. *NEJM* 2017; epub June 6

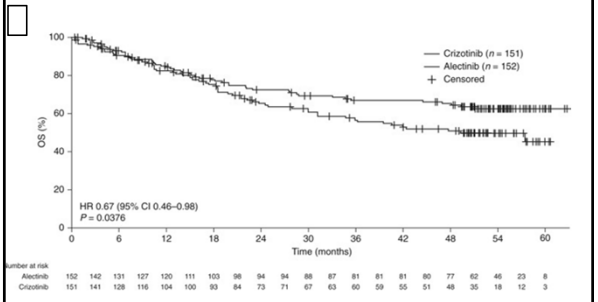
Current Standards and Studies for Metastatic NSCLC
Alectinib for First Line NSCLC-PFS

Alectinib | **2015 Accelerated Approval for Previously Rx ALK+ NSCLC**
2017 Approval for UnRx ALK+ NSclc



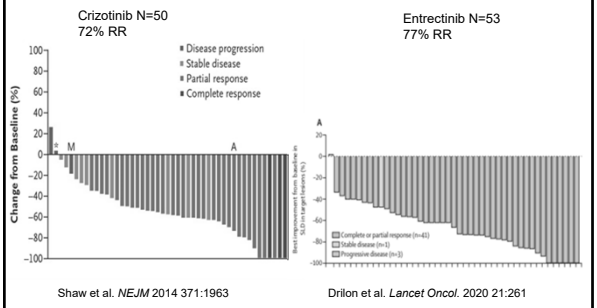
Mok et al. *Ann Oncol* 2020 Aug;31(8):1056

Current Standards and Studies for Metastatic NSCLC
Alectinib for First Line NSCLC-Survival



Mok et al. *Ann Oncol* 2020 Aug;31(8):1056

ROS1+ NSCLC Rx with Crizotinib or Entrectinib

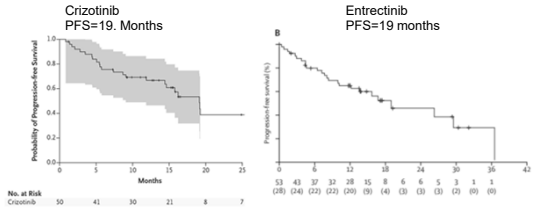


Shaw et al. *NEJM* 2014 371:1963

Drilon et al. *Lancet Oncol.* 2020 21:261

ROS1+ NSCLC Rx with Crizotinib or Entrectinib

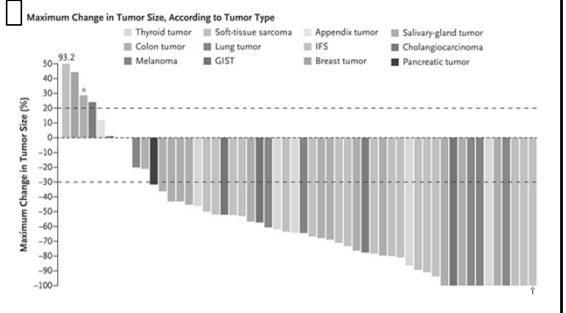
2016: Crizotinib approved for ROS1 Positive NSCLC in US
2020: Entrectinib FDA approved for ROS1 Positive NSCLC in US



Shaw et al. *NEJM* 2014 371:1963

Drilon et al. *Lancet Oncol* 2020 21:261

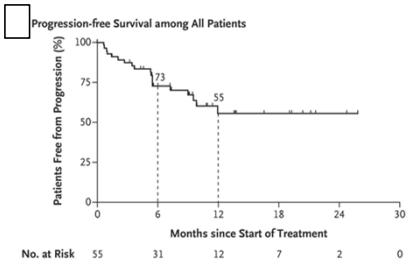
NTRK+ Cancers Rx with Larotrectinib



Drilon et al. *New Engl J Med* 2018 378(8):731

NTRK+ Cancers Rx with Larotrectinib

November 2018: FDA grants accelerated approval to larotrectinib for adult & pediatric patients with solid tumors with NTRK gene fusion



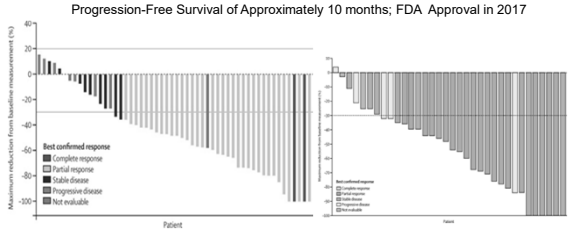
Drilon et al. *New Engl J Med* 2018 378(8):731

RR of 57 BRAF V600E NSCLC with Dabrafenib plus Trametininb as 2nd Line+ Rx and 36 1st Line

Second Line+
36/57 (64%) Patients had a CR (2) or PR (34)

First Line
23/36 (64%) Patients had a CR (2) or PR (21)

Progression-Free Survival of Approximately 10 months; FDA Approval in 2017

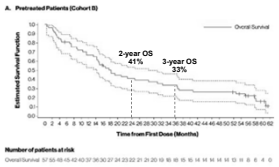


Planchard et al. *Lancet Oncol* 2016 Jul; 17(7):984-93

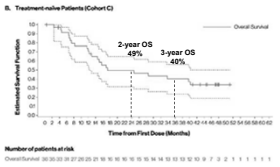
Planchard et al. *Lancet Oncol* 2017 18:1307

Updated Survival
BRAF V600E NSCLC Treated with Dabrafenib + Trametininb

Median OS, months: 18.2 (95% CI, 14.3-28.6)



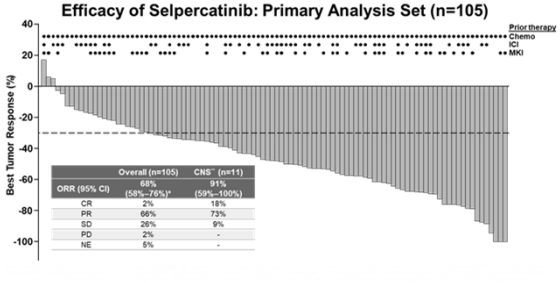
Median OS, months: 17.3 (95% CI, 12.3-40.2)



Planchard D, et al. ASCO 2020. Abstract 9593.

Selpercatinib for *RET* fusion+ Previously Rx NSCLCs

Efficacy of Selpercatinib: Primary Analysis Set (n=105)



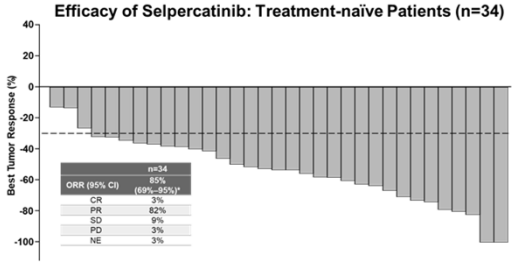
ORR (95% CI)	Overall (n=105) 68% (58%–76%)*	CNS^ (n=11) 91% (59%–100%)
CR	2%	18%
PR	66%	73%
SD	26%	9%
PD	2%	-
NE	5%	-

Drilon et al, WCLC 2019

Selpercatinib for *RET* fusion+ Previously UnRx NSCLCs

May 2020, the FDa granted accelerated approval to selpercatinib for patients with metastatic RET fusion-positive NSCLC

Efficacy of Selpercatinib: Treatment-naïve Patients (n=34)

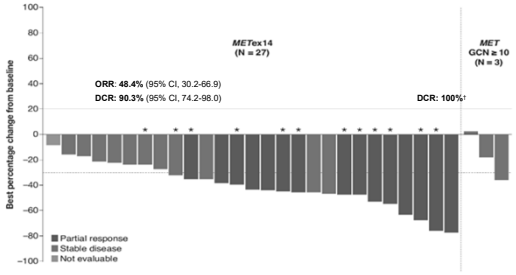


ORR (95% CI)	n=34 85% (69%–95%)*
CR	3%
PR	82%
SD	9%
PD	3%
NE	3%

Drilon et al, WCLC 2019

Capmatinib in Patients with METex14-mutated or High-level MET-amplified Advanced NSCLC

May 2020: FDA grants accelerated approval to capmatinib for NSCLC patients whose tumors have a MET exon 14 skipping mutation



*Patients still on treatment; †All 3 patients had stable disease per BIRC assessment and were on treatment for 48, 85, and 97 days.
BIRC, blinded independent review committee; DCR, disease control rate; GCN, gene copy number; *METex14*, *MET* exon 14 skipping mutation; ORR, overall response rate.

Groen HJM, et al. ASCO 2020. Abstract 9520.

Targeted Therapy for NSCLC (7)

- Osimertinib for EGFR mutant NSCLC
- Alectinib for ALK rearranged NSCLC
- Crizotinib or Entrectinib for ROS1 Rearranged NSCLC
- Dabrafenib plus Trametinib for V600E BRAF mutant NSCLC
- Capamatinib for MET exon 14 Skip Mutations
- Selpercatinib for RET rearranged NSCLC
- Larotrectinib and Entrectinib for NTRK rearranged NSCLC

Management of Untreated & Treated NSCLC

- Screening for Lung Cancer
- Adjuvant Therapy for Early Stage
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease

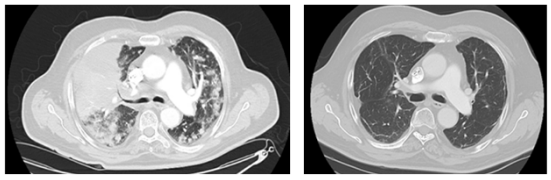
Current Standards and Studies for Metastatic NSCLC
Targeted Therapy • **Immunotherapy**

- Relapsed Non-Small Cell Lung Cancer

Checkpoint Inhibitors as Single Agents

84-Year-Old Smoking Gentleman with Adenocarcinoma Treated on a Checkpoint Inhibitor as a Single Agent

PD-L1 >95%
Tumor Mutational Burden/Megabase: 11.4



December 2017 **June 2019**

Pembrolizumab vs. Chemotherapy in Advanced Previously Untreated NSCLC

- NSCLC
- >50% PD-L1 Positive
- No Prior Therapy
- ECOG 0 or 1
- No Immune Disorders

RANDOMIZE*

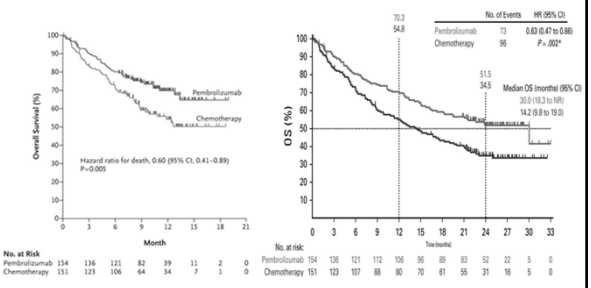
Pembrolizumab 200 mg q 3 weeks

Investigator Choice Platinum-Based Chemotherapy

Reck M et al. *NEJM* 2016 Nov 10;375(19):1823

Pembrolizumab vs. Chemotherapy in Advanced Previously Untreated NSCLC

2016: US FDA grants approval of Pembrolizumab for Pts with NSCLC and >50% PD-L1 Staining of Tumor Cells



Reck M et al. *NEJM.* 2016 Nov 10;375(19):1823 Reck et al. *J Clin Oncol* 2019 Mar 1;37(7):537

Pembrolizumab plus Chemo vs. Chemo in Advanced Previously Untreated NSCLC

- NonSquamous NSCLC
- PD-L1 <1% versus PD-L1 >1%
- No Prior Therapy
- No EGFR or ALK
- ECOG 0 or 1
- No Rx for Immune Disorders

RANDOMIZE*

2

Pembrolizumab Plus Pemetrexed Platinum-Based Chemo

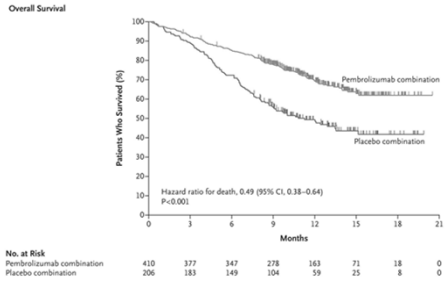
1

Pemetrexed Platinum-Based Chemo

Gandhi et al. *NEJM* 2018: May 31;378(22):2078

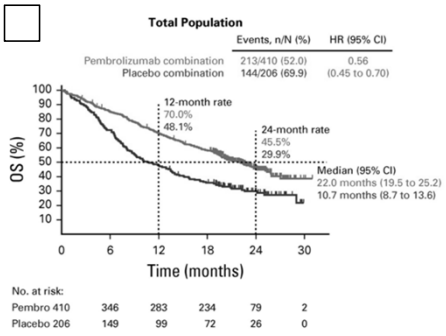
Pembrolizumab plus Chemo vs. Chemo in Advanced Previously Untreated Non-Squamous NSCLC

2018: FDA grants approval to Pembrolizumab + Pem/Carbo for Pts with Non-Squamous NSCLC



Gandhi et al. *NEJM* 2018: May 31;378(22):2078

Pembrolizumab plus Chemo vs. Chemo in Advanced Previously Untreated Non-Squamous NSCLC; Updated



Gandhi et al. *NEJM* 2018: May 31;378(22):2078
Gadgeel et al. *J Clin Oncol* 2020 May 10;38(14):1505

Nivolumab plus Ipilimumab vs. Platinum-Based ChemoRx in Previously unRx Advanced Stage NSCLC

- Squamous and NonSquamous Cell Lung Cancer
- No Prior Therapy regimen
- ECOG 0 or 1
- No EGFR Mutations or ALK Rearrangements
- No Immune Disorders

R A N D O M I Z E *

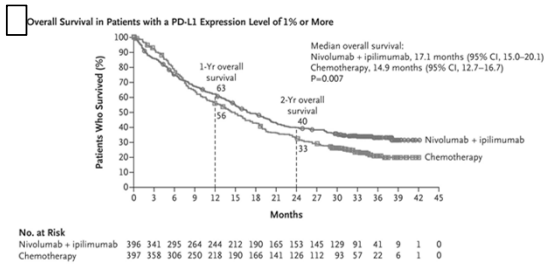
Nivo 3 mg/kg q 2 wks
Ipi 1 mg/kg q 6 wks

Platinum-Based Regimen q 3 wks

Hellman et al. *NEJM* 2019 381:2020

Nivolumab plus Ipilimumab vs. Platinum-Based ChemoRx in Previously unRx Advanced Stage NSCLC

May 15, 2020: FDA approves combination as a first-line treatment for certain Pts with metastatic NSCLC whose tumors express PD-L1 ≥ 1%



Hellman et al. *NEJM* 2019 381:2020

Nivolumab plus Ipilimumab Plus 2 Cycles of Platinum-Based ChemoRx versus ChemoRx in unRx Advanced Stage NSCLC

- Squamous and NonSquamous Cell Lung Cancer
- No Prior Therapy regimen
- ECOG 0 or 1
- No EGFR Mutations or ALK Rearrangements
- No Immune Disorders

R A N D O M I Z E *

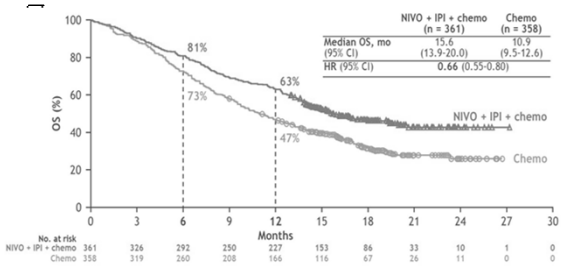
Nivo 3 mg/kg q 2 wks
Ipi 1 mg/kg q 6 wks
+ 2 Cycles Plat-Based Regimens q 3 wks

Platinum-Based Regimen q 3 wks

Reck et al. ASCO 2020.#9501

Nivolumab plus Ipilimumab Plus 2 Cycles of Platinum-Based ChemoRx versus ChemoRx in unRx Advanced Stage NSCLC

May 26, 2020: FDA approves nivolumab plus ipilimumab and 2 cycles of platinum-doublet ChemoRx for Pts with Advanced NSCLC



Reck et al. ASCO 2020.#9501

Pembrolizumab plus Chemo vs. Chemo in Advanced Previously Untreated Squamous NSCLC

- Squamous NSCLC
- PD-L1 <1% versus PD-L1 >1%
- No Prior Therapy
- No EGFR or ALK
- ECOG 0 or 1
- No Rx for Immune Disorders

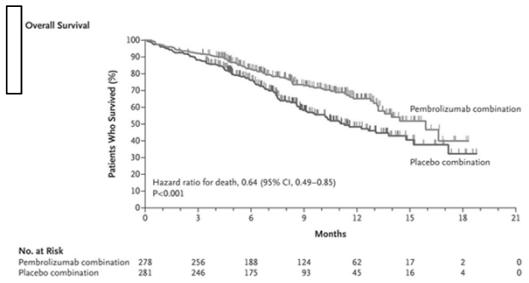
RANDOMIZE*

1 → **Pembrolizumab Plus Paclitax/nab-Paclitax/Carbo**

1 → **Paclitax/Nab-Paclix/Carbo**

Pas-Ares et al. *N Engl J Med* 2018 Nov 22;379(21):2040

Pembrolizumab plus Chemo vs. Chemo in Advanced Previously Untreated Squamous NSCLC



Pas-Ares et al. *N Engl J Med* 2018 Nov 22;379(21):2040

Management of Untreated NSCLC

Immunotherapy (80%)

- Patients with >50% PD-L1 staining in their tumor should be treated with pembrolizumab if not candidate for chemotherapy
- Patients non-squamous NSCLC with PD-L1 staining of less than 50% should be treated with pembrolizumab plus pem/carbo
- Patients squamous NSCLC with PD-L1 staining of less than 50% should be treated with pembrolizumab plus paclitaxel/nab-paclitaxel/carboplatin
- Patients who are not candidates for chemotherapy can be treated with nivolumab and ipilimumab

Management of Untreated & Treated NSCLC

- Screening for Lung Cancer
- Adjuvant Therapy for Early Stage
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease
- Current Standards and Studies for Metastatic NSCLC Targeted Therapy • Immunotherapy

Relapsed Non-Small Cell Lung Cancer

Nivolumab vs. Docetaxel in Previously Rx Advanced Squamous-Cell NSCLC

- Squamous Cell Lung Cancer
- Prior Therapy with Platin-based regimen
- ECOG 0 or 1
- No Immune Disorders

RANDOMIZE*

Nivolumab 3 mg/kg q 2 weeks

Docetaxel 75 mg/m2 q 3 weeks

Brahmer et al. *NEJM* 2015; 373:123

Nivolumab vs. Docetaxel in Advanced Squamous-Cell NSCLC

- NonSquamous NSCLC
- Prior Therapy with Platin-based regimen
- ECOG 0 or 1
- No Immune Disorders

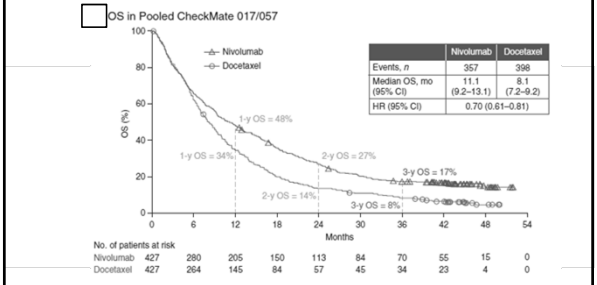
RANDOMIZE*

Nivolumab 3 mg/kg q 2 weeks

Docetaxel 75 mg/m2 q 3 weeks

Borghaei H et al. *NEJM* 2015;373:1627

Nivolumab vs. Docetaxel in Previously Rx NSCLC



	Nivolumab	Docetaxel
Events, *n*	357	398
Median OS, mo (95% CI)	11.1 (9.2–13.1)	8.1 (7.2–9.2)
HR (95% CI)	0.70 (0.61–0.81)	

Brahmer et al. *NEJM* 2015; 373:123
Borghaei H et al. *NEJM* 2015;373:1627
Vokes EE, et al., *Ann Oncol* 2018; Apr 1;29(4):959

Pembrolizumab vs. Docetaxel in Advanced NSCLC

- NSCLC
- <1% PDL Positive
- Prior Therapy with Platin-based regimen
- ECOG 0 or 1
- No Immune Disorders

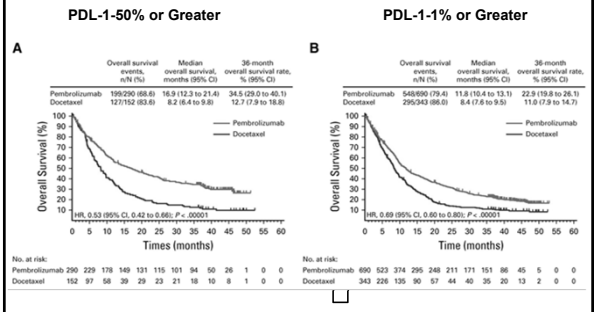
RANDOMIZE*

Pembrolizumab 2 mg/kg or 10 mg/kb q 3 weeks

Docetaxel 75 mg/m2 q 3 weeks

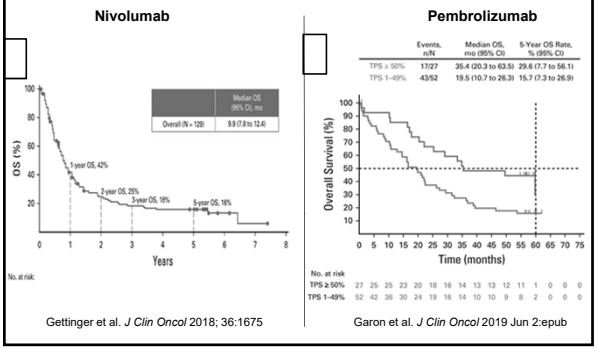
Herbst et al. *Lancet* 2016; 387:1540

Pembrolizumab vs. Docetaxel in Advanced NSCLC



Herbst et al. *J Clin Oncol* 2020 May 10;38(14):1580

Nivolumab and Pembrolizumab NSCLC; 5 Yr FU



	Median OS (95% CI), mo
Overall (N = 129)	9.9 (7.8 to 12.4)

	Events, n/N	Median OS, mo (95% CI)	5-Year OS Rate, % (95% CI)
TPS ≥ 50%	17/27	35.4 (20.3 to 63.5)	29.6 (7.7 to 56.1)
TPS 1–49%	43/52	19.5 (10.7 to 26.3)	15.7 (7.3 to 26.9)

Gettinger et al. *J Clin Oncol* 2018; 36:1675

Garon et al. *J Clin Oncol* 2019 Jun 2:epub

Checkpoint Inhibitors for Previously Rx NSCLC

- October 9, 2015: FDA approves **nivolumab** for treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy (No PD-L1 testing).
- October 2, 2015: FDA grants accelerated approval to **pembrolizumab** for treatment of previously treated patients with metastatic NSCLC whose tumors express PD-L1
- October 18, 2016: FDA approves **atezolizumab** for treatment of previously treated patients with metastatic NSCLC
- **There are Patients with NSCLC with advanced disease who have survived for longer than 5 years without any evidence of cancer**
- Cytotoxic chemotherapy (docetaxel, pemetrexed, and gemcitabine) remain options for patients with contraindications for immunotherapy

Management of Untreated & Treated NSCLC

- Screening for Lung Cancer
- Adjuvant Therapy for Early Stage
- Chemotherapy With Surgery and Radiation in Locally Advanced Disease
- Current Standards and Studies for Metastatic NSCLC (Targeted Therapy-Immunotherapy)
- Relapsed Non-Small Cell Lung Cancer

50

Small Cell Lung Cancer

Bruce E. Johnson, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

50 – Small Cell Lung Cancer

Bruce E. Johnson, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Post Marketing Royalties for EGFR mutation testing: DFCI**
- **Paid Consultant: Novartis, Checkpoint Therapeutics, Chugai, Daichi Sankyo, Foundation Medicine, G1 Therapeutics, GSK, Hengrui Therapeutics, Lilly**
- **Unpaid Member of a Steering Committee: Pfizer**
- **Research Support: Novartis, Cannon Medical Imaging**

- **Resolution - Reviewed and found to be unbiased**

Small Cell Lung Cancer

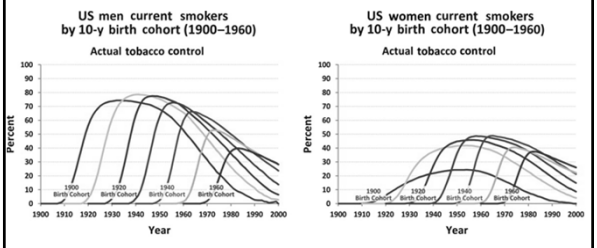
- **Pathology and molecular pathogenesis**
- Presentation
- Staging
- Treatment
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

Small Cell Lung Cancer-2015

The Recalcitrant Cancer Research Act of 2012 (H.R. 733) requires the National Cancer Institute (NCI) to "develop scientific frameworks" that will assist in making "progress against recalcitrant or deadly cancers." Small cell lung cancer (SCLC) is a recalcitrant cancer as defined by its five-year relative survival rate of less than 7 percent and the loss of approximately 30,000 lives per year. While it is true that the outcomes for the other common forms of lung cancer (squamous cell and adenocarcinoma) need to be greatly improved, each of the three major types of cancer that originate in the lung present very different problems, requiring different solutions.

http://deainfo.nci.nih.gov/advisory/ctac/workgroup/SCLC/SCLCCongressionalResponse

Epidemiology



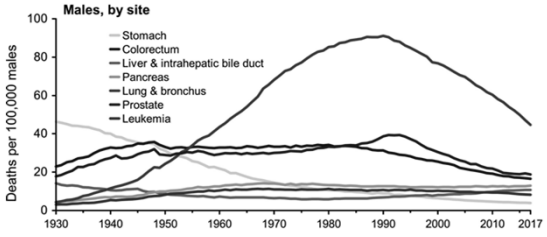
Moolgavkar et al. *JNCI* 2012

Epidemiology

- The Median Prevalence of Cigarette Smoking across the United States in 2018 is 14% (16% for men and 12% for women)
- The Prevalence Ranged from 9% in Utah to 26% in West Virginia in 2017
- The smoking by region of the US goes from 11% in the West to 16% in the Midwest
- The smoking by socioeconomic status showed the prevalence is 21% for those who earn less than $35,000 and 7% for earn more than $100,000

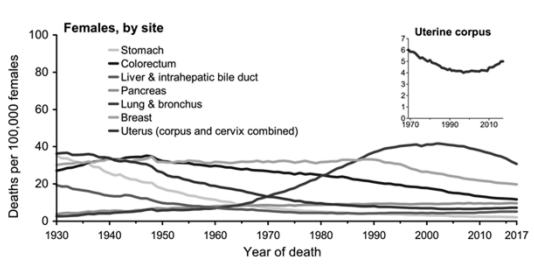
https://www.cdc.gov/tobacco/data_statistics/fact_sheets/adult_data/cig_smoking/index.htm

Cancer Death Rates
Males, US, 1930-2017



Siegel et al. *CA Cancer J Clin*. 2020 70:7-30

Cancer Death Rates
Females, US, 1930-2017



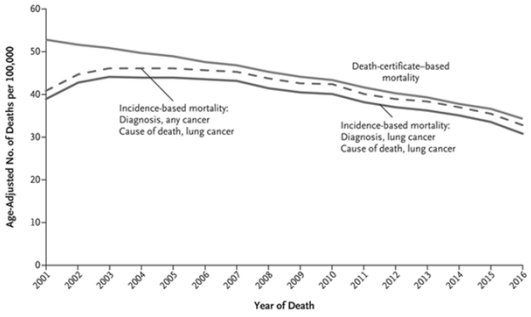
Siegel et al. *CA Cancer J Clin*. 2020 70:7-30

Epidemiology

- 228,820 people (116,300 men and 112,520 women) will be diagnosed at a median age of 70
- 135,720 men and women will die of cancer of the lung and bronchus in 2020
- The overall 5-year relative survival for 2008-2014 from 9 SEER geographic areas is 20%
- The percentage with localized disease at time of presentation is 16%, regional is 22%, and distant is 57% (5% is unstaged)

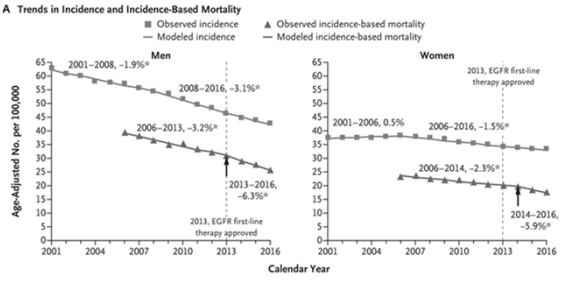
Siegel et al. *CA Cancer J Clin*. 2020 70:7-30
http://seer.cancer.gov/statfacts/html/lungb.html#survival

Mortality Estimates from Death Certificates and Two Measures of Incidence among Lung Cancer.



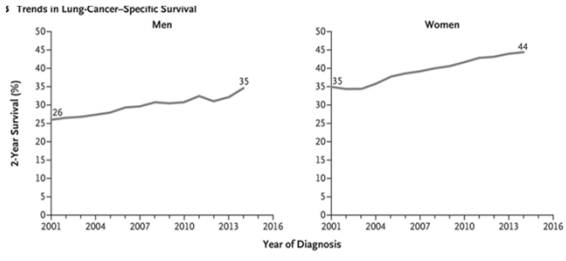
Howlader et al. *N Engl J Med* 383:640-649

Non-Small Cell Lung Cancer Incidence and Mortality



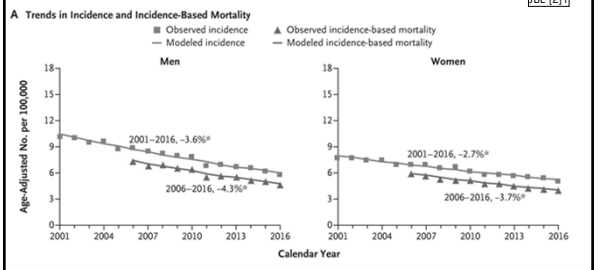
Howlader et al. *N Engl J Med* 383:640-649

Non-Small Cell Lung Cancer-Specific Survival



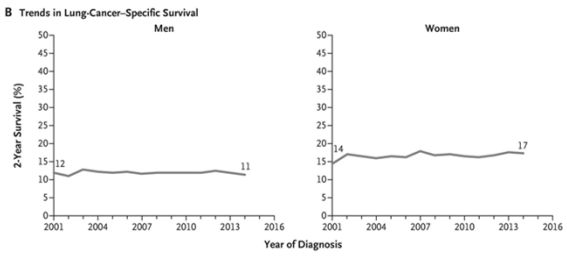
Howlader et al. *N Engl J Med* 383:640-649

Small Cell Lung Cancer Incidence and Mortality



Howlader et al. *N Engl J Med* 383:640-649

Small Cell Lung Cancer-Specific Survival



Howlader et al. *N Engl J Med* 383:640-649

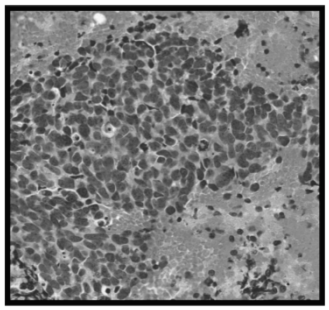
Pathology and Molecular Pathogenesis

- Non-Small Cell Lung Cancer 87%
- Small Cell Carcinoma 13%
  - Small Cell Carcinoma >90%
  - Variant (Combined Small Cell Carcinoma) < 10%

Pathology and Molecular Pathogenesis: Smoking

- Small cell lung cancer is the most closely linked with cigarette smoking.
  - >97% of patients have a history of cigarette smoking.
- Squamous cell carcinoma and large cell carcinoma are intermediately linked with cigarette smoking.
  - Approximately 80% of patients have a history of cigarette smoking.
- Adenocarcinoma is least closely linked to cigarette smoking.
  - 70% of patients have a history of cigarette smoking.
- Pulmonary carcinoid tumors are not associated with cigarette smoking.

Small Cell Lung Cancer



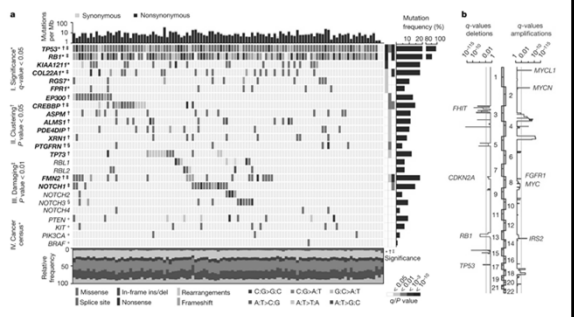
Pathology and Molecular Pathogenesis

Markers of neuroendocrine differentiation

- Chromogrannin A
- Synaptophysin
- CD56 or Neural Cell Adhesion Molecule (NCAM)

Yatabe et al. *J Thorac Oncol.* 2019 Mar;14(3):377

Small Cell Lung Cancer: Genomic Characterization



J George et al. *Nature* 524, 47–53, 2015

Update on Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- **Presentation**
- Staging
- Treatment
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

Presentation

Paraneoplastic Syndromes

Syndrome	Protein	Pts with SCLC
Hyponatremia of Malignancy	Arginine Vasopressin and Atrial Natriuretic Peptide	15%
Hypercalcemia of Malignancy	Parathyroid Hormone Related Peptide	<1%
Ectopic ACTH Syndrome	Adrenocorticotrophic Hormone	3%
Acromegaly	Growth Hormone Releasing Hormone	<1%

Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- **Staging**
- Treatment
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

Staging

Small Cell Lung Cancer

The staging classification for these patients is a simple two-stage Veterans Administration Lung Study Group System, updated in 1989 by International Association for the Study of Lung Cancer.

- –Limited stage: Disease confined to 1 hemithorax with regional lymph nodes including either ipsilateral or bilateral hilar, mediastinal, and supraclavicular lymph node metastases and without ipsilateral pleural effusion that fit within a tolerable chest radiation field
- –IASLC now recommends staging them using TNM; stage I-III and IV is roughly equivalent to limited or extensive stage disease.1
- –Extensive stage: Disease beyond these boundaries

Valliers et al. *Journal of Thoracic Oncology.* 2009;4:1049-1059

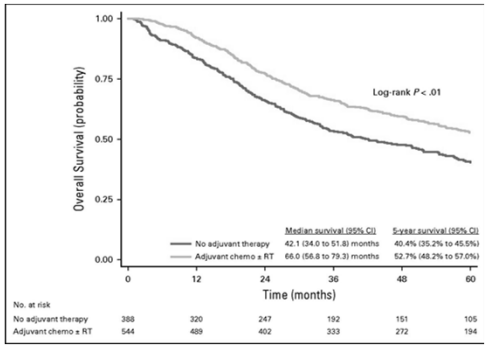
Staging

Resectable Disease

- 1,574 patients had pT1-2N0M0 SCLC from 2003-2011
- 954 patients (61%) underwent complete R0 resection
- 566 (59%) were treated with adjuvant therapy
- 354 were treated with chemotherapy alone
- 190 were treated with chemotherapy plus irradiation
- 99 patients who underwent cranial irradiation) and 22 radiation alone

Yang, et al. *J Clin Oncol.* 2016; Apr 1;34(10):1057

Staging
Resectable Disease



Yang, et al. *J Clin Oncol*. 2016:Apr 1;34(10):1057

Staging
Limited Stage Small Cell Lung Cancer

- Patients with a solitary pulmonary nodule and a diagnosis of SCLC should undergo evaluation for resection (2-3%)
- Patients should have mediastinoscopy because 20% will have positive lymph nodes
- Patients should be treated with adjuvant chemotherapy following resection

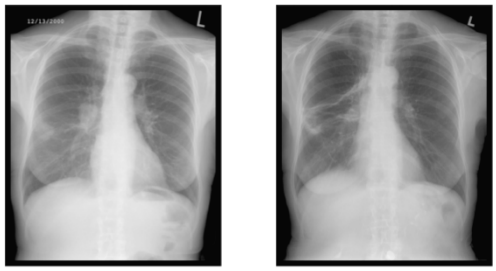
Strand TE, et al. *Thorax*. 2006;61(8):710-715

Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- Staging
- **Treatment**
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

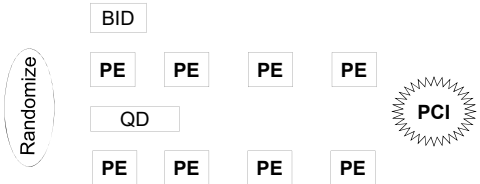
Treatment
Limited Stage Small Cell Lung Cancer

Pre-treatment **2 Years after Treatment**



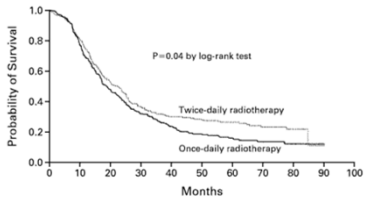
Treatment
Limited Stage Small Cell Lung Cancer

Platinum - 60; Etoposide - 120 / Cycle Q 21 days PCI: 25 Gy



Turrisi AT 3rd, et al. *NEJM* 1999;340(4):265-271.

Treatment
Limited Stage Small Cell Lung Cancer

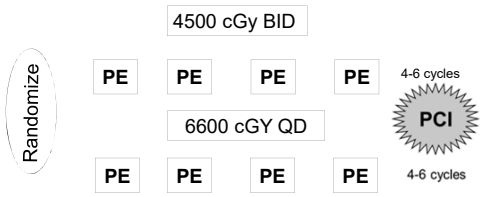


Treatment Group	0–20 Mo	20–40 Mo	40–60 Mo	60–80 Mo	80–100 Mo
	no. of deaths/no. at risk				
Once daily	108/206	48/96	15/47	4/21	0/5
Twice daily	100/211	47/109	7/62	5/42	1/14

Turrisi AT 3rd, et al. *NEJM*. 1999;340(4):265-271

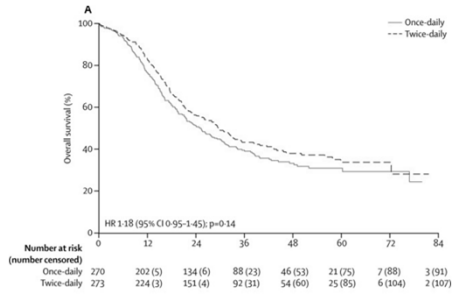
Treatment
Limited Stage Small Cell Lung Cancer

Cisplatin – 75 (or 25X3); Etoposide - 100 / Cycle Q 21 days PCI: 25 Gy



Faivre-Finn. *Lancet Oncol.* 2017; Aug;18(8):1116-1125

Treatment
Limited Stage Small Cell Lung Cancer



Faivre-Finn. *Lancet Oncol.* 2017; Aug;18(8):1116-1125

Treatment
Limited Stage Small Cell Lung Cancer

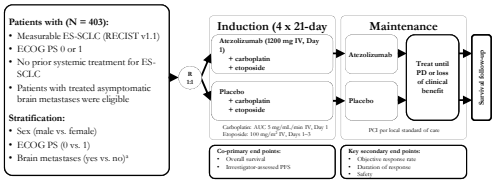
- Patients with limited stage SCLC should be treated with concurrent chest radiotherapy with etoposide plus cisplatin. These patients lived longer than patients treated with chemotherapy alone.
- Chest radiotherapy should start with cycle 1 or 2.
- Chest radiotherapy should be given twice daily over 3 weeks, a higher dose (6600 cGY) given once daily for 33 doses gives similar results.
- An ongoing trial in the US comparing etoposide cisplatin plus 45 Gy given twice daily over 3 weeks versus 70 Gy once daily in 2 Gy fractions (NCT00632853-Opened in 2008; in follow-up).

Treatment
SCLC Metastatic Sites

- Bone-35%
- Liver-25%
- Bone marrow-20%
- Brain-20%
- Extrathoracic lymph nodes-5%
- Subcutaneous masses-5%

Treatment: Extensive Stage SCLC
Etoposide + Carboplatin with/without Atezolizumab

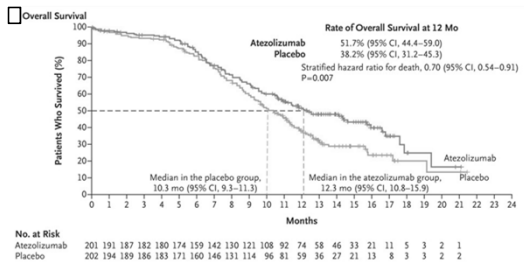
IMpower133: Global Phase randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC



Horn et al, *N Engl J Med.* 2018 Dec 6;379(23):2220

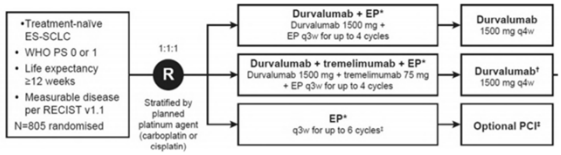
Treatment: Extensive Stage SCLC
Etoposide + Carboplatin with/without Atezolizumab

March 2019: FDA approves atezolizumab with carboplatin and etoposide for the first-line Rx of patients with extensive-stage SCLC



Horn et al, *N Engl J Med.* 2018 Dec 6;379 :2220

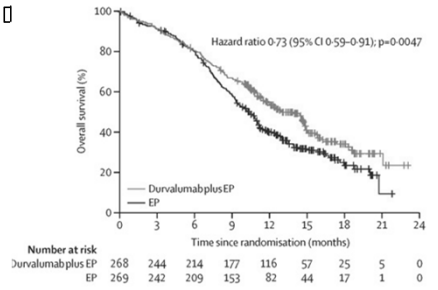
Treatment: Extensive Stage Rx SCLC
Etoposide + Carboplatin with/without Durvalumab



Paz-Ares et al. *Lancet* 2019; 394(10212):1929

Treatment: Extensive Stage SCLC
Etoposide + Carboplatin with/without Durvalumab

March 2020: FDA approves durvalumab in combination with etoposide and platinum as first-line treatment of patients with extensive-stage SCLC



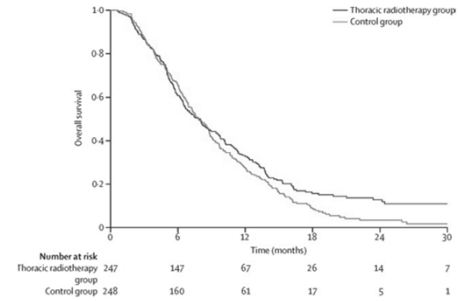
Paz-Ares et al. *Lancet* 2019; 394(10212):1929

Treatment: Extensive Stage SCLC
Thoracic Radiation

- 498 patients with extensive stage SCLC with response to 4 to 6 cycles of chemotherapy
- Thoracic treatment volume considered treatable using acceptable radiation fields; prophylactic cranial RT was used as well
- Patients were followed for time to progression and survival

Slotman BJ et al. *Lancet* 2015;385:36

Treatment: Extensive Stage SCLC
Thoracic Radiation



Slotman BJ et al. *Lancet* 2015;385:36

Treatment
Extensive Stage Small Cell Lung Cancer

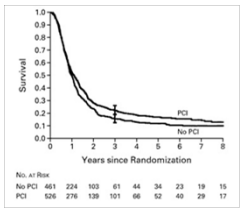
- Fit patients with extensive stage SCLC should be treated with etoposide carboplatin with atezolizumab or durvalumab
- Patients with residual chest masses after chemotherapy should be referred to radiation oncologists for consideration of chest RT

Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- Staging
- Treatment
- **Prophylactic cranial irradiation**
- Relapsed small cell lung cancer

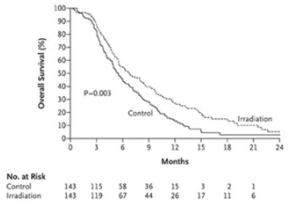
Prophylactic Cranial Irradiation
Limited and Extensive Stage SCLC

Survival for Limited & Extensive Stage
N = 987



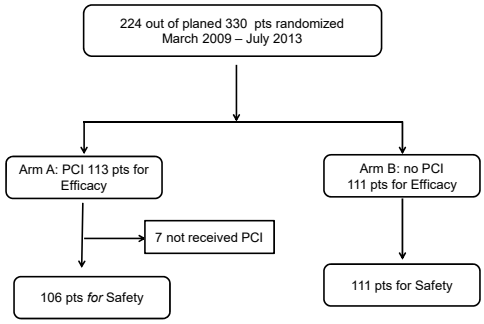
Auperin et al. *NEJM*. 1999;341-476

Survival for Extensive Stage
N = 286



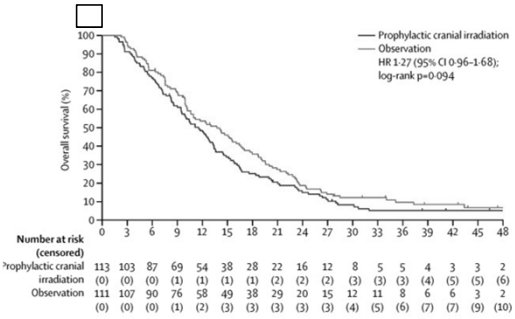
Slotman B, et al. *NEJM*. 2007;357:664

Prophylactic Cranial Irradiation
Small Cell Lung Cancer



Takahashi T et al. *Lancet Oncol* 18:663, 2017

Prophylactic Cranial Irradiation
Survival by PCI Arm



Takahashi T et al. *Lancet Oncol* 18:663, 2017

Prophylactic Cranial Irradiation
In Summary

- Patients with SCLC have a 60-80% actuarial risk of developing brain metastases within 2 years after the start of treatment
- PCI has been shown to prolong survival for patients with both limited stage SCLC with a response to chemotherapy
- PCI (2500 cGy) administered at the time of complete remission can reduce the chance of developing brain metastases by 50-67%
- The data recently published does not support administering PCI to patients with extensive stage disease

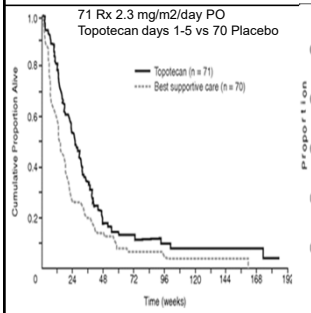
Arrigada R, et al. *J Natl Cancer Inst*. 1995;87(3):183-190. Auperin A, et al. *NEJM*. 1999;341(7):476-484. Slotman B, et al. *NEJM*. 2007;357(7):664-672. Le Pechoux C, et al. *Lancet Oncol* 2009;10:467 Takahasi T et al. *Lancet Oncol* 2017;18:663

Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- Staging
- Treatment
- Prophylactic cranial irradiation
- **Relapsed small cell lung cancer**

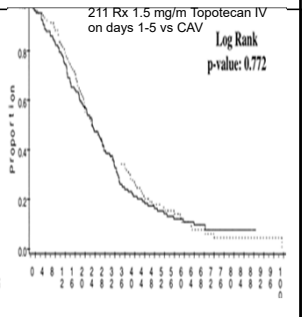
Relapsed SCLC
Topotecan

71 Rx 2.3 mg/m2/day PO
Topotecan days 1-5 vs 70 Placebo



O'Brien ME, et al. *J Clin Oncol*. 2006;24:5441

211 Rx 1.5 mg/m Topotecan IV
on days 1-5 vs CAV



von Pawel et al. *J Clin Oncol*. 1999;17:658

Relapsed SCLC

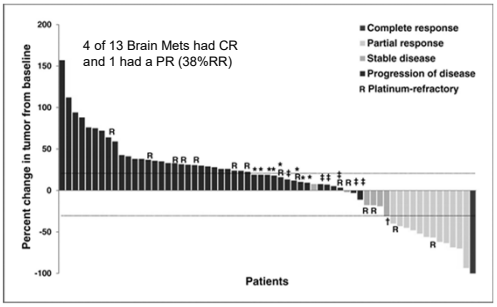
Temozolomide

- Previously treated patients with sensitive relapse SCLC (48) or refractory SCLC (16)
- 24 had brain metastases including 13 with target lesions assessable by RECIST
- Treated with 21/28 days of 75 mg/m2 of temozolomide
- Followed for toxicity, response, time to progression, and survival

Pietanza et al. *Clin Cancer Res* 2012; 18:1138

Relapsed SCLC

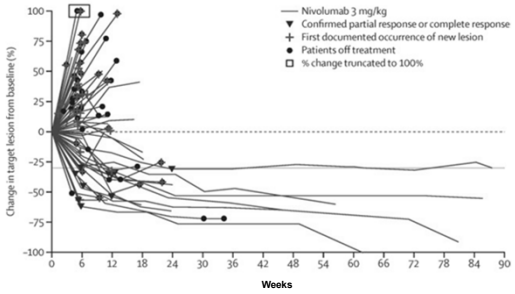
Temozolomide



Pietanza et al. *Clin Cancer Res* 2012; 18:1138

Relapsed SCLC

98 Patients Treated with Nivolumab 3mg/kg

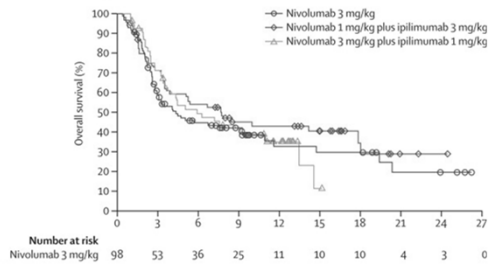


Antonia et al. *Lancet Oncol* 2016; 17:883

Relapsed SCLC

98 Patients Treated with Nivolumab 3mg/kg

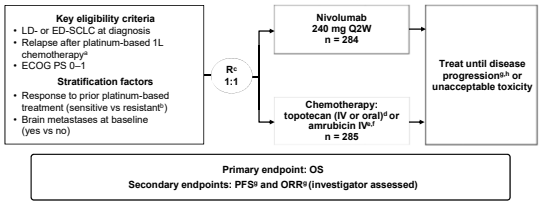
2018: FDA grants accelerated approval to nivolumab for Pts with metastatic SCLC with progression after platinum-based chemotherapy and at least one other line of therapy



Antonia et al. *Lancet Oncol* 2016; 17:883

Relapsed SCLC

CheckMate 331 Study Design

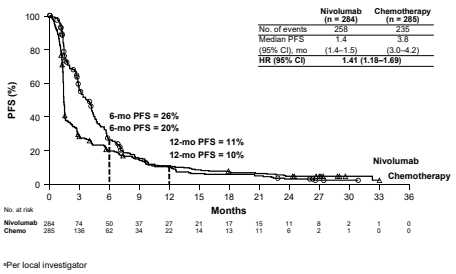


- Database lock: 28 September 2018; minimum follow-up for OS: 15.8 months
- Median follow-up: 7.0 months (nivolumab), 7.6 months (chemotherapy)

[a]Patients must have had ≥4 cycles of platinum-based, 1L chemotherapy or if <4 cycles, must have had a BOR of at least partial or complete response. [b]Platinum resistance defined as progression-free interval <90 days after completion of platinum therapy. [c]Crossover between treatment groups was not allowed. [d]Administered at 1.5 mg/m² IV or 2.3 mg/m² oral capsule once daily on days 1–5 of a 21-day cycle. [e]40 mg/m² IV once daily on days 1–3 of a 21-day cycle. [f]Where locally approved. [g]Defined by RECIST 1.1. [h]Patients assigned to nivolumab may be treated beyond progression under protocol-defined circumstances. Time between randomization date and last known date alive (for patients who are alive) or death

Relapsed SCLC

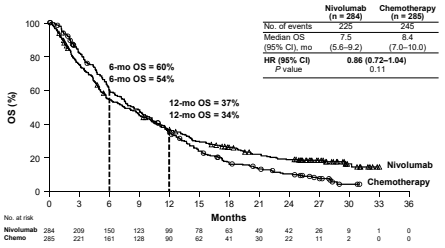
PFS with Nivolumab vs. Chemo



[a]Per local investigator

Relapsed SCLC

Primary Endpoint: OS with Nivolumab vs. Chemo



Minimum follow-up: 15.8 months; 59 patients (21%) in the nivolumab arm and 40 patients (14%) in the chemotherapy arm were censored

Relapsed SCLC

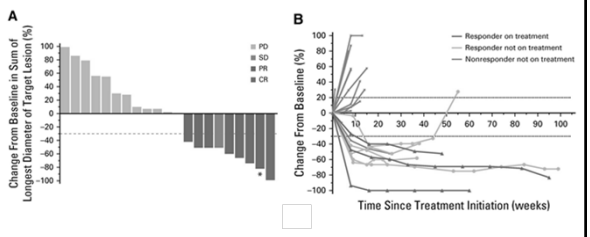
Pembrolizumab for Previously Rx SCLC

- 24 Patients with Previously SCLC (21 had a least two prior therapies)
- ECPG Performance Status of 0,1
- PD-L1 IHC staining of at least 1% of Tumor Cells (32% of those screened)
- Treated with Pembrolizumab 10 mg/kg every 2 weeks for 24 Months

Ott et al. *J Clin Oncol* 2017; Dec 1;35(34):3823

Relapsed SCLC

24 Pts Treated with Pembrolizumab 10 mg/kg



Ott et al. *J Clin Oncol* 2017; Dec 1;35(34):3823

Relapsed SCLC

83 Pts Treated with Pembro after ≥ 2 Chemo Regimens

2019: FDA grants accelerated approval to Pembrolizumab for Pts with metastatic SCLC with progression after platinum-based chemotherapy & at least one other line of therapy

Trial	Pts #	RR	Duration Response	PFS in Months	Survival Months
KEYNOTE 028 (PD-L1+)	21	8/21(38%)	19.4 Mo	1.9	9.7
KEYNOTE 158	62	8/62 (13%)	>9 Mo	2.0	9.1
Total	83	16/83 (19%)	>18 Mo		

Ott et al. *J Clin Oncol* 2017; Dec 1;35(34):3823
Chung et al *J Clin Oncol* 36, 2018 Supp; May 20:8506
https://www.fda.gov/drugs/resources-information-approved-drugs/fda

Relapsed SCLC

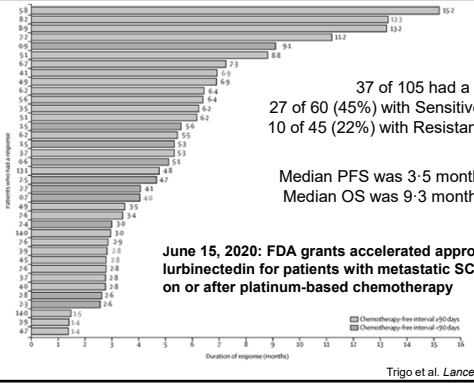
Lurbinectedin for Previously Rx SCLC

- 105 Patients with Previously SCLC
- One Previous Regimen
- ECOG Performance Status of 0-2
- Treated with 3·2 mg/m2 of lurbinectedin administered as a 1-h intravenous infusion once every 3 weeks

Trigo et al. *Lancet Oncol* 2020; 21:645

Relapsed SCLC

Duration of Response Lurbinectedin for Previously Rx SCLC



37 of 105 had a PR (25%)
27 of 60 (45%) with Sensitive Disease
10 of 45 (22%) with Resistant Disease

Median PFS was 3·5 months
Median OS was 9·3 months

June 15, 2020: FDA grants accelerated approval to lurbinectedin for patients with metastatic SCLC progression on or after platinum-based chemotherapy

Trigo et al. *Lancet Oncol* 2020; 21:645

Bruce E. Johnson, MD

Update on Small Cell Lung Cancer

- Pathology and molecular pathogenesis
- Presentation
- Staging
- Treatment
- Prophylactic cranial irradiation
- Relapsed small cell lung cancer

51

Adjuvant Therapy for Breast Cancer

Nancy E. Davidson, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

51 – Adjuvant Therapy of Breast Cancer

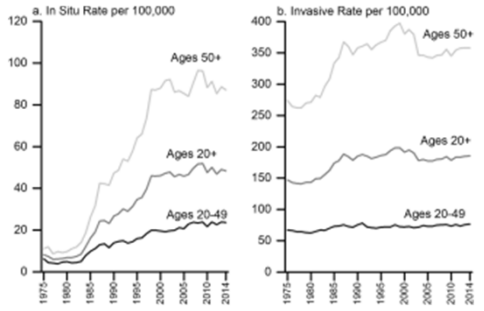
Nancy E. Davidson, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

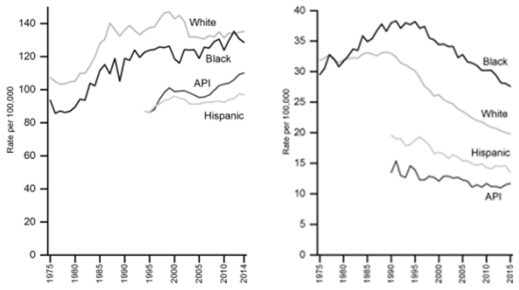
- **None**

In Situ and Invasive Breast Cancer Incidence in US—Impact of Screening



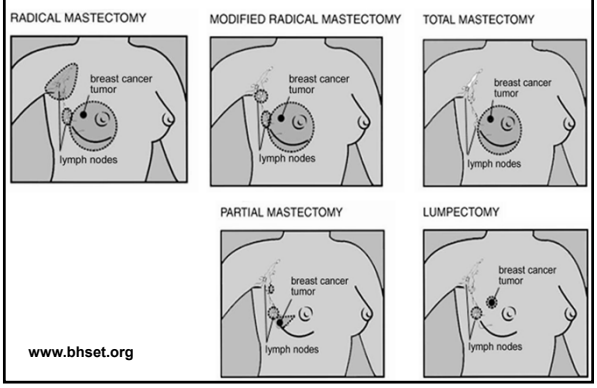
DeSantis et al, CA Cancer J Clin 2017

Breast Cancer Trends in US



DeSantis et al, CA Cancer J Clin 2017

Evolution of Breast Cancer Surgery



www.bhset.org

Breast Cancer Therapy Local

- **6 randomized trials of mastectomy vs. lumpectomy and radiation (BCT)**
- **Over 20 year follow-up**
- **No survival difference**
- **NIH Consensus – BCT preferred**

Breast Cancer Therapy Local

- Lumpectomy +/- radiation
- Modified radical mastectomy +/- reconstruction
- Axillary staging via sentinel node localization or dissection
- Randomized trials
  - Confirm utility of sentinel lymph node localization
  - May avoid dissection in some sentinel node-positive patients

Breast Cancer Therapy Contraindications to BCT

- Patient preference
- Poor cosmetic outcome
- Multifocal disease
- Previous radiation
- Ongoing pregnancy
- Connective tissue disorder?

Ductal Carcinoma in Situ

20% of breast cancers thanks to mammography

Local therapy—to reduce recurrence in ipsilateral breast

- Lumpectomy +/- radiotherapy
- Mastectomy
- No role for routine sentinel node sampling

Systemic therapy—to reduce ipsilateral and contralateral breast cancer

- Tamoxifen for premenopausal women
- Aromatase inhibitor > tamoxifen for postmenopausal
- No role for chemotherapy

Evolution of Breast Cancer Staging

- Building on traditional TNM to include biomarkers
- Clinical prognostic versus pathological prognostic staging

Clinical prognostic--pretreatment	Pathological prognostic—postop
• History • Physical exam • Imaging • Biopsies • Biomarkers—grade, ER, PR, HER2	• Pathology-defined TNM • Biomarkers including multigene panels **Preferred in US**

AJCC Cancer Staging Manual 8th Edition 2018

Some Adjuvant Therapy Questions

- Prognostic and predictive markers
- Endocrine therapy—tamoxifen, AI, OFS/OA
- Chemotherapy
  - Selection of agents
  - Dose intensity/density
  - Preoperative therapy
- Sequencing of therapy
- Anti-HER-2 therapy
- Use of bisphosphonates
- Integration of other biologics
- Follow-up of early breast cancer survivors

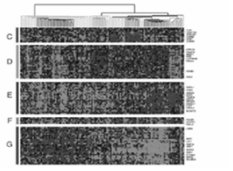
Biology and Breast Cancer

Prognostic Factors	Predictive Factors
Nodal status	Steroid receptors
Tumor size	HER-2
Steroid receptors	Multigene assays
HER-2	
Histologic grade	
Histologic subtype	
Proliferative rate	
Age	

Not Just One Disease…

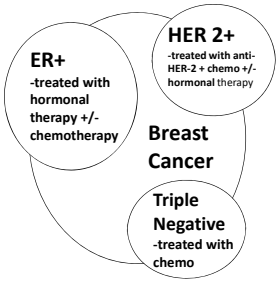
Molecular Differences

Luminal Subtype A | Luminal Subtype B | ERBB2+ | Basal Subtype | Normal Breast–like



Sorlie et al, PNAS, 2001

Treatment Differences



Importance of Accurate Testing ASCO-CAP Guidelines

ER and PR testing

- Up to 20% inaccuracy in past
- Determine on all invasive and recurrent cancers
- Positive if ≥ 1% positive tumor nuclei
- Low-positive if 1-10%

HER-2 testing

- Up to 20% inaccuracy in past
- Determine on all invasive cancers
- Positive if 3+ IHC or positive FISH

Wolff et al, J Clin Oncol, 2007, 2013, 2018

Hammond et al, J Clin Oncol, 2010 ; Allison et al, J Clin Oncol, 2020

From ER, PR, HER-2 to a Proliferation of Predictive and Prognostic Multigene Tests

prosigna™ Breast cancer gene signature assay

oncotype DX® Breast Cancer Assay

mammaprint®

EndoPredict®

Breast Cancer INDEX® Prediction. Personalized.

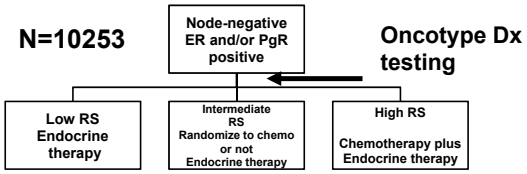
blueprint™

MAMMOSTRAT

- Estimate prognosis
- Predict response to chemotherapy
- Gauge role of extended adjuvant endocrine therapy

See ASCO guidelines in Harris et al, J Clin Oncol, 2016

Tailorx Trial of Oncotype DX



Sparano et al, N Engl J Med, 2015
Sparano et al, N Engl J Med, 2018
Sparano et al, N Engl J Med, 2019
Sparano et al, JAMA Oncology, 2019

Role of Patient and Disease Factors in Adjuvant Systemic Therapy Decision Making for Early-Stage, Operable Breast Cancer

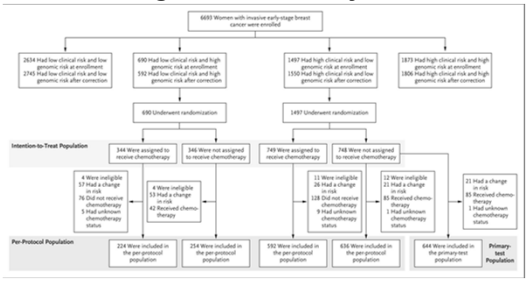
For patients with hormone receptor–positive, HER2 not overexpressed, axillary node–negative breast cancer, the recommendations below are based on Oncotype DX recurrence score and age

Age	Recurrence Score	Recommendation
> 50 years old	< 26	Endocrine therapy
	26 - 30	Consider chemoendocrine therapy
	> 30	Chemoendocrine therapy
≤ 50 years old	< 16	Endocrine therapy
	16 - 30	Consider chemoendocrine therapy
	> 30	Chemoendocrine therapy

Henry et al *J Clin Oncol* 2019
asco.org/breast-cancer-guidelines

ASCO Guidelines

MINDACT
A 70 Gene Signature for Early Breast Cancer



Primary Endpoint: To test whether among patients with high risk clinical features and low risk gene expression profile, who did not recieve chemo, the lower boundary of the 95%CI for 5-yr DMFS would be 92% or higher

Cardoso F et al. N Engl J Med 2016 and ASCO 2020

ASCO Guidelines for Mammaprint

- Can use to inform decision on adjuvant chemotherapy in HR-positive, HER-2-negative N0 or N1-3 positive nodes who are at high clinical risk of recurrence
- If high clinical/low genomic risk, then 5 yr DMFS=94.7% in absence of chemo (Cardoso et al, N Engl J Med, 2016)
- Should not use in women with low clinical risk for recurrence per MINDACT results

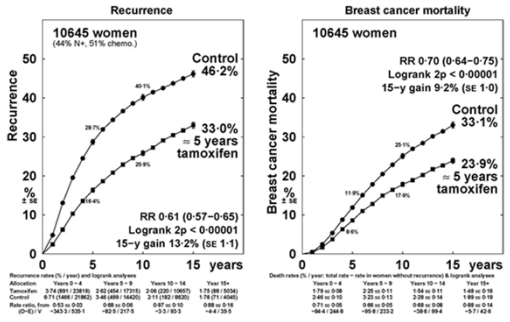
Krop et al, J Clin Oncol, 2017

Some Adjuvant Therapy Questions

Prognostic and predictive markers
Endocrine therapy—tamoxifen, AI, OFS/OA
Chemotherapy
- Selection of agents
- Dose intensity/density
- Preoperative therapy

Sequencing of therapy
Anti-HER-2 therapy
Use of bisphosphonates
Integration of other biologics
Follow-up of early breast cancer survivors

Effect of 5 Years of Tamoxifen on 15 Year Outcome in ER-positive Breast Cancer

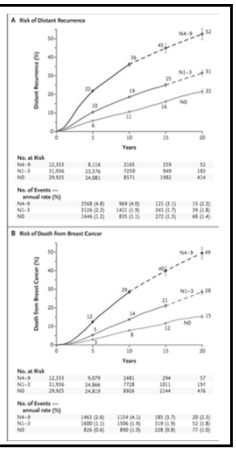


EBCTCG, Lancet, 2011

20-Year Risk of Breast Cancer Recurrence and Death after Endocrine Therapy at 5 Years

- Meta-analysis of 88 trials of 62,923 women who were disease-free after 5 years of endocrine therapy
- Rate of distant recurrence and death strongly correlated with original tumor size (T) and nodal status (N)
- Tumor grade, Ki67, and PR were less predictive of outcome
- Rates of contralateral breast cancer was 0.3%/year and not related to age or TN status

Pan H et al. N Engl J Med, 2017



Outcomes in Randomized ATLAS and aTTom Trials of 10 vs 5 years of Tamoxifen

	Breast Cancer Mortality	Overall Survival
Years 5-9	0.97 (0.84-1.15)	0.99 (0.89-1.10)
Years 10+	0.75 (0.65-0.86)*	0.84 (0.77-0.93)*
All years	0.85 (0.77-0.94)*	0.91 (0.84-0.97)*

* P < 0.05 favoring 10 years

Gray et al, ASCO, 2013

Adjuvant Tamoxifen

- No dose response – 20 mg daily
- Duration of at least 5 years
- Effective only for steroid receptor – positive cancers
- Effective in women of any age or menopausal status
- Avoid coadministration of SSRI if possible
- No clear role for CYP2D6 testing

Adjuvant Endocrine Therapy

Premenopausal women
- Ovarian ablation/suppression

Postmenopausal women
- Aromatase inhibitor vs tamoxifen

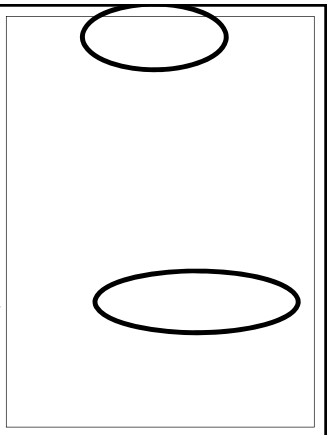
Ovarian Ablation/Suppression

Direct
- Surgery
- Radiation
- LH-RH agonist

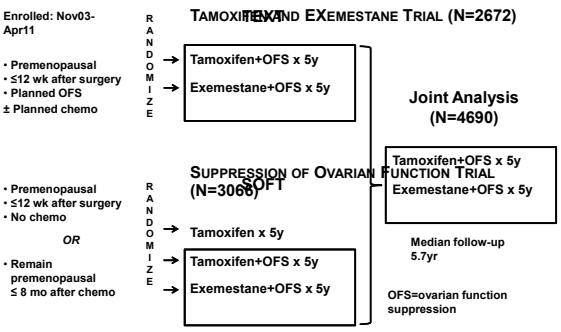
Indirect
- Chemotherapy-induced

2006 EBCTCG

- OA/OS vs not
- No chemo
- Not selected for ER



TEXT and SOFT Designs



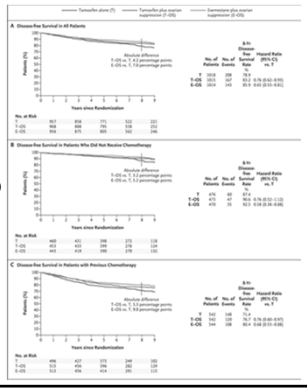
Pagani et al, N Engl J Med, 2014

8 Year DFS in SOFT by Chemo or Not

All

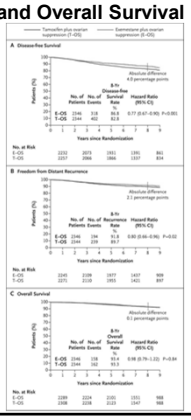
No Chemo

Chemo



Francis et al, N Engl J Med, 2018

Disease-free Survival, Freedom from Distant Recurrence, and Overall Survival in the Combined SOFT and TEXT Population



- Improved DFS and FDR with exemestane over tamoxifen
- No survival difference between exemestane and tamoxifen

Francis et al, N Engl J Med, 2018

ASCO Guidelines for Ovarian Function Suppression

ADVISE OFS	DO NOT ADVISE OFS
Stage II or III who would receive chemo	Stage I not warranting chemo
Stage I or II who would consider chemo	T ≤ 1 cm N0

Recommend OFS X 5 yr
Prefer monthly LHRH agonist
If OFS recommended, combine with tamoxifen or AI

Burstein et al, J Clin Oncol, 2016

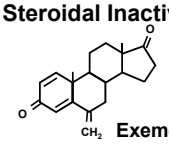
Adjuvant Endocrine Therapy

Premenopausal women
Ovarian ablation/suppression

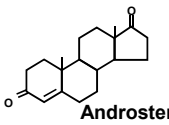
Postmenopausal women
Aromatase inhibitor vs tamoxifen

The Aromatase Inhibitors Highly Specific Inhibitors of CYP19

Steroidal Inactivator

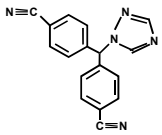


Exemestane

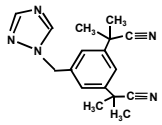


Androstenedione

Nonsteroidal Inhibitors



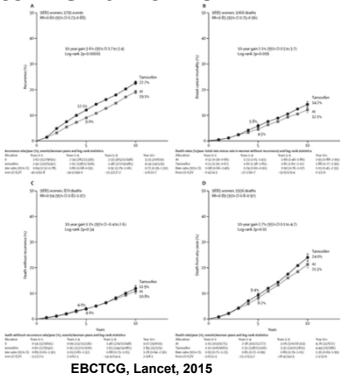
Letrozole



Anastrozole

EBCTCG Meta-analysis of Aromatase Inhibitor vs Tamoxifen

- Meta-analysis of 31,920 postmenopausal women with ER+ breast cancer in 9 trials
- Reduced recurrence, breast-cancer mortality and all cause mortality with AI
- No clear differences between AIs
- No predictors of resistance
- More uterine cancer with tamoxifen and more fractures with AI



EBCTCG, Lancet, 2015

ASCO Clinical Practice Update on Adjuvant Endocrine Therapy in Postmenopausal Women

- Consider AI as primary therapy or after 2 or 3 years of tamoxifen
- Do not extend AI beyond 5 years
- Recommend switch from tamoxifen to AI at 2-3 years but can also do after 5 years

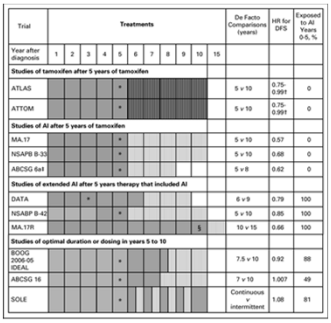
Burstein et al, J Clin Oncol, 2010

ASCO Clinical Practice Update on Adjuvant Endocrine Therapy in Postmenopausal Women

- No identified predictive marker for choice of endocrine therapy
- Variable toxicities may influence choice of therapy
- No known meaningful clinical difference between available AI
- Tamoxifen is drug of choice for premenopausal women and men

Burstein et al, J Clin Oncol, 2010

ASCO Guidelines--Optimal Duration of Aromatase Inhibitor



Burstein et al J Clin Oncol, 2019

- Do not routinely offer extended AI to women with N0 breast cancer
- Do offer extended AI to women with N+ breast cancer
- Do not offer more than 10 years of total adjuvant endocrine therapy
- As prevention of contralateral breast cancer is a major benefit of extended AI, consider risk of second breast cancer
- Shared decision-making with patient is critical

Potential Side Effects of Adjuvant Endocrine Therapy

	Tamoxifen	Ovarian Suppression	Aromatase inhibitors
Postmeno-pausal symptoms	X	X	X
Endometrial cancer	X		
DVT/PE	X		
Cardiac events			X?
Arthralgias			X
Osteoporosis/ fractures		X	X
Cognitive	?	?	?

Some Adjuvant Therapy Questions

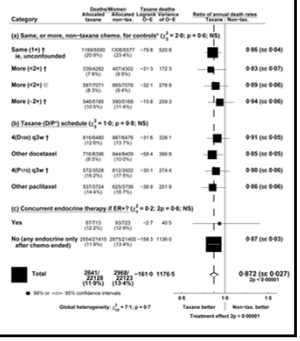
- Prognostic and predictive markers
- Endocrine therapy—tamoxifen, AI, OFS/OA
- Chemotherapy
  - Selection of agents
  - Dose intensity/density
  - Preoperative therapy
- Sequencing of therapy
- Anti-HER-2 therapy
- Use of bisphosphonates
- Integration of other biologics
- Follow-up of early breast cancer survivors

EBCTCG Metaanalysis of Adjuvant Polychemotherapy

Metanalysis of 100,000 women in 123 randomized trials

- Taxane vs not
- Anthracyclines vs CMF
- Polychemo vs nil

Taxane vs Not--Deaths



EBCTCG, Lancet, 2011

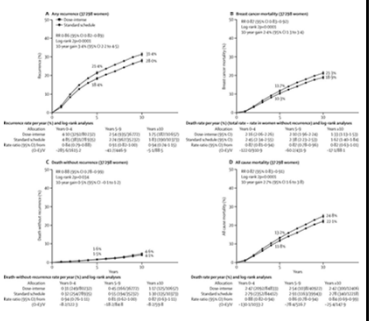
EBCTCG Findings About Chemotherapy

- Multidrug better than single agent
- Duration of 3-6 months sufficient
- Anthracycline-containing regimens modestly better than CMF-like
- Uncertainty about magnitude of effect in ER-positive vs ER-negative

EBCTCG, Lancet, 2005

EBCTCG Metanalysis of Dose Intensity of Adjvuant Chemotherapy

- 37,298 women in 26 randomized trials of dose-intense vs standard schedule chemotherapy
- Generally <70 yr and node-positive
- Strategies include shorter intervals or sequential administration
- Significant improvement in all outcomes
- Similar proportional reduction in ER-positive and ER-negative tumors



EBCTCG, Lancet, 2019

CCO/ASCO Guidelines for Adjuvant Chemotherapy for Early Breast Cancer

Indications for adjuvant chemo include:

- **1+ lymph nodes with met > 2mm**
- **ER-negative with T > 5 mm**
- **HER2+ tumors**
- **High-risk lymph node negative T> 5 mm**
- **Adjuvant!Online 10y risk of breast cancer death of >10-15%**

Henry et al, J Clin Oncol, 2016

CCO/ASCO Guideline on Optimal Adjuvant Chemotherapy

- **Anthracycline-taxane regimen preferred, especially for high risk**
- **Do not exceed 240 mg/m2 doxorubicin**
- **Several acceptable regimens**
- **TC or CMF are alternatives if anthracycline not preferred**
- **Consider capecitabine X 6-8 cycles for postneoadjuvant residual disease (esp HR-negative)**
- **No role for gemcitabine**
- **Further data needed on role of platinum salts in TNBC**

Denduluri et al, J Clin Oncol, 2016 and 2018

Summary of Trials of Adjuvant vs Neoadjuvant Therapy

•Survival is similar with preoperative or adjuvant chemotherapy (EBCTCG, Lancet Oncology, 2018)

•Preoperative therapy increases breast conservation in a fraction of patients (higher in breast recurrence?)

•Value of in vivo assessment of tumor response is a promising research direction—focus on use of pathological CR by FDA

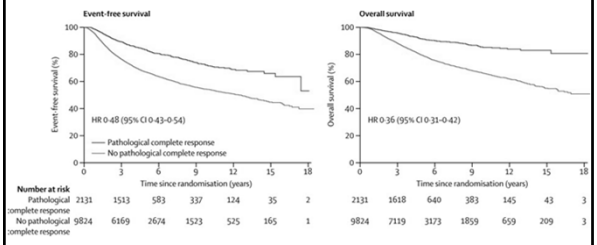
•Best contemporary evidence in HER-2 positive or TNBC where neoadjuvant therapy is commonly used

•Increasing interest in preop endocrine therapy

CTNeoBC Pooled Analysis of pCR and Clinical Benefit

12 preop trials of >200 pts

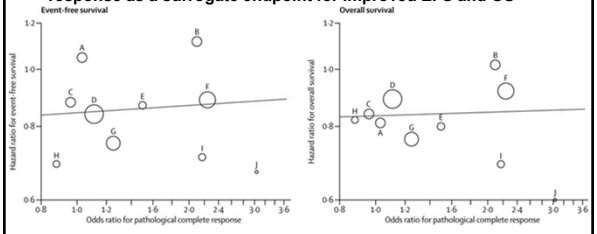
- **3 yr median followup**
- **N=11955 patients**



Cortazar et al, Lancet, 2014

CTNeoBC Pooled Analysis of pCR and Clinical Benefit

Patients who attain pathological complete response defined as ypT0 ypN0 or ypT0/is ypN0 have improved survival. The prognostic value is greatest in aggressive tumour subtypes. Our pooled analysis could not validate pathological complete response as a surrogate endpoint for improved EFS and OS



Cortazar et al, Lancet, 2014

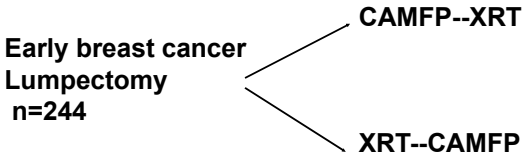
Potential Toxicities of Adjuvant Chemotherapy

Acute	Chronic
Nausea, vomiting	Ovarian failure
Hair loss	Late end organ damage
Bone marrow suppression	Second malignancy
Mucositis	Cognitive dysfunction?
Weight gain	
Fatigue	

Some Adjuvant Therapy Questions

- Prognostic and predictive markers
- Endocrine therapy—tamoxifen, AI, OFS/OA
- Chemotherapy
  - Selection of agents
  - Dose intensity/density
  - Preoperative therapy
- Sequencing of therapy
- Anti-HER-2 therapy
- Use of bisphosphonates
- Integration of other biologics
- Follow-up of early breast cancer survivors

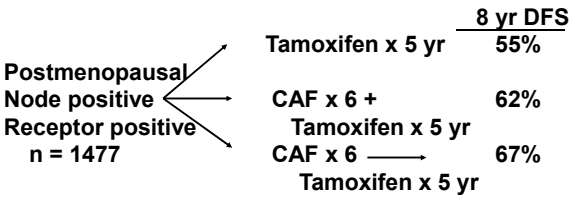
Sequence of Chemotherapy and Radiation



No difference in outcomes at 135 months

Bellon, J Clin Oncol, 2005

Sequential vs Concurrent Chemohormonal Therapy INT 0100



Statistically significant advantage for sequential therapy

Albain et al, Lancet, 2009

Sequencing of Therapy

In a non-trial setting, a sequence of chemotherapy followed by tamoxifen is favored

Timing of aromatase inhibitor and chemotherapy is unexplored—extrapolate from tamoxifen

Some Adjuvant Therapy Questions

- Prognostic and predictive markers
- Endocrine therapy—tamoxifen, AI, OFS/OA
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- Integration of other biologics
- Follow-up of early breast cancer survivors

Rationale for Adjuvant Trastuzumab Trials

- Some breast cancers overexpress HER2
- Trastuzumab alone or with chemotherapy provides effective palliation in metastatic disease with HER2-overexpression
- Cardiac toxicity is seen with trastuzumab, especially with anthracycline

Major Adjuvant Trastuzumab Trials

NSABP B-31

H…x 52

BCIRG 006

H…x 52

H…x 52

NCCTG 9831

H…x 52

H…x 52

HERA

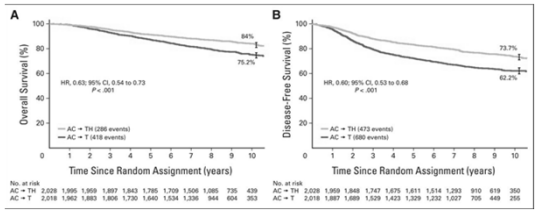
Standard ChemoRx

No therapy

H…x 1 years

H…x 2 years

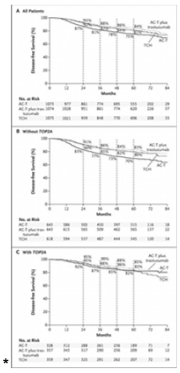
Improved Outcomes with Adjuvant Trastuzumab



- **Acceptable toxicity**
- **No predictors of response beyond HER-2 overexpression**
- **Role of other anti-HER-2 agents?**
- **Need for chemo?**

Perez et al, J Clin Oncol, 2014

Chemotherapy +/- Adjuvant Trastuzumab--BCIRG 06



N=3222 women with HER-positive node-positive or high risk node-negative breast cancer

	AC-T	TCH	AC-TH
5 yr DFS	75%	81%*	84%*
5 yr OS	87%	91%*	92%*
CHF	0.7%	0.4%	2%*
AML	0.6%	0.1%	0.1%

Slamon D et al. N Engl J Med, 2011

ASCO Guidelines for HER-2 Positive Breast Cancer

- **Results demonstrate a 30-50% reduction in recurrence with 1 year of trastuzumab in women with HER-2 positive breast cancer.**
- **Chemo + trastuzumab recommended for HER2+ node-positive and node-negative > 1 cm (and can be considered for ≤ 1 cm)**
- **Use standard chemo regimens**
- **Concurrent therapy preferred for non-anthracycline and sequential therapy preferred for anthracycline.**
- **Accurate HER-2 testing is required.**
- **Two trials of adjuvant lapatinib—modest benefit (TEACH, Lancet Oncol, 2013; ALTTO, J Clin Oncol, 2016)**

Denduluri et al, J Clin Oncol, 20162016

Duration of Trastuzumab

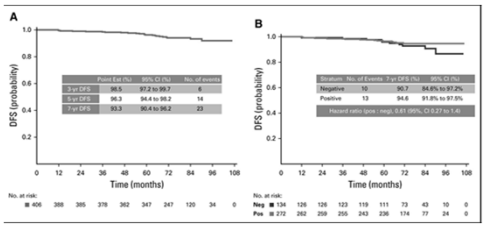
HERA-- 2 years not better than 1 year (Goldhirsch et al, Lancet, 2013)

PHARE—unable to show that 6 months of trastuzumab is non-inferior to 12 months (Pivot et al, Lancet Oncology, 2019)

PERSEPHONE– 6 months of trastuzumab is non-inferior to 12 months (Earl et al, Lancet, 2019)

Excellent Outcomes in Small N0 HER-2 Positive Breast Cancer with Reduced Intensity Therapy-APT

- **N=410 with T<3 cm N0**
- **Median f/u=6.5 yr**
- **Weekly paclitaxel/trastuzumab X 12 w►trastuzumab X 9 mo**
- **7 yr DFS=93% and OS=95%**



Tolaney et al, N Engl J Med, 2015 and J Clin Oncol, 2019

Dual Anti-HER-2 Therapy

ExteNET
- 2840 HER-2 positive early breast cancer who completed adjuvant chemo + trastuzumab
- Randomized to neratinib or placebo X 1 yr
- Median f/u = 5.2 yrs
- HR=0.73 for iDFS (95%CI=0.57-0.92 p=0.0083)

APHINITY
- 4805 HER-2 positive high risk N0 or N-positive breast cancer receiving chemo + trastuzumab
- Randomized to pertuzumab or placebo X 1 yr
- Median f/u =45 mo
- HR=0.81 for 3-yr DFS (95%CI=0.66-1.00, p=0.045)

Martin et al, Lancet Oncol, 2017 Von Minckwitz et al, N Engl J Med 2017

Role of TDM-1 in Early Breast Cancer---

Phase III KATHERINE trial: FDA approval in May 2019 for TDM-1 as adjuvant treatment of patients with residual disease after neoadjuvant trastuzumab and chemotherapy (von Minckwitz et al, N Engl J Med, 2019)

Phase III KRISTINE trial: Neoadjuvant TCHP gave better EFS and similar IDFS than T-DM1 + P (Hurvitz et al, J Clin Oncol, 2019)

Phase III KAITLIN trial: Adjuvant trastuzumab + pertuzumab + taxane vs TDM-1 + pertuzumab after anthracycline—no difference (Harbeck et al, ASCO 2020)

RP2 ATEMPT trial: Adjuvant TDM-1 X 1 year vs paclitaxel + trastuzumab X 12 weeks + trastuzumab X 9 months in stage 1—no DFS or safety advantage (Tolaney et al, SABCS 2019)

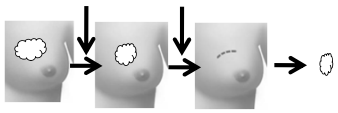
Neoadjuvant Therapy with Anti HER Agents

Using pCR as endpoint:

Lowest pCR

Highest pCR

- Lapatinib
- Pertuzumab
- Trastuzumab
- Lapatinib + trastuzumab
- Trastuzumab + pertuzumab



Some Adjuvant Therapy Questions

- Prognostic and predictive markers
- Endocrine therapy—tamoxifen, AI, OS/OA
- Chemotherapy
  - Selection of agents
  - Dose intensity/density
  - Preoperative therapy
- Sequencing of therapy
- Anti-HER-2 therapy
- Use of bisphosphonates
- Integration of other biologics
- Follow-up of early breast cancer survivors

Rationale for Adjuvant Bisphosphonate Trials

- Bone is a common site of breast cancer recurrence
- Bisphosphonate use with standard chemotherapy or endocrine therapy reduces skeletal morbidity in advanced breast cancer (ASCO Guidelines)
- Preclinical studies suggest potential direct antitumor effects

EBCTCG Adjuvant Bisphosphonate Metaanalysis

18766 women in 26 randomized trials
Median follow-up=6.4 years

RR for	All N=18766	Postmeno N=11767
Recurrence	0.94 (0.87-1.01)	0.86 (0.78-0.94)*
Distant recurrence	0.92 (0.85-0.99)	0.82 (0.74-0.92)*
Bone recurrence	0.83 (0.73-0.94)*	0.72 (0.60-0.86)*
Breast cancer death	0.91 (0.83-0.99)	0.82 (0.73-0.93)*

* Statistically significant EBCTCG, Lancet, 2015

CCO/ASCO Guidelines on Adjuvant Bisphophonates

- Consider zolendronic acid (4 mg IV q 6 mo for 3-5 yr) or clodronate (1600 mg/day po for 2-3 yr) for postmenopausal women who are candidates for adjuvant systemic therapy
- Postmenopausal includes natural menopause or OFS by LHRH agonists
- No evidence for denosumab or other agents at present
  - D-CARE study of adjuvant denosumab vs placebo was negative (Coleman et al, Lancet Oncol, 2020)

Dhesy-Thind et al, J Clin Oncol, 2017

Some Adjuvant Therapy Questions

Prognostic and predictive markers
Endocrine therapy—tamoxifen, AI, OFS/OA
Chemotherapy
- Selection of agents
- Dose intensity/density
- Preoperative therapy

Sequencing of therapy
Anti-HER-2 therapy
Use of bisphosphonates
Integration of other biologics
Follow-up of early breast cancer survivors

Some (Neo) Adjuvant Trials of New Approaches

Agent	Status	
	Preop	Adjuvant
Bevacizumab	Better pCR	Negative
CDK 4/6 inhibitors	N/A	+/- by press release
Everolimus	N/A	In progress
PARP inhibitors	N/A	In progress
Checkpoint inhibitors	Better pCR	In progress
Aspirin, metformin	N/A	In progress
Weight loss	N/A	In progress

Some Adjuvant Therapy Questions

Prognostic and predictive markers
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Sequencing of therapy
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Integration of other biologics
Follow-up of early breast cancer survivors

Follow-up for Early Breast Cancer Survivors

•Regular history and physical examination

•Routine mammography

•Other preventive health measures eg pelvic exam

•Lack of evidence to support routine lab studies or imaging in the absence of symptoms (two negative randomized trials)

Katcherassian et al, JCO, 2013
www.asco.org and www.nccn.org

Some Adjuvant Therapy Questions

Prognostic and predictive markers
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Follow-up of early breast cancer survivors

52

Metastatic Breast Cancer

Claudine Isaacs, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

52 – Metastatic Breast Cancer

Claudine Isaacs, MD, FRCPC

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consultant: AstraZeneca, Novartis, Genentech, PUMA, Pfizer, Seattle Genetics**
- **Research: Tesaro**
- **Speaker/Teaching Engagements: Genentech**

Characteristics

- Median survival approximately 3 years, with a 5-yr survival of about 25%
- About 10% of women present with *de novo* metastatic breast cancer (MBC)
- Metastatic disease is considered incurable

Goals of treatment of MBC

- Prolongation of survival
- Improved quality of life
  - Reduce cancer-related symptoms
  - Minimize toxicity of therapy
    - Delay time to chemotherapy
  - Increase progression-free survival

Survival Improved over Time and Subtype Dependent

Consecutively diagnosed patients 1985-2014 Swedish County (n=784)

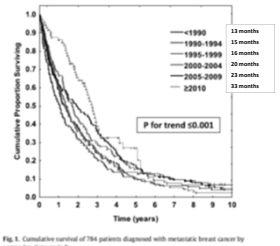
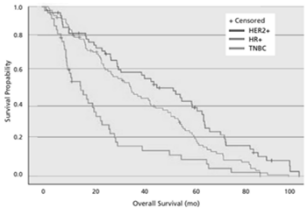


Fig. 1. Cumulative survival of 784 patients diagnosed with metastatic breast cancer by successive time periods.

German study also suggested improvements limited to those with HER2+ or HR+ disease



Sundquist M et al. The Breast 2017;31:46
Weide et al. SpringerPlus 2014;3:535

Approach to Management of MBC

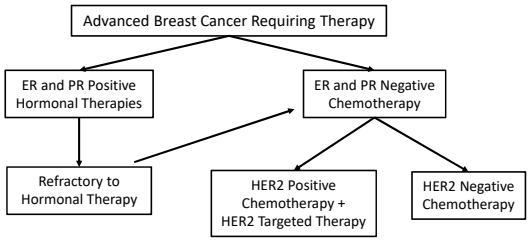
Tumor Characteristics	• ER/PR status • HER2 status • Sites and extent of disease • Presence of visceral crisis

Prior Therapy	• Adjuvant setting
	  • Type and disease-free interval
	• Metastatic setting
	  • Type and duration of response

Patient Related	• Symptoms • Co-morbidities • Preference

Individualize treatment to tumor and patient related factors

Approach to Treatment

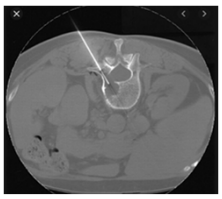


Metastatic Breast Cancer Outline

- Work-up
- Treatment of HER2 positive mBC
- Endocrine therapy for mBC
- Chemotherapy for mBC
- Bone directed therapy

Do you biopsy at time of Recurrence?

- To confirm recurrence
- To confirm receptor status
  - Discordance on ER/PR in 14%
  - Discordance HER2 in 5%-15%



BC Cancer Agency Outcome Unit McFarlane R et al. ASCO 2008;abs 1000
ASCO 2010: Absracts 1007-1009

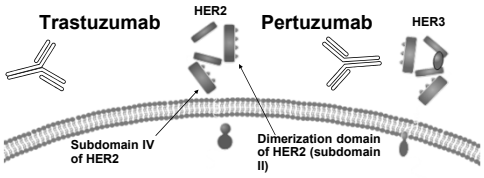
HER2 POSITIVE DISEASE

Pivotal Phase III Trastuzumab Studies in MBC

Study	Median Overall Survival		*P*-value
	Chemotherapy Alone	Chemotherapy + Trastuzumab	
Slamon (NEJM 2001)	20.3 months	25.1 months	0.046
Marty (JCO 2005)	22.7 months	31.2 months	0.0325

Slamon et al. *N Engl J Med.* 2001;344:783-792; Marty et al. *J Clin Oncol.* 2005;23:4265-4274.

Pertuzumab Mechanism of Action



- Pertuzumab targets the extracellular dimerization domain (subdomain II) of HER2
  - blocks ligand-dependent heterodimerization of HER2 with other HER family members, including EGFR, HER3, and HER4
- Trastuzumab binds to subdomain IV and disrupts ligand-independent HER2 signaling

Dual HER2 Targeting - CLEOPATRA
Pertuzumab First Line

N = 808

Eligibility:
- HER2+ MBC
- No prior chemo for MBC
- No prior HER2 Tx for MBC*
- Normal LVEF

→ Docetaxel 75 mg/m² Q3wks + Trastuzumab 6 mg/kg Q 3wks + Placebo

→ Docetaxel 75 mg/m² Q3wks + Trastuzumab 6 mg/kg Q 3wks + Pertuzumab 840 mg loading then 420 mg Q3wks

- Main side effects with pertuzumab: increased diarrhea, rash, neutropenia
- No increased incidence of cardiac toxicity noted (in adjuvant setting 0.4% increase)

Continue chemo x 6-8 cycles then targeted therapy alone (add endo therapy if HR+)

	Placebo	Pertuzumab	P value
PFS	12.4 mos	18.5 mos	< 0.001
ORR	69.3%	80.2%	0.001
OS*	40.8 mos	57.1 months	HR 0.68 (p < .001)
Alive at 8 yrs	23%	37%	

* Only ~10% prior (neo)adj trastuzumab

Baselga et al. NEJM 2012; 366:109; Swain et al. NEJM 2015;372:724; Bwaiin et al. Lancet Oncol 2020; 21:519

Optimal Therapy at PD
TDM-1 - EMILIA

Eligibility:
- HER2+ (central) LABC or mBC
- 1st, 2nd, or 3rd Regimen
- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mos of adj tx

→ T-DM1 3.6 mg/kg Q3wks

→ Capecitabine 1000mg/m² D1-14 q3wks + Lapatinib 1250 mg/day

N = 991

	Cape+ Lap	TDM-1	P value
PFS	6.4 mos	9.6 mos	0.0001
ORR	31%	44%	0.0002
OS*	25.9 mos	29.9 mos	HR 0.75 (CI 0·64–0·88)

Verma et al. NEJM 2012:367:19; Dieras Lancet Oncol 2017;18:732

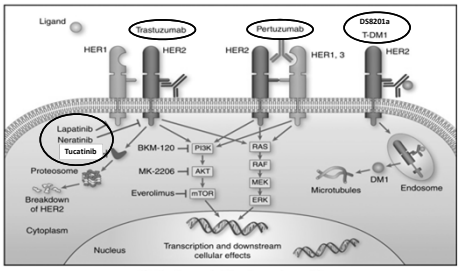
EMILIA
Toxicity (Grade 3 or 4)

	Cape + Lapa (N=488)	TDM-1 (N=490)
Grade ≥ 3 AE	57%	41%
Diarrhea	21%	1.6%
HFS	16%	0%
Vomiting	4.5%	0.8%
Neutropenia	4.3%	2.0%
Thrombocytopenia	0.2%	13%
Anemia	1.6%	2.7%
Increased ALT/AST	1.5%	2.8%
LVEF < 50% or ↓ 15%	1.6%	1.7%

TDM1 + Pertuzumab NOT superior to Paclitaxel + Trastuzumab 1st line

Perez et al. JCO 2016;35:141 Verma et al. NEJM 2012:367:19

HER2 Targeted Therapies



Singh et al. British J of Cancer 2014;111:1888

HER2+ mBC Beyond 2nd Line - - A Lot of New Options!!

TRIAL (Agent and MOA) FDA indication	SCHEMA	PFS	OS
HER2CLIMB (n=612) Tucatinib HER2 TKI FDA ≥ 2nd line	**Tucatinib + Capecitabine + trastuzumab vs Placebo + Capecitabine + trastuzumab** (CNS activity also noted - ~50% had brain mets)	**Δ 2.2 mos 7.8 vs 5.6 mos HR 0.54 (*P* < 0.001)**	**Δ 4.5 mos 21.9 vs 17.4 mos HR 0.66 (*P* = 0.005)**
DESTINY Breast01 (n=184) Trastuzumab deruxtecan ADC (payload Topo1 inhib) FDA ≥ 3rd line	**Phase 2 Single agent post T-DM1**	**Median PFS 16.4 mos ORR 60.9% CBR 97.3%**	
NALA (n = 621) Neratinib Irreversible pan-HER Tki FDA ≥ 3rd line	**Neratinib + Capecitabine vs Lapatinib + Capecitabine** (CNS activity also noted)	**Δ 2.2 mos 8.8 vs 5.6 mos (*P* = 0.0003)**	**Δ 1.7 mos 24.0 vs 22.2 mos (*P* = 0.2)**

Toxicities (to know for boards):
- Neratinib – diarrhea; minimized with dose escalation and antidiarrheals
- Tucatinib -- diarrhea – seems less than with neratinib
- Trastuzumab deruxtecan – Interstitial lung disease 13.6% (2.2% death due to ILD)

Murthy. NEJM. 2019;382:597; Modi et al. NEJM 2020; 382:610-621; Saura et al. ASCO 2019; Abs 1002

Current Approach for Sequencing Therapy: Advanced HER2+ Breast Cancer

First Line[1]
- Taxane + Trastuzumab + Pertuzumab

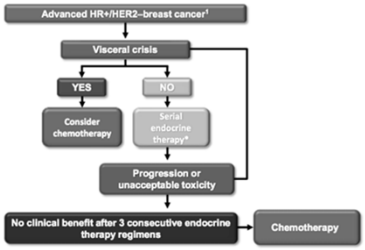
Second Line[1]
- T-DM1
- Tucatinib + Capecitabine + Trastuzumab

Third Line and Beyond[1]
- Tucatinib + Cape + Trastuzumab
- Trastuzumab Deruxtecan(DS-8201a)
- Neratinib + Capecitabine
- Lapatinib + Capecitabine
- Chemo + Trastuzumab (eribulin, vinorelbine, gem, capecitabine, CMF…)
- Endo therapy + Anti-HER2 (for HR+)
- Trastuzumab/Pertuzumab or T-DM1, if not received prior

1. Giordano SH, et al. *J Clin Oncol.* 2018;36(26):2736-2740; 2. NCCN. Breast Cancer. V2.2020. Feb 5, 2020.

ENDOCRINE THERAPY

Guidelines for Management HR+/HER2- MBC



NCCN Clinical Practice Guidelines in Oncology: Breast Cancer V2.2017; Cardoso F et al. Ann Oncol 2014;25:1871

Endocrine Therapy Options

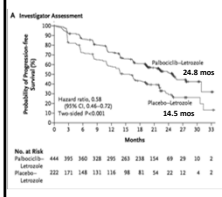
- **Premenopausal:**
  - Tamoxifen or toremifene (SERMs)
  - *Ovarian ablation/suppression and treatment + endo therapy as for postmenopausal women*
- **Postmenopausal:**
  - Non-steroidal AI + CDK4/6 inhibitor (Category 1*)
  - Fulvestrant + CDK4/6 inhibitor (Category 1*)
  - Fulvestrant + Alpelisib
  - Steroidal AI + everolimus
  - Aromatase inhibitors
  - Fulvestrant (SERD)
  - Tamoxifen or toremifene (SERMs)
  - Megestrol acetate
  - Fluoxymesterone
  - Ethinyl estradiol

*Category 1: Based on high-level evidence, there is uniform NCCN consensus that the intervention is appropriate

Adapted from NCCN Clinical Practice Guidelines in Oncology: Breast Cancer V1.2020

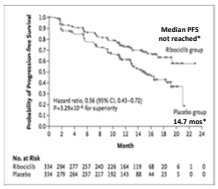
Phase III Trials of AI +/- CDK4/6 Inhibitor 1st Line Endo Therapy in Postmenopausal Women

PALOMA 2 - Palbo



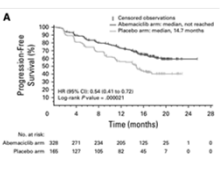
Palbociclib 125 mg po 3weeks on/1 week off

MONALEESA 2 - Ribo



Ribociclib 600 mg po 3weeks on/1 week off

MONARCH 3 - Abema



Abemaciclib 150 mg bid continuous

*Median PFS AI + Placebo 16 mos vs AI + Ribo 25.3 mos (p<.001)

Finn et al. NEJM 2016; 375;1925; Hortobagyi al. NEJM 2016; 375;1738; Hortobagyi ASCO 2016; Abs 1038; Goetz JCO 2017;32:3638

CDK4/6 Inhibitors Toxicities ≥ 15% Patients

	Palbo + Letrozole (N=444) Any (G3/4) %	Placebo + Letrozole (N=222) Any (G3/4)%
Neutropenia	**80 (66)**	**6 (<2)**
Anemia	**24 (5)**	**9 (2)**
Thrombocytopenia	**16 (2)**	**1 (0)**
Fatigue	**37 (2)**	**28 (<1)**
Alopecia	**33**	**16**
Rash	**18 (1)**	**12 (<1)**
Asthenia	**17 (2)**	**12 (0)**
Stomatitis	**15 (<1)**	**6 (0)**

SAEs: Febrile neutropenia 1.6% palbo vs 0 placebo arm
Monitoring: CBC 1st day of each cycle and day 15 of 1st to cycles

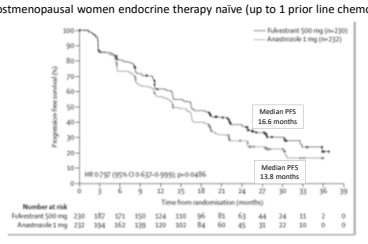
Ribociclib:
- Neutropenia G3/4: 59% (FN 1.5%)
- ↑LFT G3/4: 9.3%; Hy's law: 1.2%
- QTcF > 480ms: 3.3%
- Nausea (51.5 vs 28.5%)
- Alopecia (33 vs 15.5%

Abemaciclib:
- Neutropenia G3/4: 21% (FN 0.4%)
- Diarrhea 81% (G3/4 9.5%)

Finn, Slamon et al. NEJM 2016; Hortobagyi al. NEJM 2016; 375;1738; Di Leo A et al. ESMO 2017; Abs 2360

First Line Fulvestrant 500 mg vs AI

Postmenopausal women endocrine therapy naïve (up to 1 prior line chemo)



Recent findings showing 8 mos OS benefit for 1L Fulvestrant 250 mg bid + anastrozole vs anastrozole alone

Mehta et al. NEJM 2019;380:1226

Robertson J et al. Lancet 2016;388:2997

ENDOCRINE THERAPY: SECOND LINE SETTING

RCT - - Fulvestrant + CDK4/6i or Placebo

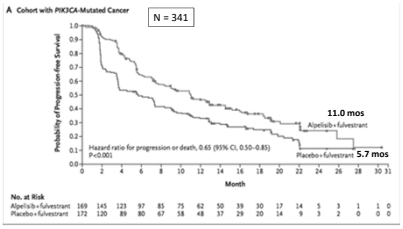
	PFS Median Placebo vs CDK4/6i		OS Median Placebo vs CDK4/6i	
Second line + Fulvestrant:	PFS mos	HR (p value)	OS mos	HR (p value)
PALOMA-3 (Palbo)	4.6 vs 11.2 (▲6.6)	0.50 (p <.001)	34.9 vs 28 (▲6.9)	0.81 (p = .09)
MONARCH-2 (Abema)	9.3 vs 16.4 (▲ 7.1)	0.56 (p <.001)	46.7 vs 37.3 (▲9.4)	0.76 (p = .01)
MONALEESA-3 (Ribo)	12.8 vs 20.6 (▲7.8)	0.59 (p <.001)	NR vs 40.0	0.72 (p = .005)

Trial populations are different in terms of extent of pretreatment, menopausal status, definitions of endocrine resistance
THUS, should not compare across trials

Turner NC et al. NEJM 2018;379:20; Sledge JAMA Oncol 2020;6:116; Slamon D et al. ESMO 2019 LBA

PIK3CA-mutated HR+/HER2- mBC
P3 RCT of Fulvestrant + Alpelisib/Placebo (SOLAR-1)

PIK3CA mutations occur in about 40% HR+/HER2- breast cancers
Alpelisib is α selective PI3Ki



Key characteristics:
- Lung or liver mets 50%
- 1st line 52%; 2nd line 46%
- Prior CDK4/6i 6%

Key toxicities alpelisib:
- Hyperglycemia (G3/4 36%)
- Rash (G3/4 10%)
- Diarrhea (G3/4 7%)

No difference in *PIK3CA* wt

Andre et al. NEJM 2019;380:1929

Overcoming Endocrine Resistance
Role of mTOR inhibition

Eligibility Criteria:
- Metastatic disease
- Postmenopausal
- ER+/PgR+; HER2 negative
- Measurable disease
- Refractory to nonsteroidal AI ie PD for advanced breast cancer OR <12 mos from d/c adjuvant therapy

2:1

Exemestane 25 mg QD + Everolimus 10 mg QD (n = 485)

Exemestane 25 mg QD + PLACEBO (n = 239)

	Placebo	Everolimus	P value
PFS (local)	2.8 mos	6.9 mos	<0.001
ORR	0.4%	7.0%	<0.001
OS (immature)	26.6 mos	31.0 mos	NS

Major side effects: mucositis, diarrhea; hyperglycemia; rare pneumonitis

Baselga et al. NEJM 2012:366:520; Piccart M Annals Oncol 2014;25:2357

Endocrine Therapy Summary*

First Line
- AI + CDK4/6 inhibitor (palbociclib/ribociclib/abema)
- In premenopausal OFS + AI + ribociclib
- Fulvestrant +/- CDK4/6 inhibitor (If relapsed < 12 mos after completing adj endo therapy)
- Unclear who could do endo therapy alone

Second Line
- Fulvestrant +/- CDK4/6 inhibitor (if no prior CDK4/6 inhib)
- Fulvestrant + Alpilesib for *PIK3CA* mutated
- Exemestane +/- everolimus

Third Line
- Tamoxifen or toremifene
- Exemestane +/- everolimus
- Estradiol 2mg tid
- Megace
- Reintroduction prior agent

Paucity of data for CDK4/6i post progression on CDK4/6i

* For premeno -- Ovarian ablation/suppression + same endo therapy as for postmenopausal women

CHEMOTHERAPY

Metastatic Disease
Chemotherapy

- Offers good palliation, but no cures
- Many chemotherapy options available
- For HER2 positive add HER2 targeted therapy
- For ER+ if in visceral crisis or exhausted endocrine therapy options
- Currently only SOC option for TNBC

Chemotherapy Options for HER2 negative MBC

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2020
Invasive Breast Cancer

NCCN Guidelines Index
Table of Contents
Discussion

SYSTEMIC THERAPY REGIMENS FOR RECURRENT OR STAGE IV (M1) DISEASE[a,b,c]

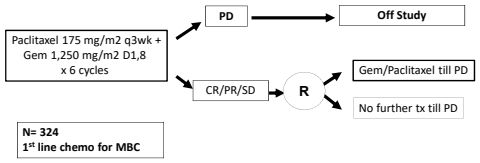
HER2-Negative

Preferred Regimens	Other Recommended Regimens[f]	Useful in Certain Circumstances[f]
• Anthracyclines ▸ Doxorubicin ▸ Liposomal doxorubicin • Taxanes ▸ Paclitaxel • Anti-metabolites ▸ Capecitabine ▸ Gemcitabine • Microtubule inhibitors ▸ Vinorelbine ▸ Eribulin • For germline BRCA1/2 mutations[d] see additional targeted therapy options (BINV-R)[e] • Platinum (for TNBC and germline BRCA1/2 mutation)[d] ▸ Carboplatin ▸ Cisplatin • For PD-L1–positive TNBC see additional targeted therapy options (BINV-R)[e]	• Cyclophosphamide • Docetaxel • Albumin-bound paclitaxel • Epirubicin • Ixabepilone • Sacituzumab govitecan-hziy (for TNBC)[g]	• AC (doxorubicin/cyclophosphamide) • EC (epirubicin/cyclophosphamide) • CMF (cyclophosphamide/methotrexate/fluorouracil) • Docetaxel/capecitabine • GT (gemcitabine/paclitaxel) • Gemcitabine/carboplatin • Paclitaxel/bevacizumab[h] • Carboplatin + paclitaxel or albumin-bound paclitaxel

Combination Chemotherapy
General Principles

- Combination chemotherapy generally associated with higher RR and often longer duration of PFS
- No survival benefit in trials comparing combination vs sequential approach
- Reserve combination chemotherapy for those with:
  - Patients with rapid clinical progression or life-threatening visceral metastases
  - Patients in need of rapid symptom and/or disease control

Korean Cancer Study Group
Maintenance Chemotherapy

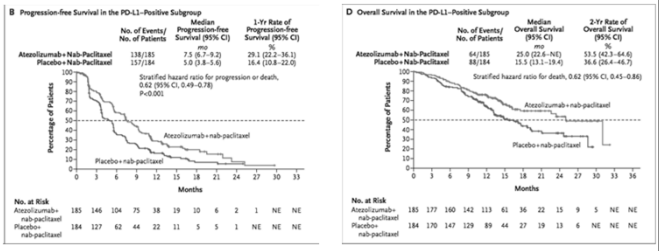


	Maintenance	No treatment	P value
PFS from randomization	7.5 mos	3.8 mos	0.03
Overall Survival	32 mos	23 mos	0.05

Beyond PD ~ 70% received further chemo (median regimens similar); 40% further endo tx

YH Park et al. JCO 2013;31:1732

1L mTNBC - Role for Immunotherapy



Recent data on Pembro 1L Keynote 355

Schmid et al N Engl J Med 2018;379:2108-21

Sacituzumab Govitecan mTNBC beyond 2nd line

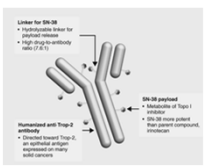


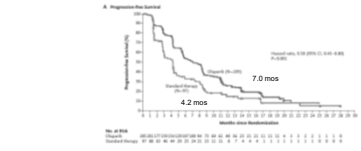
Table 3. Summary of Treatment Efficacy, According to Local Assessment.

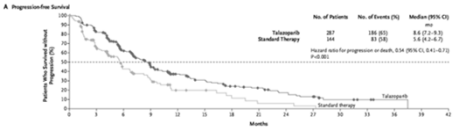
Variable	Patients (N=108)
Complete response — no. of patients (%)	3 (2.8)
Partial response — no. of patients (%)	33 (30.6)
Stable disease — no. of patients (%)	40 (37.0)
Progressive disease — no. of patients (%)	28 (25.9)
Not evaluated — no. of patients (%)*	4 (3.7)
Objective response rate†	
No. of patients	36
% of patients (95% CI)	33.3 (24.6–43.1)
Clinical benefit rate‡	
No. of patients	49
% of patients (95% CI)	45.4 (35.8–55.2)
Median duration of response (95% CI) — mo	7.7 (4.9–10.8)

Primary toxicity – neutropenia, fatigue, diarrhea
FDA in 4/2020 granted accelerated approval following ≥ 2L therapy
Definitive P3 RCT stopped due to compelling evidence of efficacy – 3.9 month PFS benefit (5.6 vs 1.7 mos) and OS benefit (6/2020)

Bardia A et al. NEJM 2019; 380:8

RCT of PARP inhibitors in g*BRCA1/2* carriers with HER2 neg mBC





TPC: Capecitabine, Eribulin, Vinorelbine
TPC: Capecitabine, Eribulin, Vinorelbine, or Gemcitabine

Robson et al. NEJM 2017; AACR 2018; Litton J et al. NEJM 2018

Bone Modifying Agents

Only recommended in patients with evidence bone mets

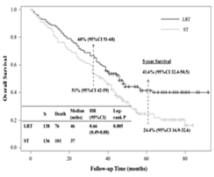
- Given in conjunction with systemic therapy
- Options include:
  - Denosumab 120 mg qmos
  - Pamidronate 90 mg
  - Zoledronic acid 4 mg q3mos or monthly x 12 then q3mos
- Recommend dental evaluation and preventive dentistry before initiating therapy and maintenance of optimal oral health
- Duration unclear

Himelstein et al JAMA 2017; 317:48; Van Poznak et al ASCO Guidelines, JCO 2017; 35:3978-3986

ROLE OF LOCAL THERAPY

De novo Stage IV Disease - Role of Early Local Therapy

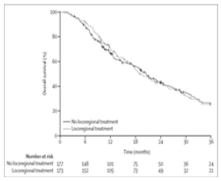
Turkish Federation RCT



- Randomized upfront
- Greater benefit in ER+ vs ER-
- Greater benefit with solitary bone met

Soran A et al. Annals Surgical Oncol 2018

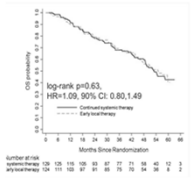
TATA Memorial Hospital RCT



- Randomized those responding to chemo
- No HER2 targeted therapy (30% HER2+)

Badwe et al. Lancet Oncol 2015:16:1380

ECOG/ACRIN RCT



- Randomized those not progressing on 4-8 mos systemic therapy
- Japanese and Dutch trials ongoing

Kahn S et al. ASCO 2020; Plenary session

Summary

- For metastatic disease, goals of therapy critical
- For HER2+
  - 1st line Taxane + Trastuzumab + Pertuzumab; 2nd line TDM-1; 3rd line Tucatinib/Cape/Trastuzumab, Trastuzumab Deruxtecan, Neratinib + Capecitabine
- For HR+ disease, endocrine therapy usually first choice
  - Typically 1st line Endo therapy + CDK4/6 inhibitors
  - Alpelisib + Fulvestrant 2nd line if PIK3CAm
- Number of chemotherapy options
  - Combination therapy reserved for very symptomatic
  - Atezolizumab + nab-paclitaxel for 1L PD-L1+ mTNBC
  - Role of PARP inhibitors in *BRCA1/2*
- Increasing role of molecular profiling for treatment decision making
- Bone targeted therapy for those with bone mets
- No role of local therapy in those with *de novo* mBC (except in specific circumstances)

ADDITIONAL SLIDES

Survival Improvement over Time

Consecutively diagnosed patients 1985-2014 Swedish County (n=784)

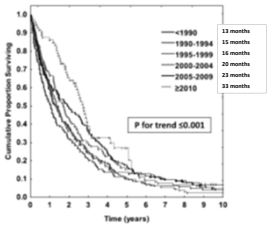
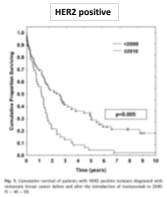


Fig. 1. Cumulative survival of 784 patients diagnosed with metastatic breast cancer by successive time periods.

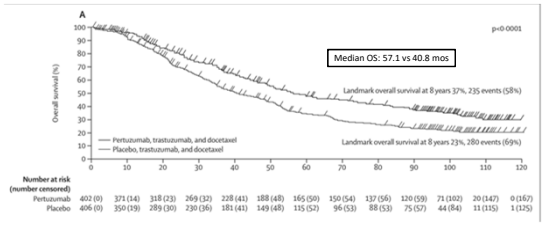


German study also suggested improvements limited to those with HER2+ or HR+ disease

Sundquist M et al. The Breast 2017;31:46
Weide et al. SpringerPlus 2014;3:535

CLEOPATRA: 1L Docetaxel, Trastuzumab +/- Pertuzumab

End-of-Study OS in ITT Population*

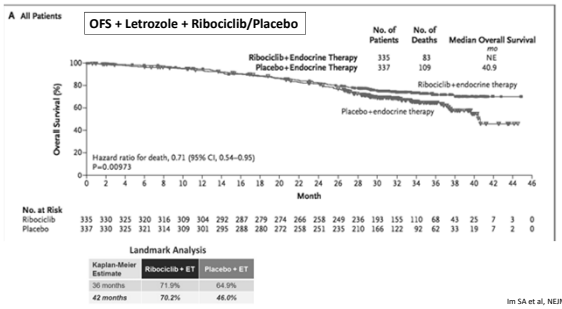


* Cross over patients analyzed in placebo arm
OS compared between arms using log-rank test, stratified by prior treatment status and geographical region

- Main side effects with pertuzumab (typically low grade) – increased diarrhea, rash, neutropenia
- No increased incidence of cardiac toxicity noted

Swain et al. NEJM 2015;372:724; Swain et al. Lancet Oncol 2020; 21:519

MONALEESA 7 – Overall Survival Benefit 1L CDK4/6i in Premenopausal Patients



Landmark Analysis

Kaplan-Meier Estimate	Ribociclib + ET	Placebo + ET
36 months	71.9%	64.9%
42 months	*70.2%*	*46.0%*

Im SA et al, NEJM 2019 381;4

First Line Therapy RCT AI +/- CDK4/6 Inhibitors

	Median PFS Placebo	Median PFS CDK4/6i	HR (p value)
First line + Aromatase Inhibitor:			
PALOMA-2 (Palbociclib)	14.5 mos	24.8 mos	0.58 (p<.001)
MONALEESA-2 (Ribociclib)	16 mos	25.3 mos	0.57 (p<.001)
MONARCH-3 (Abemaciclib)	14.8 mos	28.2 mos	0.54 (p<.0001)
First line premenopausal	OS Placebo	OS CDK4/6i	
MONALEESA-7 (Ribociclib)	40.9 mos	NR	0.71 (p=0.01)

Finn, Slamon et al. NEJM 2016; Hortobagyi al. NEJM 2016; 375;1738; Goetz JCO 2017;32:3638

53

Neuro-Oncology

Mark Gilbert, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

53 – Neuro-Oncology

Mark Gilbert, MD

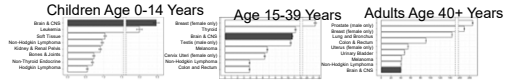
Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

BRAIN AND CENTRAL NERVOUS SYSTEM TUMOR INCIDENCE

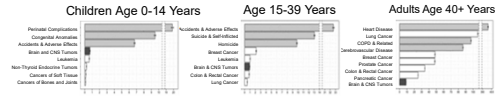
- 361,802 primary brain and CNS tumors diagnosed in 2009-2013 in the US



Age-Adjusted Incidence Rates of All Primary Brain and Other CNS Tumors Compared to Other Common Cancers

CBTRUS Statistical Report. *Neuro Oncol.* 2016;18(suppl_5):1-75

MORTALITY



Annual Age-Adjusted Mortality Rates of All Primary Brain and Other CNS Tumors Compared to Other Common Cancers and Top Three Non-Cancer Causes of Death

CBTRUS Statistical Report. *Neuro Oncol.* 2016;18(suppl_5):1-75

STAGING & CLASSIFICATION OF GLIOMAS

- TNM classification not relevant
- Histology and grade determined by cellular characteristics and molecular testing
- Primary gliomas rarely spread outside of the central nervous system

WHO Classification	Histologic Subtype
Grade I	Pilocytic astrocytoma
Grade II	Astrocytoma Oligodendroglioma
Grade III	Anaplastic astro Anaplastic oligo
Grade IV	Glioblastoma IDH mut astrocytoma

GLIOMAS: MEDIAN SURVIVAL IMPORTANCE OF HISTOLOGIC GRADING

Tumor Type	MS (mos)
Low-grade oligodendroglioma	~120
Low-grade astrocytoma	~60
Anaplastic oligodendroglioma	~60
Anaplastic astrocytoma	~36
Glioblastoma	12 - 15

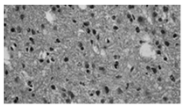
ASTROCYTOMA
KEY FEATURES

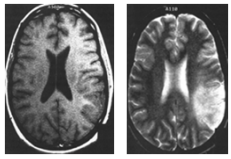
Histology:
Increased astrocytic cellularity

Median Survival:
5 - 7 years

Notes:
Often present with seizures

Often undergo malignant transformation





ANAPLASTIC ASTROCYTOMA
KEY FEATURES

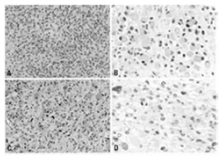
Histology:
Increased astrocytic cellularity

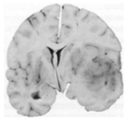
Cellular atypia and mitosis, no necrosis

Median Survival:
3-4 years

Notes:
Tissue sampling a major issue

Progression to glioblastoma in some



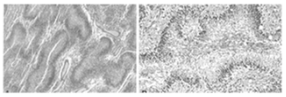


GLIOBLASTOMA
KEY FEATURES

Histology
Necrosis, mitosis, neovascularization and pseudopallisading

1993 WHO guidelines: hypercellular, mitosis, pleomorphism, & neovascularization or necrosis

Median Survival
12-15 months



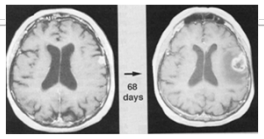
GLIOBLASTOMA

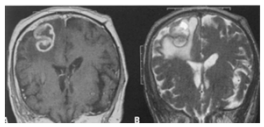
Rapid progression

Enhancing tumor

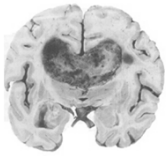
Surrounding edema

contains tumor



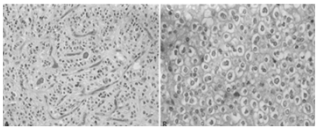


T1 post-contrast T2



OLIGODENDROGLIOMA

Histology reveals characteristic "fried egg" appearance
Often microscopic and macroscopic calcification
Classified as low-grade or anaplastic
Very responsive to treatment: chemotherapy and radiation
Prognosis and response to treatment strongly correlated with 1p & 19q LOH

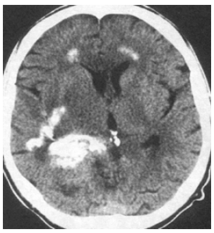


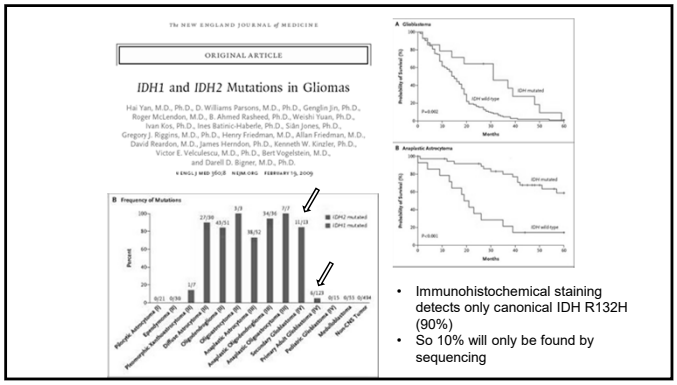
Dense network of branching capillaries

Clear cytoplasm and well-defined plasma membrane

OLIGODENDROGLIOMA

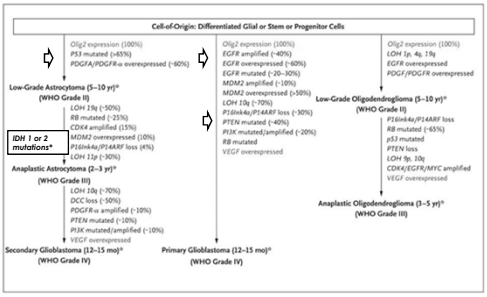
- Noncontrast CT shows macroscopic calcification
- MRI not very good at evaluating calcification





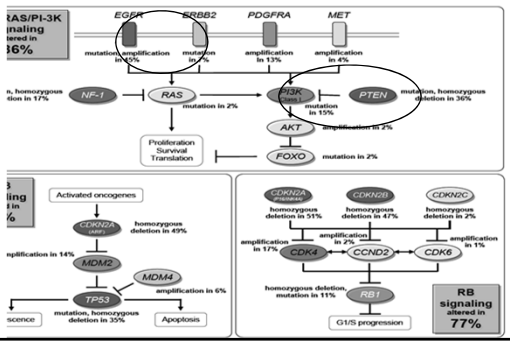
- Immunohistochemical staining detects only canonical IDH R132H (90%)
- So 10% will only be found by sequencing

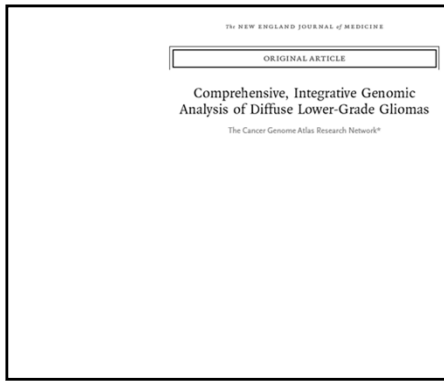
MOLECULAR BASIS OF GLIOMAGENESIS



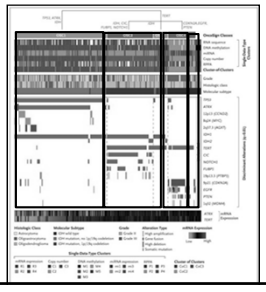
*Yan H. et al. NEJM 360:765, 2009

GENETIC ABERRATIONS INTEGRATE INTO PATHWAYS
PATHWAYNESS CRITICAL (TCGA GLIOMA)



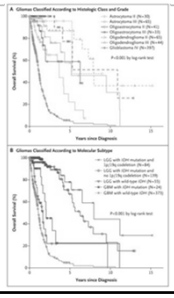


MULTIPLATFORM ANALYSIS OF LOWER GRADE GLIOMAS



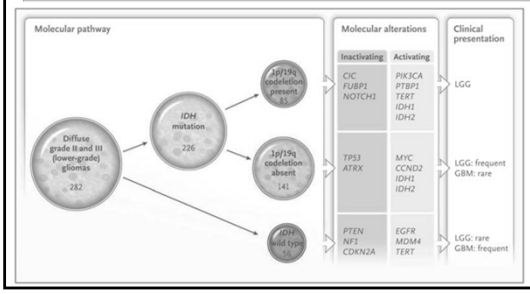
- Astrocytoma
- Oligodendroglioma
- Pre-glioblastoma
- ?Pilocytic Astrocytoma

Clinical Outcomes



Laila Poisson

SUMMARY OF MOLECULAR CLASSIFICATION OF GLIOMAS



2019 C-IMPACT

- **IDH wt grade III astrocytoma with Chr 7 gain; 10 loss; CDKN2A amp = glioblastoma**
- **IDH mut grade IV = Grade IV astrocytoma ≠ *GBM***

CANCER RISK/PROTECTIVE FACTORS

- Established risk factors
  - High-dose radiation
  - Hereditary syndromes
  - Male
  - Increasing age
  - Race (comparing white vs. African origin)
- Probable risk factors
  - Family history of primary brain tumors
  - Mutagen sensitivity (lab-based test)
  - Allergies and asthma (protective)
  - Chickenpox or anti-VZV (protective)

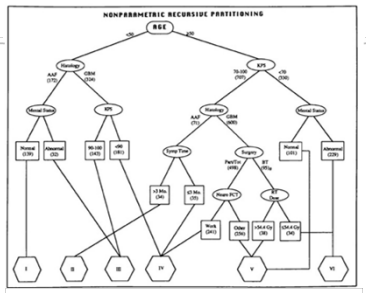
GENETIC SYNDROMES WITH HIGH RISK OF BRAIN TUMORS

Genetic Syndrome	Associated Chromosome or gene
• Neurofibromatosis 1	• Chromosome 17q11
• Neurofibromatosis 2	• Chromosome 22q12
• Tuberous sclerosis 1	• Chromosome 9q34
• Tuberous sclerosis 2	• Chromosome 16p13
• Li-Fraumeni	• Chromosome 17p13
• Turcot Syndrome and Multiple hamartoma syndrome	• APC, hMLH1, hMSH2, PMS2, PTEN
• Lynch Syndrome	• Mismatch repair genes

CLINICAL PROGNOSTIC FACTORS

- Tumor grade
- Age
- Functional status (usually KPS)
- Extent of resection (somewhat controversial)
- Tumor location (may correlate with functional status)
- Radiation therapy

PROGNOSTIC FACTORS AMONGST CLINICAL PARAMETERS



Curran et al. JNCI 85: 704-710, 1993
Adapted from: Weller et al JCO epub Oct. 5, 2009

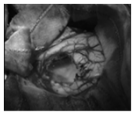
CURRENT STANDARDS OF CARE

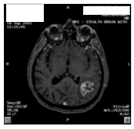
TREATMENT OF PATIENTS

Evidence-Based Review: Extent of Resection on Survival in Malignant Glioma

•Literature Review: text word astrocytoma 1966-2004; more than 12,000 references (T. Ryken)

•Review and selection of papers providing data on cytoreductive surgery in newly diagnosed malignant glioma





Results

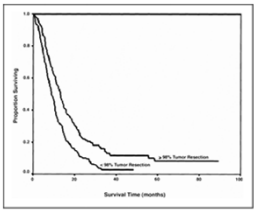
- Randomized trials - 0
- Meta-analysis - 1
- Critical reviews - 2
- Prospective data collection - 8
- Matched pair analysis - 1
- Retrospective data collection - 19

5-ALA Trial (Stummer et al)

- Lancet Oncology 7:392-401, 2006
- Randomized trial
- White light vs 5-ALA
- Measured residual tumor
  - Compared none vs some residual
- Median survival 17.9 vs 12.9 months (p < 0.001)
- Factor significant in multivariate analysis
  - P = 0.006

THERAPEUTIC ROLE OF SURGERY IN MALIGNANT GLIOMAS

- The role of maximal resection remains controversial
- Analysis of 416 patients with GBM undergoing resection at MDACC
- Preoperative and postoperative tumor volumes measured
- Controlled for other prognostic variables such as age, performance status, tumor characteristics (necrosis, enhancement), and location
- Significant increase in survival with >98% resection: 13 vs 8.8 month median (*P* <0.0001)
- Other studies support this finding



Lacroix M, et al. *J Neurosurg.* 2001;95:190-198.

EXTERNAL BEAM RADIOTHERAPY FOR MALIGNANT GLIOMA

- Current standard is 60 Gy/2 Gy/fx to GTV + 2 - 3 cm margin
- 3D; conformal, multiple fields
- Pooling of 6 randomized trials (RT vs no RT) improved survival
  - Mean survival time 3 - 6 months without RT; 9 - 12 months with RT*

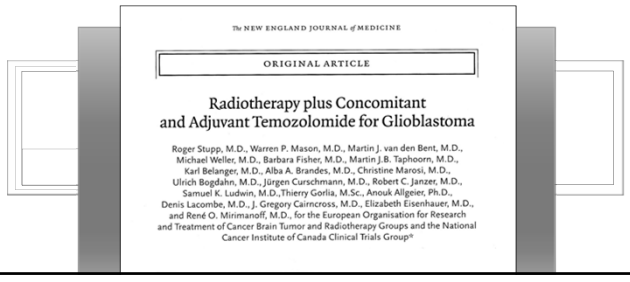
Author	N	Schema	Results
Andersen *Acta Radiol Oncol Radiat Phys Biol* 1978	108	RT vs best supportive care	Post-op RT significantly improves survival compared to best supportive care
Walker *J Neurosurg* 1978	303	BCNU vs RT vs BCNU +RT, vs best supportive care	Patients receiving RT had significantly longer MS than patients receiving BCNU or best supportive care
Walker *N Engl J Med* 1980	467	Semustine vs RT vs semustine + RT vs BCNU +RT	Patients receiving RT had significantly longer survival than patients receiving semustine alone
Kristiansen *Cancer* 1981	118	RT vs RT + bleomycin vs supportive care	MS with RT alone 10.2 months compared to 5.2 months with supportive care

*Walker MD, et al. *N Engl J Med.* 1980;303:1323-1329.

LIMITATIONS OF CHEMOTHERAPY IN TREATING BRAIN TUMORS

- Poor drug penetration into tumor (e.g., blood-brain barrier, hypoxia, intracranial pressure, etc.)
- Systemic toxicity
  - Serious myelosuppression
- Drug-drug interactions
  - Corticosteroids (phenytoin concentration)
  - Anticonvulsants (paclitaxel and CPT-11 clearance)
- Intrinsic resistance of brain tumors
  - MGMT overexpression, for example

NEWLY DIAGNOSED GBM: CHANGING THE STANDARD OF CARE WITH CONCOMITANT RADIATION & TEMOZOLOMIDE



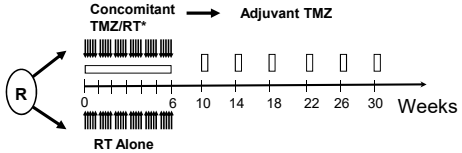
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Roger Stupp, M.D., Warren P. Mason, M.D., Martin J. van den Bent, M.D., Michael Weller, M.D., Barbara Fisher, M.D., Martin J.B. Taphoorn, M.D., Karl Belanger, M.D., Alba A. Brandes, M.D., Christine Marosi, M.D., Ulrich Bogdahn, M.D., Jürgen Curschmann, M.D., Robert C. Janzer, M.D., Samuel K. Ludwin, M.D., Thierry Gorlia, M.Sc., Anouk Allgeier, Ph.D., Denis Lacombe, M.D., J. Gregory Cairncross, M.D., Elizabeth Eisenhauer, M.D., and René O. Mirimanoff, M.D., for the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group*

Phase III Study: New GBM Radiation +/- Temozolomide



Temozolomide 75 mg/m² po qd for 6 weeks, then 150–200 mg/m² po qd d1–5 every 28 days for 6 cycles

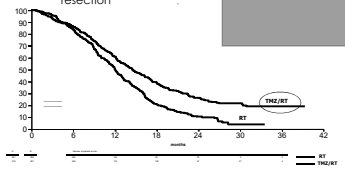
Focal RT daily — 30 x 200 cGy
Total dose 60 Gy

*PCP prophylaxis was required for patients receiving TMZ during the concomitant phase.

PHASE III EORTC/NCIC TRIAL: RESULTS

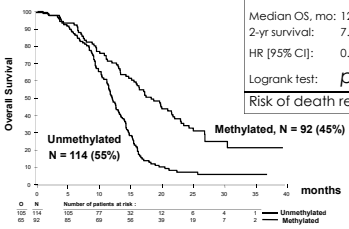
- 573 patients accrued
  - RT/TMZ = 287;RT alone = 286
  - Groups matched well for prognostic factors: age, PS, extent of tumor resection

	RT	RT/TMZ	p-value
Progression-free survival	5.0 months	7.2 months	P < 0.001
Median survival	12.1 months	14.6 months	P < 0.001
2-year survival	10%	26%	P < 0.001



MGMT Promoter Methylation is a Positive Prognostic Factor for Outcome in Glioblastoma Patients of this Trial

MGMT	Unmeth	Meth
Median OS, mo:	12.2	18.2
2-yr survival:	7.8%	34.1%
HR [95% CI]:	0.45 [0.32-0.61]	
Logrank test:	*p* <0.0001	
Risk of death reduced by 55%		



Total N=206

M. Hegi et al N Engl J Med. 2005, 352:997-1003

MGMT PROMOTER METHYLATION AND OUTCOME BASED ON TREATMENT

	2 yr surv
Unmeth, RT	2 %
Unmeth, RT/TMZ	13.8 %
Meth, RT	22.7 %
Meth, RT/TMZ	46.0 %

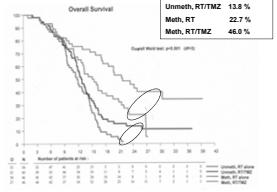


Table 1: Effect of MGMT Promoter Methylation Status on Survival, According to Random Treatment Assignment.*

Promoter Status and Outcome	Radiotherapy (N=106)	Temozolomide plus Radiotherapy (N=206)
Methylated MGMT promoter		
No. of patients	46	46
Progression-free survival		
Median duration (mo)	5.9 (5.3–7.7)	10.3 (6.5–14.9)
Rate at 6 mo (%)	47.8 (33.4–62.3)	68.9 (55.4–82.4)
Hazard ratio for death	1.00	0.46 (0.31–0.73)
Overall survival		
Median duration (mo)	15.3 (13.0–20.9)	21.7 (17.4–30.4)
Rate at 2 yr (%)	22.7 (10.3–35.1)	46.0 (31.2–60.8)
Hazard ratio for death	1.00	0.51 (0.31–0.84)
Unmethylated MGMT promoter		
No. of patients	54	60
Progression-free survival		
Median duration (mo)	4.4 (3.1–6.0)	5.3 (5.0–7.6)
Rate at 6 mo (%)	35.2 (22.5–47.9)	40.0 (27.6–52.4)
Hazard ratio for death	1.00	0.62 (0.42–0.92)
Overall survival		
Median duration (mo)	11.8 (9.7–14.1)	12.7 (11.5–14.4)
Rate at 2 yr (%)	<27	13.8 (4.8–22.7)
Hazard ratio for death	1.00	0.69 (0.47–1.00)

Hegi et al., NEJM, 2005

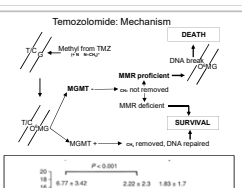
- MGMT promoter methylation not a perfect predictor of durable response to TMZ
- Patients without MGMT promoter methylation also benefited from TMZ

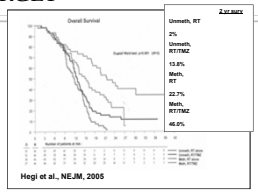
FIVE-YEAR FOLLOW UP DATA

Treatment	RT-Unmeth	TMZ/RT-unmeth	RT meth	TMZ/RT - meth
Median(m)	11.8	12.7	15.3	23.4
2y OS(%)	1.9	14.8	23.9	46.9
5y OS(%)	0.0	8.3	5.2	13.8
Hazard Ratio	0.66 [0.45-0.97]		0.51 [0.33-0.81]	

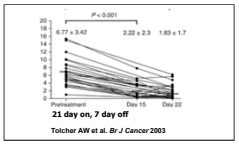
From: Stupp et al Lancet Oncol 10:459-66, 2010

MGMT: A POTENTIAL THERAPEUTIC TARGET





Hegi et al., NEJM, 2005

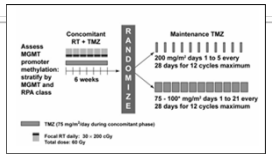


Tolcher AW et al. *Br J Cancer* 2003

- Can the efficacy of temozolomide be enhanced by a dose-dense schedule?
- Will the therapeutic benefit be specific to a sub-group based on MGMT methylation status?

RTOG 0525/EORTC 26052-22053

- International randomized phase III clinical trial involving RTOG, EORTC and NCCTG
- Primary study objective: determine if dose-intensifying the adjuvant temozolomide improves OS
- Secondary objectives:
  - Impact of dose-dense on PFS
  - Impact of dose-dense on OS and PFS by MGMT methylation status
  - Toxicity profiles
  - Compare symptom burden, NCF and HRQOL between the two treatment arms

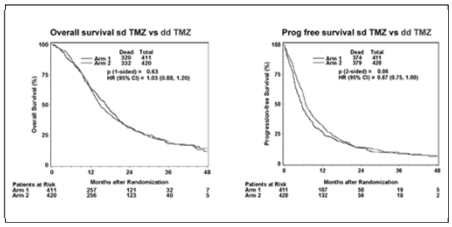


Treatment
Concomitant RT + TMZ
Focal (not IMRT) RT: 30 fx x 200 cGy
TMZ 75 mg/m² daily during RT

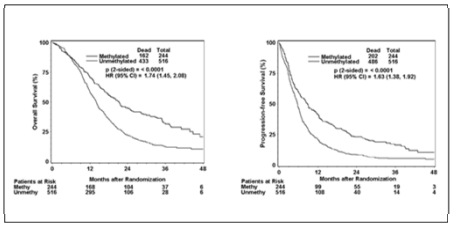
Arm 1: 150 - 200 mg/m² days 1-5 of 28 day cycle; 6 - 12 cycles

Arm 2: 75 - 100 mg/m² days 1-21 of 28 day cycle; 6 -12 cycles

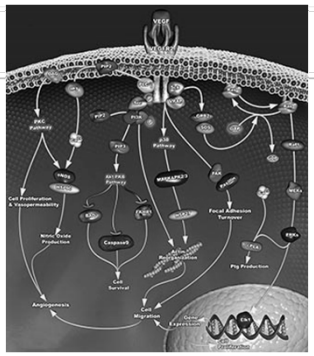
PRIMARY OUTCOMES BY TREATMENT



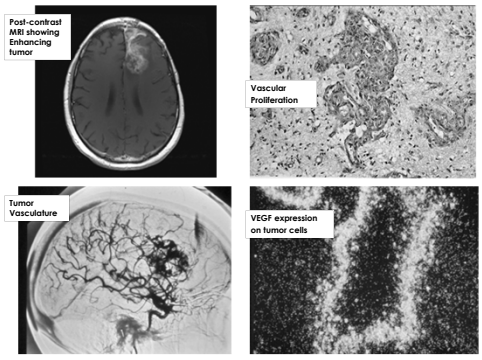
OUTCOMES BY MGMT STATUS



ANGIOGENESIS INHIBITORS

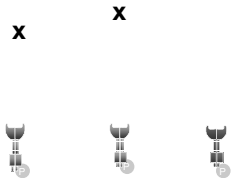


- Many of the early studies of angiogenesis used glioblastoma as the tumor model.
- Tumor cells make high levels of VEGF, particularly VEGF-A
- VEGF production is very high in areas of necrosis, stimulating additional vascular proliferation.
- Newly formed blood vessels are often tortuous with blind loops and endothelial gaps
  - Accounts for intravenous contrast leakage



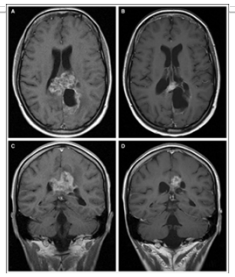
MODE OF ACTION OF BEVACIZUMAB

Bevacizumab, a monoclonal antibody functions by sequestering cirulating VEGF-A.

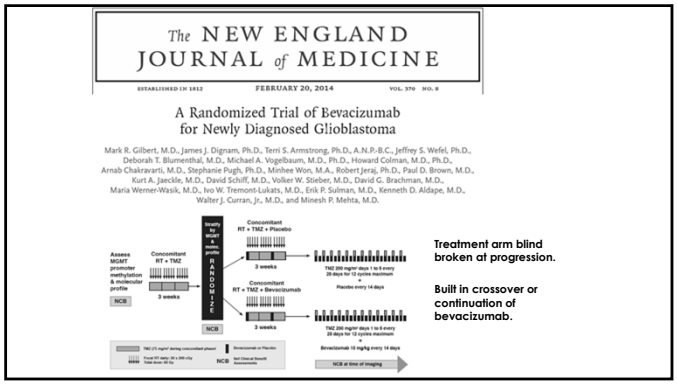


Angiogenesis Lymphangiogenesis

EXAMPLE OF IMAGING RESPONSE



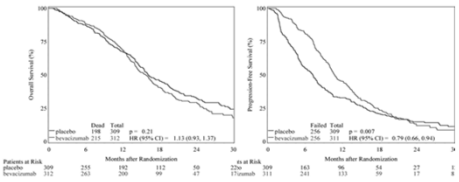
Vredenburgh, J. J. et al. J Clin Oncol; 25:4722-4729 2007



Treatment arm blind broken at progression.

Built in crossover or continuation of bevacizumab.

Primary Outcomes by Treatment



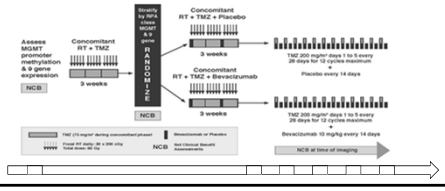
Median overall survival
Placebo: 16.1 months
Bevacizumab: 15.7 months
HR (bev/placebo:1.13 (95%CI:0.93,1.37))

Median progression free survival
Placebo: 7.3 months
Bevacizumab: 10.7 months
HR (bev/placebo:0.79 (95%CI:0.66,0.94))

Neither OS or PFS achieved pre-specified endpoints

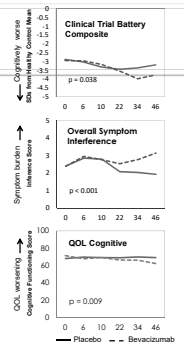
NET CLINICAL BENEFITS
TERRI ARMSTRONG, JEFFREY WEFEL

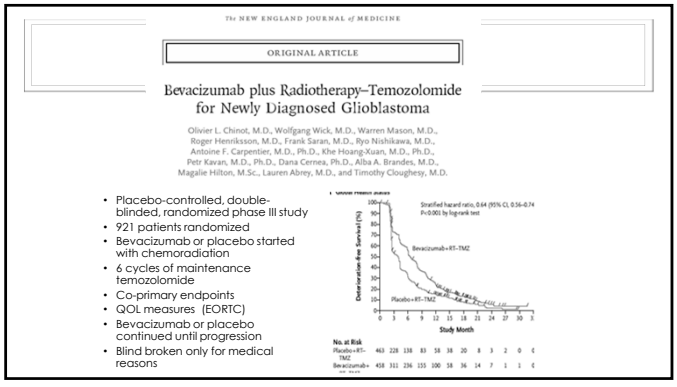
- Longitudinal measure of patient reported outcomes (PROs: MDASI-BT, EORTCQLQ30/BN20) and neurocognitive function (NCF)
- Inter-arm Analyses:
  - Discrete time points: differences in proportion with worsening/stable-improved
  - Longitudinal: changes in PROs and NCF over time



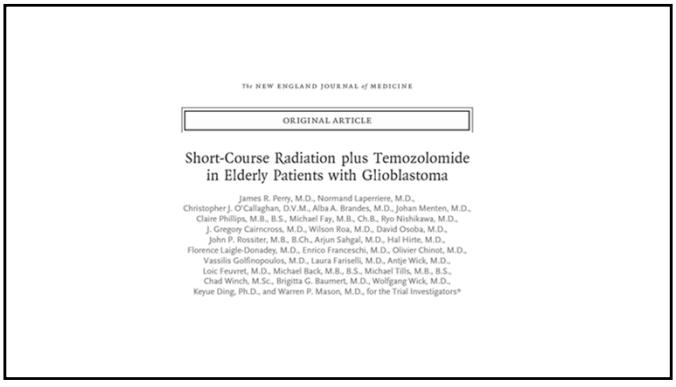
NET CLINICAL BENEFITS

- Longitudinal evaluation
  - General linear modeling with fixed effects; covariates: MGMT status and RPA class
  - Comparison between the 2 treatment arms in patients deemed progression free
  - P-value ≤ 0.05 was considered significant
- Results
  - Significant results found in both Objective (neurocognitive function) and Patient Reported (Symptom Burden and Quality of Life) Outcomes
  - Patients on Bevacizumab arm had significant worsening over time compared to Placebo arm



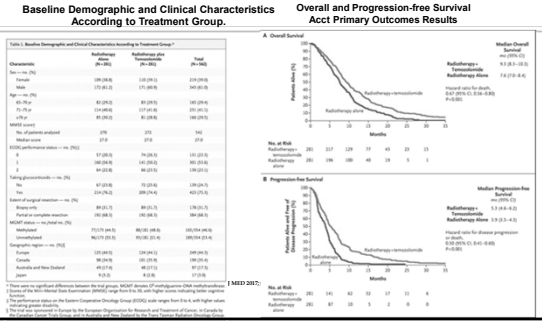


- Placebo-controlled, double-blinded, randomized phase III study
- 921 patients randomized
- Bevacizumab or placebo started with chemoradiation
- 6 cycles of maintenance temozolomide
- Co-primary endpoints
- QOL measures (EORTC)
- Bevacizumab or placebo continued until progression
- Blind broken only for medical reasons



Baseline Demographic and Clinical Characteristics According to Treatment Group.

Overall and Progression-free Survival Acct Primary Outcomes Results



I MED 2017;

Exploratory Analyses of Overall Survival Rate at 12, 18, and 24 Months According to Treatment Group and MGMT Status.

Table 3. Exploratory Analyses of Overall Survival Rate at 12, 18, and 24 Months According to Treatment Group and MGMT Status.

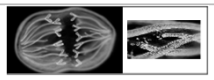
Population	At 12 Months	At 18 Months	At 24 Months
		percent (95% confidence interval)	
All patients			
Radiotherapy alone	22.2 (17.5–27.3)	10.8 (7.4–14.8)	2.8 (1.2–5.4)
Radiotherapy plus temozolomide	37.8 (32.1–43.6)	20.0 (15.5–24.9)	10.4 (7.1–14.5)
Patients with unmethylated MGMT			
Radiotherapy alone	21.3 (13.7–30.0)	12.7 (6.9–20.3)	3.8 (1.1–9.6)
Radiotherapy plus temozolomide	32.3 (23.0–42.0)	13.4 (7.3–21.2)	6.7 (2.7–13.1)
Patients with methylated MGMT			
Radiotherapy alone	29.9 (19.9–40.5)	13.6 (7.0–22.4)	4.1 (1.1–10.4)
Radiotherapy plus temozolomide	55.7 (44.7–65.3)	34.1 (24.4–44.0)	17.8 (10.5–26.7)

PERRY JR ET AL. N ENGL J MED 2017;376:1027-1037.

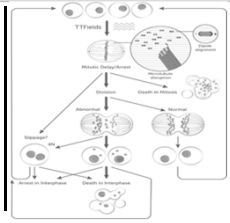
PROSPECTIVE, MULTI-CENTER PHASE III TRIAL OF TUMOR TREATING FIELDS TOGETHER WITH TEMOZOLOMIDE COMPARED TO TEMOZOLOMIDE ALONE IN NEWLY DIAGNOSED GLIOBLASTOMA

Roger Stupp, Ahmed Idbaih, David M. Steinberg, William Read, Steven Toms, Gene Barnett, Garth Nicholas, Chae-Yong Kim, Karen Fink, Andrea Salmaggi, Frank Lieberman, Jay Zhu, Lynne Taylor, Giuseppe Stragliotta, Andreas F. Hottinger, Eilon D. Kirson, Uri Weinberg, Yoram Palti, Monika E. Hegi, and Zvi Ram on behalf of the EF-14 Trial investigators

TUMOR TREATING FIELDS - MODE OF ACTION



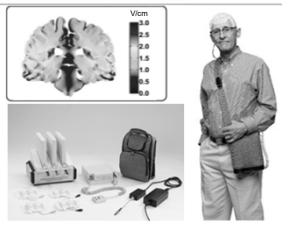
- Action on dividing cells
  - Effect on spindle apparatus
- Alternating fields effect on polar tubulin→
  - Disruption of microtubule assembly
  - Cell cycle arrest
    - → prolongation of mitosis
  - Aneuploidy



Giladi M et al., Sci Rep. 2015 Dec 11;5:18046

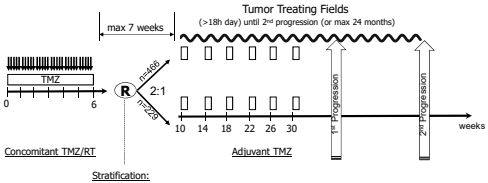
DELIVERY SYSTEM AND FIELD DISTRIBUTION

- TTFields are delivered to the supratentorial brain using a portable medical device
- The device includes:
  - a field generator
  - batteries and power supply
  - four transducer arrays at a time
- Following EF-14 termination a second generation device is available
  - half size and weight of gen 1
  - device with battery weigh 2.7 lbs



•Miranda PC et al., Phys Med Biol.; 2014; 59(15): 4137–4147

EF14: TREATMENT SCHEME & STUDY DESIGN



Stratification:
Resection: complete *vs* parital *vs* biopsy
MGMT methylation status

•Stupp R et al., JAMA; 2015; 314:2535-43

ENDPOINTS & STATISTICAL CONSIDERATIONS

Primary:
- Progression-free survival
  - blinded central radiology review
  - 80% power; p=0.05; HR = 0.78

Secondary:
- Overall survival
  - Only if PFS positive
  - 80% power; p=0.05; HR=0.76
- PFS6
- Landmark survival rates every 12 months
- Quality of life

- Randomization 2 : 1
- 700 patients / 4 yrs
  - (630 pts + 10% for lost to follow-up)
- Planned interim analysis
  - *Stupp et al. JAMA Dec 2015*
- **Final analysis**
  - PFS - stratified Log Rank test
    - *P* <0.04574 (*at final analysis)
  - **OS – stratified log Rank test**
    - ***P* <0.0481 (*at final analysis)**
- **All results presented as**
  - **ITT** (intent-to-treat)

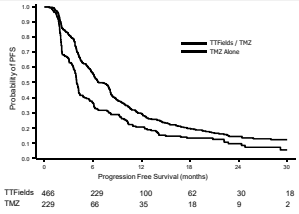
**Based on the Lan-DeMets – O'Brien-Fleming method*

SAFETY (GRADE 3-4 AES) IN ≥ 2% OF PATIENTS

	TTFields / TMZ (N=456)		TMZ Alone (N=216)	
System Organ Class \ Preferred Term	Grade 3	Grade 4	Grade 3	Grade 4
Number of Patients with >=1 AE	37%	14%	36%	12%
Blood and lymphatic system disorders	9%	4%	9%	2%
Leukopenia	2%	0	<1%	0
Lymphopenia	3%	1%	3%	0
Neutropenia	2%	1%	1%	<1%
Thrombocytopenia	6%	3%	4%	1%
Gastrointestinal disorders	5%	<1%	3%	<1%
General disorders + administration site conditions	9%	<1%	6%	0
Asthenia	3%	0	1%	0
Fatigue	4%	0	3%	0
Gait disturbance	2%	0	1%	0
Infections and infestations	7%	<1%	4%	1%
Injury, poisoning and procedural complications	5%	0	3%	0
Fall	2%	0	1%	0
Medical device site reaction	2%†	0	0	0

†: Grade 1+2 skin irritations in 52% of patients

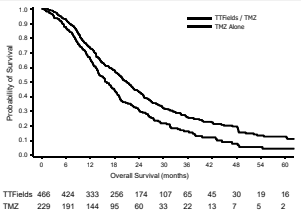
PROGRESSION FREE SURVIVAL - ITT *(n = 695)*



TTFields	466	229	100	62	30	18	
TMZ	229	66	35	18	9	2	

Progr.-free	TTFields/TMZ	TMZ
Median	6.7 mo 6.1 – 8.1	4.0mo 3.8 – 4.4
Hazard ratio	0.63 (CI 0.52 – 0.76)	
P-value	0.00005	
PFS from diagnosis:		
Median	11.2 mo 10.0 – 11.8	7.8mo 7.3 – 8.2

OVERALL SURVIVAL - ITT *(n = 695)*



TTFields	466	424	333	256	174	107	65	45	30	19	16
TMZ	229	191	144	95	60	33	22	13	7	5	2

Survival (from random)	TTFields/TMZ	TMZ
Median 95% CI	20.9 mo 19 .3 – 22.7	16.0 mo 14.0 – 18.4
2-year 95% CI	43.1 % (38.7 – 48.0)	30.7 % (25.1 – 37.5)
Hazard ratio	0.63 (CI 0.53 – 0.76)	
P-value	0.00006	
Survival from diagnosis (I):		
Median 95% CI	24.5 mo 22.8 – 26.3	19.8 mo 17.6 22.1

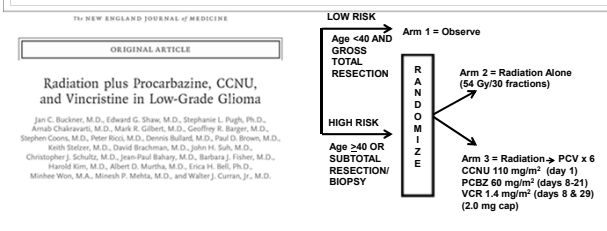
SUBGROUP ANALYSIS FOR OS

Subgroup	No. of Patients (%)	Hazard Ratio	Median Survival (months) Optune + TMZ	TMZ Alone
Overall	695 (100)		20.9	16.0
MGMT (central)				
→ **Unmethylated**	304 (44)		16.9	14.7
Methylated	214 (31)		31.6	21.2
Resection				
→ **Biopsy**	89 (13)		16.5	11.6
Partial	234 (34)		21.4	15.1
Gross total	372 (53)		22.6	18.5
Age				
<65 y	583 (84)		21.6	17.1
→ **65+ y**	112 (16)		16.0	10.9
KPS				
90-100	457 (67)		23.3	17.8
≤80	228 (33)		14.9	11.0
Gender				
Female	222 (32)		24.6	18.5
Male	473 (68)		19.1	15.5

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0 1.1 1.2

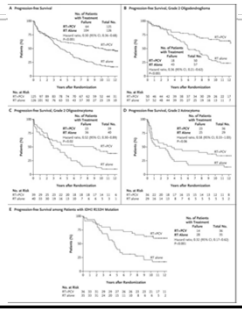
Optune + TMZ Better | TMZ Alone Better

SCHEMA



LOW RISK
Age <40 AND GROSS TOTAL RESECTION
Arm 1 = Observe
HIGH RISK
Age >40 OR SUBTOTAL RESECTION/ BIOPSY
RANDOMIZE
Arm 2 = Radiation Alone (54 Gy/30 fractions)
Arm 3 = Radiation → PCV x 6
CCNU 110 mg/m² (day 1)
PCBZ 60 mg/m² (days 8-21)
VCR 1.4 mg/m² (days 8 & 29)
(2.0 mg cap)

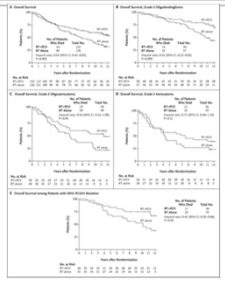
PROGRESSION FREE SURVIVAL ON 98-02



The addition of PCV to radiation treatment improved progression-free survival in all subtypes of grade II gliomas:
1.Oligodendroglioma
2.Oligoastrocytoma (no longer a diagnosis)
3.Astrocytoma

IDH mutations also predicted for improved benefit with combination therapy

OVERALL SURVIVAL ON 98-02



The addition of PCV to radiation treatment improved survival in all subtypes of grade II gliomas:
1.Oligodendroglioma
2.Oligoastrocytoma
3.Astrocytoma

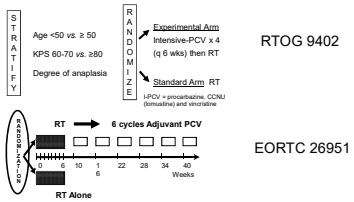
IDH mutations also predicted for improved benefit with combination therapy

- **The addition of PCV chemotherapy to radiation improves both progression-free and overall survival**
- **This impact was even more pronounced in tumors with mutation in the IDH-1 gene**
- **Although this study confirms the benefit of combined radiation and chemotherapy for low grade gliomas, it is not known if temozolomide will work as well as PCV**

RANDOMIZED TRIALS EVALUATING TREATMENT FOR NEWLY DIAGNOSED ANAPLASTIC OLIGODENDROGLIOMA

- Two randomized trials comparing radiation and chemotherapy with radiation alone in anaplastic oligodendroglial tumors
- Large, prospective trials:
  - RT vs PCV then RT (RTOG)
  - RT vs RT then PCV (EORTC)

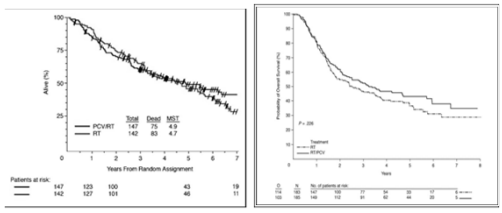
STUDY SCHEMAS



RTOG 9402

EORTC 26951

INITIAL RESULTS (2006) OS

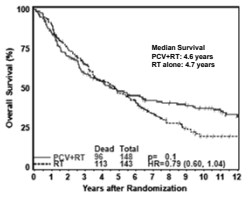


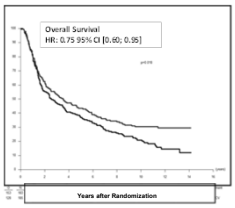
RTOG 94-02 **EORTC 26951**

LONG-TERM FOLLOW UP

- Maturation of outcome data
  - Median survival for 1p 19 q co-deleted cohorts not reached in initial reports (2006)
- Major effort to obtain missing tumor samples to improve statistical power for 1p 19q subgroups
  - RTOG (2006) 70% → 90%
  - EORTC overall 86%

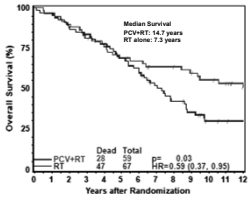
CURRENT RESULTS: ALL PATIENTS

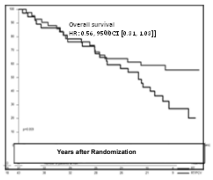




RTOG 94-02 **EORTC 26951**

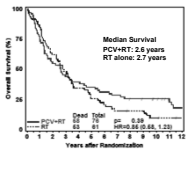
CURRENT RESULTS: 1P 19Q CO-DELETED

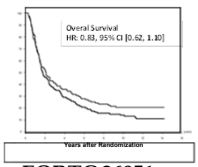




RTOG 94-02 **EORTC 26951**

CURRENT RESULTS: 1P 19Q NOT-CODELETED





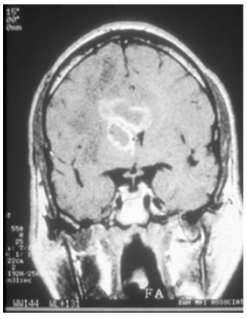
RTOG 94-02 **EORTC 26951**

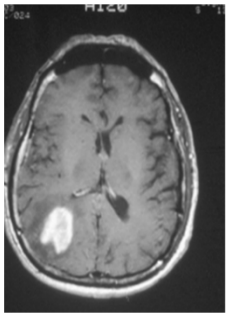
CONCLUSIONS

- Long term results of two cooperative group phase III trials determine radiation and chemotherapy as the new standard of care for newly diagnosed anaplastic oligodendroglioma with 1p 19q loss.
  - Perseverance in data and tumor collection
- Establishes 1p 19q loss as a predictive marker in addition to a prognostic marker
  - Underscores importance of prospective tumor collection and hypothesis-based clinical trials.

PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA (PCNSL)

- Neurologic Involvement of the CNS in systemic NHL: 5-29%
- PCNSL accounts for 1-2% of NHL
- Large increase in incidence for both population at risk:
  - Immunocompetent
  - Immunocompromised
    - Aids
    - Organ allograft recipients
    - Congenital
- Focal Lesion most common presentation: others include diffuse, uveal, leptomeningeal, and intramedullary.
- Infiltrates normal brain diffusely.
- Spreads along CSF pathways.
- Rarely spreads outside the CNS.



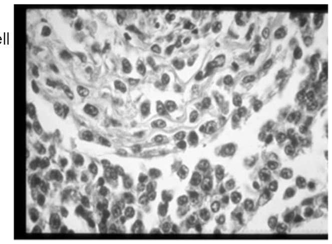


PCNSL: DIAGNOSIS/STAGING

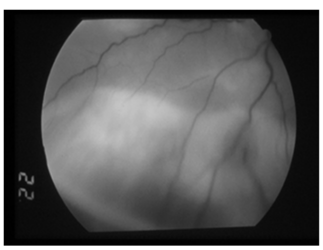
- Lumbar Puncture (if safe)
  - 80% of patients have a CSF pleocytosis
  - < 10% have obvious lymphomatous involvement of CSF.
- Surgery: diagnosis, little data to support resection
- CNS Axis staging:
  - Spinal evaluation (MRI)
  - Ophthalmic Slit Lamp Examination
    - 10-20% of patients develop lymphomatous uveitis.
- Systemic staging
  - Physical exam, CxR, bloods
    - ? Utility of BM bx, body CT scans, gallium scans

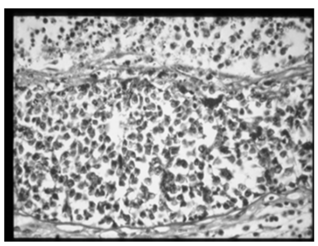
PCNSL: HISTOLOGY

- Most are diffuse large B-cell lymphoma (>90%)
- Rarely Burkitt, low grade or T cell
- B cell with three molecular subgroups
  - B-cell like
  - Activated B-cell like
  - Type 3
- NfkappaB activation in B cell subtype



OCULAR INVOLVEMENT





PRIMARY CNS LYMPHOMA TREATMENT

Radiotherapy

- Historically standard Tx
- 80% radiographic CR
- Recurrence local +/- CSA
- 14-18 month median survival
- Associated with significant neurotoxicity in patients over 60

Chemotherapy

- Chemotherapy appears much more effective in non-irradiated tumors.
- Typical DNHL treatment regimens are not optimal
- BBB crossing agents (e.g. methotrexate, cytarabine, topotecan, temozolomide) seem to be best
- Rituxan also has activity.
- Glucocorticoids gives response rates up to 40%:
  - Direct lympholoxic effect
  - **Can obscure diagnosis**

PCNSL:PRE-RADIATION CHEMOTHERAPY

	# Pts	Age	Chemotherapy	Response	Radiation (cGy)	Survival (mo)
RMH:	10	53	MACOP-B	90% CR	4000-1500	14
MGH:	13	62	hdMTX	69% CR	3000	27+
OHSU:	39	56	CTX/MTX/PCB +BBBD	85% CR	0 or 5000	41
MSKCC:	31	58	Hd/tMTX/araC	77% PR	4000-1440	42.5
RTOG: (88-06)	51	60	CHOP		4140+1440	16.1
Blay:	25	51	COP/COPADEM	56% CR	2000+2000	70% 5yr

Table 1. Prospective Upfront Treatment Trials in Primary CNS Lymphoma

First Author	Year	Agents	No. of Patients	Median Age (years)	ORR, PR+CR (%)	Median PFS (months)	Median OS (months)
Radiation only							
Nelson[23]	1992	RT(40+20 boost)	41	NR	21/26 (80)	NR	12.2
Chemoradiation							
DeAngelis[25]	1992	M(1)+RT(40+14 boost)+AraC(3)	31	58	27/31 (87)	41	42.5
Glass[26]	1994	M(3.5)+RT(30-40)	25	56	23/25 (90)	32	33
Schultz[27]	1996	CHOP+RT(41.4+18 boost)	52	NR	10/52 (19)	9.2	16.1
O'Neill[28]	1999	CHOP+RT(50.4) + AraC	55	60	32/53 (60)	6.7	9.7
Mead[29]	2000	RT(40+14 boost)±CHOP	53	57	NR	10 v 22	NR
O'Brien[30]	2000	M(1)+RT(45+5.4 boost)	46	58	44/46 (96)	NR	33
Abrey[31]	2000	M(3.5)+P(100)+V(1.4)+AraC(3)+IT M+IT A+RT(45)	52	65	49/52 (94)	NR	60
Ferreri[32]	2001	M(3)+P(100)+V(1.4)+AraC(3)+ RT(45)	13	54	12/13 (92)	18	≥ 25
DeAngelis[33]	2002	M(2.5)+V(1.4)+P(100)+AraC(3)+IT M+RT(45 Gy)	102 (98 treated)	56.5	47/50 (94)	24	37
Poortmans[34]	2003	M(3)+Ten(100)+B(100)+pred(60)+ IT M+IT A+RT(40)	52	51	42/52(81)	NR	46
Ferreri[35]	2009	M(3.5)+/−AraC(2)+RT(45)	79	59/58	27/39 (69) v 16/40 (40)	3 v 18	NR
Thiel[7]	2010	M(3;+ifos)±RT(45)	526 (all)/318 (PPP)	61	283/526 (53)	18.3 v 11.9	32.4 v 37.1
Morris[36]	2013	R(500)+M(3.5)+V(1.4)+P(100)+ RT(23.4)	52	60	41/52 (78)	92.4	Not reached
Glass[37]	2016	R(375)+M(3.5)+T(100)+RT(36)	66	57	30/35 (86)	63	90
Chemo only							
Herlinger[38]	2005	M(8)	37	60	13/37 (35)	10	25
Batchelor[5]	2003	M(8)	25	60	17/23 (74)	12.8	22.8+
Pels[39]	2003	M(5)+AraC(3)+V(2)+ifos(800)+ dex(10)+cyclo(200)+IT M+IT A+IT P	65	62	43/61 (71)	21	50
Rubinstein[40]	2013	R(375)+M(8)+T(150)+AraC(2) + eto(40)	44	61	34/47(72)	48	Not reached
Ferreri[41]	2016	M(3.5)+AraC(2)±R(375)±thio (30)	227	58/57/57	40/75 (53)/51/69 (73)/65/75 (86)	6/20/not reached	12/30/not reached
Omuro[61]	2015	M(3.5)+V(1.4)+P(100)+AraC(3) v M(3.5)+T(150)	95	72/73	37/45 (82) v 34/42 (74)	9.5 v 6.1	31 v 14
Chemo only with SCT							
Abrey[43]	2003	M(3.5)+AraC(3); BEAM	28 (14 transplanted)	53	induction: 16/24 (67), SCT 11/14 (77)	5.6	Not reached
Colombat[44]	2006	M(3)+B(100)+eto(100)+pred (60); BEAM+RT(30)	25 (17 transplanted)	52	induction: 21/25 (84), SCT 16/16 (100)	40	Not reached
Illerhaus[45]	2006	M(8)+AraC(3)+thio (40 mg/m2); B(400)+thio(5mg/kg)+RT(45)	30 (23 transplanted)	54	induction: 21/30 (70), SCT 21/21 (100)	NR	Not reached
Omuro[42]	2015	R(500)+M(3.5)+V(1.4)+P(100); thio(250)+cyclo(60)+bus(3.2)	32 (26 transplanted)	57	induction: 31/32 (97), SCT 24/26 (92)	Not reached	Not reached
Illerhaus[46]	2016	R(375)+M(8)+AraC(3)+thio(40); R(375)+B(400)+thio(5mg/kg)	79 (73 transplanted)	56	induction: 73/79 (92), SCT: 72/79 (91)	74	Not reached

Abbreviations: A, cytarabine; AraC, cytarabine (g/m²); B, carmustine (mg/m²); BEAM, carmustine, etoposide, cytarabine, melphalan; bus, busulfan (mg/kg); chemo, chemotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete remission; cyclo, cyclophosphamide (mg/m²); dex, dexamethasone; eto, etoposide (mg/m²); ifos, ifosfamide (mg/m²); IT A, intrathecal cytarabine; IT M, intrathecal methotrexate; IT P, intrathecal prednisone; M, methotrexate (g/m²); NR, not reported; ORR, overall response rate; OS, overall survival; P, procarbazine (mg/m²/day); PFS, progression-free survival; PPP, per-protocol population; PR, partial remission; pred, methylprednisone (mg/m²); R, rituximab (mg/m²); RT, radiation therapy (dose used in Gy); SCT, stem cell transplant; T, temozolomide (mg/m²); Ten, teniposide (mg/m²); thio, thiotepa (mg/m²); V, vincristine (mg/m²).

Table 2. Salvage Regimen in Primary CNS Lymphoma

First author	Year	Agents	No. of Patients	Median Age (years)	ORR, PR+CR (%)	Median PFS (months)	Median OS (months)
Retrospective							
Herrlinger[70]	2000	PCV	7	57	6/7 (86)	NR	39
Arellano-Rodrigo[71]	2003	Eto+Ifos+AraC	16	54	6/16 (37)	4.5	6
Wong[72]	2004	Ritux+temozolomide	7	64	7/7 (100)	6	8
Enting[73]	2004	Ritux+temozolomide	15	69	8/15 (53)	2.2	13.6
Plotkin[74]	2004	HD-MTX	22	58	20/22 (91)	25.8	61.9
Nguyen[75]	2005	WBRT	27	66.8	20/27 (74)	9.7	10.9
Hottinger[76]	2007	WBRT	48	62	39/48 (79)	10	16
Makino[77]	2012	Temozolomide	17	68	8/17 (47)	1.9	6.7
Wong[78]	2012	Temozolomide	7	58	1/7 (14)	2	4
Zhang[79]	2013	Pemetrexed	30 (18 PCNSL)	67	18/30 (60)	4.1	22.6
Pentsova[80]	2014	HD-MTX	39	66	33/39 (85)	16	41
Chamberlain[81]	2014	Bendamustine	12	61.5	6/12 (50)	3.5	5
Houillier[82]	2015	Lenalidomide	6	73.5	3/6 (50)	1.5	2.5
Chamberlain[83]	2016	AraC	14	60	5/14 (36)	3	12
Prospective							
Fischer[84]	2006	Topotecan	27	51	9/27 (33)	2	8.4
Reni[85]	2007	Temozolomide	36	60	11/36 (31)	2.8	3.9
Soussain[86]	2008	CYVE+SCT	43	52	20/40 (50)	11.6	18.3
Batchelor[87]	2011	Ritux	12	64	5/12 (42)	1.9 (57 days)	20.9
Raizer[88]	2012	Pemetrexed	11	69.8	6/11 (55)	5.7	10.1
Rubenstein[89]	2013	IT Ritux+IT M	14 (6 PCNSL)	61	6/14 (43)	1.2	NR
Nayak[90]	2013	Ritux+temozolomide+pred	16	63	5/14 (36)	1.6 (7 weeks)	Not reached
Korfel[91]	2016	Temsirolimus	37	70	20/37 (54)	2.1	3.7

Abbreviations: AraC, cytarabine; CYVE, cytarabine plus etoposide; CR, complete response; eto, etoposide; HD-MTX, high-dose methotrexate; ifos, ifosfamide; IT M, intrathecal methotrexate; IT Ritux, intrathecal rituximab; NR, not reported; ORR, overall response rate; OS, overall survival; PCNSL, primary CNS lymphoma; PCV, procarbazine, CCNU (lomustine, bleomycin, vinblastine, dexamethasone), vincristine; PFS, progression-free survival; PR, partial response; pred, methylprednisone; Ritux, rituximab; SCT, stem cell transplant; WBRT, whole-brain radiation.

PCNSL: HIGH-DOSE METHOTREXATE

- Most active single agent.
- Anti-tumor activity related to concentration and exposure time of drug.
- Treating CNS disease with methotrexate gives large therapeutic window since the BBB is probably not permeable to reduced folates (leucovorin).
- Optimal dose and administration schedule for PCNSL not determined.
  - Currently bolus injection given over 2-3 hours is most commonly utilized.
  - Most commonly utilized doses are 3-8 gms/m2 every 2-3 wks
- Various studies report response rates for single agent MTX to be 52-88% with 2 year survivals of 58-72%.
- Various studies report response rates for methotrexate in combination with other agents of 70-94% with 2 year survivals of 43-73%.

TWO ACTIVE PCNSL REGIMENS STUDIED BY NCI COOPERATIVE GROUPS

RTOG 93-10
The "MSKCC Regimen"

- 5 cycles MTX (2.5 gms/m2)/vincristine procarbazine/intraventricular MTX followed by whole brain XRT
- 102 patients
- Following chemotherapy: 58% CR, 36% PR
- 24 month median PFS
- 36.8 month median survival
- Age a significant prognostic factor (survival 50.4 months pts < 60 y.o.; 21.8 months pts > 60 y.o.)
- Significant acute treatment-related toxicity (53% grade 3 or 4)
- Significant severe delayed neurotoxicity (15%)

NABTT 96-07

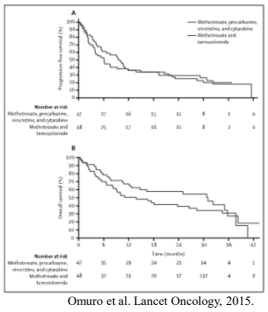
- hdMTX (8 gms/m2) every 2 weeks until CR or a maximum of 8 cycles. XRT delayed
- 25 patients
- 53% CR; 22% PR
- Median # cycles to CR was 6
- 12.8 months median PFS.
- 22.8+(not yet reached) months median survival
- 4/5 CR for intra-ocular lymphomas
- 2/3 LMD (+ CSF cytology) progressed in brain during MTX tx
- Significant acute treatment-related toxicity (48% grade 3 or 4)
- No delayed severe neurotoxicity

THE R-MVP REGIMEN: THE CURRENT STANDARD

- Multicenter phase 2 trial
- Rituximab, MTX, PCB,VCR,WBRT(either 23.4 Gy or 45 Gy) followed by Hi-DAC.
- 52 pts; med. Age 60, KPS 70
- 60% CR with R-MVP
- PFS = 3.3 yrs; Overall Survival 6.6 yrs.
- Improved executive function and memory post R-MVP. Remained relatively stable long-term.

MPV-A VS. MT IN ELDERLY PATIENTS WITH PCNSL

- > 60 y.o.
- KPS > 40
- Prophylactic G-CSF
- ORR: MPV-A (82% vs. 72%)
- PFS: MPV-A 9.5 vs 6.1 months
- OS: MVP-A (31 vs.14 months)



Omuro et al. Lancet Oncology, 2015.

CONSOLIDATION DOSE INTENSIVE CHEMOTHERAPY AND ASCT FOR PCNSL

Table 5. Trials or case series (20 or more patients) reporting outcomes in newly diagnosed PCNSL patients treated with consolidation HDC-ASCT after methotrexate-based initial treatment

Reference	N	Induction regimen	ORR to induction	HDC-ASCT regimen	Received consolidation HDC-ASCT	Received consolidation WBRT*	ORR to HDC-ASCT	Med F/u (mo)	ITT 3-y PFS	ITT 3-y OS
Regimens including WBRT to all patients										
29	30	MTX 8 g/m², Ara-C, thiotepa	80%	BCNU, thiotepa + WBRT	23 (77%)	21 (70%)	100%	63	na	69%
33	25	MTX 3 g/m², BCNU, VP-16, methylpred	94%	BEAM + WBRT	17 (68%)	24 (96%)	100%	34	58%	64%
Regimens with WBRT to patients achieving less than CR										
34	28	MTX 8 g/m²	61%	Busulfan, thiotepa + WBRT if no CR	16 (70%)	8 (29%)	69%	15	45%	48% (2 y)
Regimens without WBRT										
17	28	MTX 3.5 g/m², Ara-C	57%	BEAM	14 (50%)	0	77%	28	25%	60%
This study	32	MTX 3.5 g/m², rituximab, procarbazine, vincristine	97%	Thiotepa, busulfan, CTX	26 (81%)	0	82%	45	79%	81%

*Number of patients who received WBRT as part of initial treatment, in the absence of tumor progression.
Ara-C, cytarabine; CTX, cyclophosphamide; Med F/u, median follow-up; methylpred, methylprednisolone; MTX, methotrexate; na, not available; ORR, objective response rate; VP-16, etoposide.

High morbidity rate
May be best for younger pts
Good perf. status

Omuro et al. Blood, 2015.

PCNSL: UNIQUE FEATURES

Leptomeningeal Disease

- 5-30% have evidence of LMD at presentation.
- 40-50% of patients will have pathologic evidence of PCNSL invading the subarachnoid space.
- Majority of patients who relapse in the eptomeninges had evidence of LMD at presentation
- 90% of patients who relapse in the leptomeninges, also relapse in the brain parenchyma
  - Does treating LMD really change the overall prognosis of patients with PCNSL?

Ophthalmologic Involvement

- Untreated intraocular lymphoma will ultimately lead to CNS disease in the majority of patients.
- XRT associated with significant long-term morbidity
- Blood-eye barrier possibly more formidable than BBB.
- Systemic hdMTX can achieve lymphotoxic concentrations of MTX in the vitreous/aqueous humor
- Intra-ocular injection of MTX can temporarily eradicate disease and greatly improve vision.
  - ? No perspective study
  - No long-term follow-up

CHEMOTHERAPY FOR PCNSL: WHAT WE DO NOT KNOW

- **The role of XRT in conjunction with chemotherapy**
- Optimal dose and administration schedule for MTX
- Other agents add to the effectiveness of MTX
  - What agents
  - What dose and administration schedule
- Role of dose intense chemotherapy (ABMT)
- Is there a role for BBBD?
- Should the presence of overt leptomeningeal and/or intraocular disease change treatment approach.

- New agents undergoing evaluation:
  - Lenalidomide
  - Ibrutinib
  - Buparlisib
  - Nivolumab/pembrolizumab
  - Pemetrexed
  - Pomalidomide
  - Temsirolimus

PCNSL: CURRENT TREATMENT RECOMMENDATIONS

- **Most patients should receive pre-radiation chemotherapy with a regimen that at least contains high-dose methotrexate.**
- **Radiation therapy following chemotherapy may improve survival further; although at the risk of significant long term neurotoxicity.**
- **Older (>70 y.o…?) patients should probably not receive combined modality treatment or at least not full dose WBRT.**
  - **Methotrexate-based regimen optimal if medically appropriate**
  - **Methotrexate alone if combination not tolerable.**
  - **XRT alone for poor KPS patients who could not tolerate chemotherapy.**
- **Strongly encourage enrollment on a clinical trial.**

CONCLUSIONS AND "TAKE HOME" MESSAGES

- Malignant gliomas are staged by tumor grade, not TNM
- Key molecular features such as 1p19q LOH, IDH mutational status and MGMT methylation status assist in diagnosis, prognosis and treatment
- More precise diagnoses have enabled development of standard therapies for glioblastoma and IDH mutated tumors
- Standard of care for glioblastoma remains chemoradiation with temozolomide, but ongoing trials with immunotherapies, viral therapies and novel targeted agents hold promise
- Primary CNS lymphoma advances focus on combination chemotherapy regimens; ibrutinib and related agents may have a role; radiation should be delayed in older patients

54

Metastatic Disease to the Brain, Spine, Carcinomatous Meningitis

Mark Gilbert, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

54 – Metastatic Disease to the Brain, Spine, Carcinomatous Meningitis

Mark Gilbert, MD

Disclosures

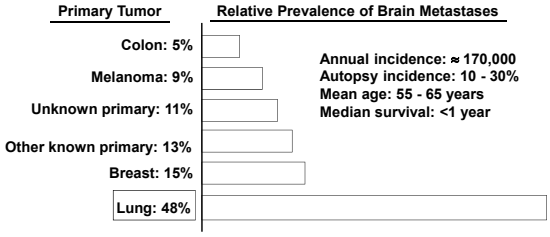
Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Brain Metastases Incidence

- **Incidence by histology dependent upon:**
  - **Incidence of cancer (lung, breast)**
  - **Predilection for brain (high in melanoma, small cell lung, low in prostate, GI cancers)**
  - **Ability to control primary neoplasm (pancreatic cancer is rare, breast cancer seen late in the illness)**
  - **Incidence increasing because of improving systemic treatment**
- Incidence increasing:
  - **Use of MRI / CT**
  - **Better systemic treatments leading to prolonged survival**
  - **Change in incidence of cancer types**
    - **Lung**
    - **Melanoma**

Epidemiology of Brain Metastases



Wen PY, et al. In: DeVita VT Jr, et al (eds). *Cancer: Principles & Practice of Oncology.* 2001:2656-2670.

Signs & Symptoms of Brain Metastases

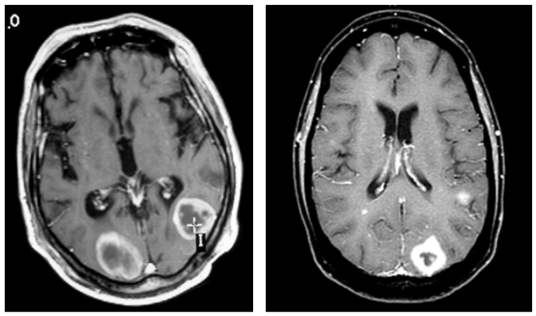
- **Signs**
  - **Hemiparesis (59%)**
  - **Cognitive problems (58%)**
  - **Hemisensory loss (21%)**
  - **Papilledema (20%)**
  - **Ataxia (19%)**
  - **Apraxia (18%)**
- **Symptoms**
  - **Headache (49%)**
  - **Mental problems (32%)**
  - **Focal weakness (30%)**
  - **Ataxia (21%)**
  - **Seizures (18%)**
  - **Speech problems (12%**

Posner, 1995

Brain Metastases Pathogenesis

- Hematogenous spread
  - **Most common; accounts for classic gray-white matter junction location**
- Leptomeningeal ⟶ parenchymal involvement
  - **Tumors adjacent to ventricles or in sulci**
- Direct extension
  - **Dural (uncommon)**

Pathogenesis of Brain Metastases



Brain Metastases: Hematogenous Origin

Brain Metastases: Leptomeningeal Origin

Evaluation of Response

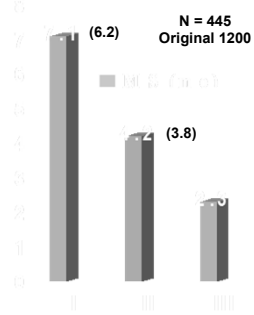
- Status of systemic cancer very important!
- Controversy re: measurement of response vs time to progression vs survival
  - Latest RTOG trial is using percent CR
- Importance of prognostic factors
  - Recursive partitioning analysis*
  - 3 prognostic groups:
    - Best: age <65, KPS > or = 70, controlled primary cancer
    - Worst: KPS < 70

Gaspar, 1997

RPA Class: Prognostic Classes

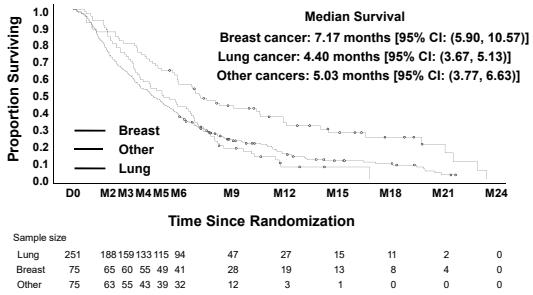
All brain metastases are not created equal

- Class I
  - <65, KPS ≥ 70,
  - Controlled primary
  - No extracranial mets
- Class II-Rest
- Class III-KPS <70



Gaspar, *IJROBP*, 47: 1001-6, 2000.
Gaspar, *IJROBP*, 37: 745-51, 1997.

Histology: Another Possible Prognostic Variable



Sample size												
Lung	251	188	159	133	115	94	47	27	15	11	2	0
Breast	75	65	60	55	49	41	28	19	13	8	4	0
Other	75	63	55	43	39	32	12	3	1	0	0	0

Mehta, JCO 2003.

Protocol PCI-P120-9801
Phase III Trial of Motexafin Gadolinium for Brain Metastases

Graded Prognostic Assessment (GPA) worksheet to estimate survival from brain metastases (BM) by diagnosis.

Non-small-cell and small-cell lung cancer	GPA Scoring Criteria			Patient
Prognostic Factor	0	0.5	1.0	Score
Age, years	> 60	50-60	< 50	___
KPS	< 70	70-80	90-100	___
ECM	Present	—	Absent	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8

Melanoma	GPA Scoring Criteria			Patient
Prognostic Factor	0	1.0	2.0	Score
KPS	< 70	70-80	90-100	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2

Breast cancer	GPA Scoring Criteria					Patient
Prognostic Factor	0	0.5	1.0	1.5	2.0	Score
KPS	≤ 50	60	70-80	90-100	n/a	___
Subtype	Basal	n/a	LumA	HER2	LumB	___
Age, years	≥ 60	< 60	n/a	n/a	n/a	___
Sum total						___

Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3

Renal cell carcinoma	GPA Scoring Criteria			Patient
Prognostic Factor	0	1.0	2.0	Score
KPS	< 70	70-80	90-100	___
No. of BM	> 3	2-3	1	___
Sum total				___

Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8

GI cancers	GPA Scoring Criteria					Patient
Prognostic Factor	0	1	2	3	4	Score
KPS	< 70	70	80	90	100	___

Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5

Sperduto P W et al. JCO 2012;30:419-425

JOURNAL OF CLINICAL ONCOLOGY

Brain Metastases Medical Management

- Corticosteroids
  - Minimum possible dose
  - Dexamethasone most commonly used
- Anticonvulsants
  - Usually reserved for patients with seizures
  - Prophylactic use discouraged although hemorrhagic tumors (melanoma, renal cell carcinoma, choriocarcinoma) are at highest risk
    - ➢Second generation anticonvulsants are now commonly used to avoid Cyp450 induction

Brain Metastases: Surgery, Radiotherapy, Radiosurgery

Brain Metastases Surgical Management

- Most studies support excision of solitary or single metastases
- Some support removal of 2 - 4 lesions
- Single lesion requires tissue sampling
- ? Radiosurgery efficacy consistent with resection for a single lesion

Surgery for Solitary or Single Brain Metastases

- Randomized trial*
  - **48 randomized patients**
  - **Most with lung cancer**
  - **Survival improved (40 vs 15 weeks) with surgery + XRT vs XRT alone**
  - **Improved local control rate**
  - **11% of patients did not have a metastatic lesion**

Patchell, et al. *N Engl J Med.* 1990;322:494.

Randomized Surgical Trials

Trial	Year	Rx	N	MS	FI	*P*-value
Patchell	90	S/RT	25	40	38	<0.01
		RT	23	15	8	
Noordijk	94	S/RT	32	43	34	0.04
		RT	31	26	21	
Mintz	96	S/RT	41	24	~	ns
		RT	43	27	~	
RTOG	*90*	*S/RT*	*25*	*55*		

59% of RT alone vs 79% of S+RT Improved or stabilized
22% of the S + RT vs 45% of RT alone pts failed in the brain

Surgery for 2 - 4 Metastases

- **Retrospective review of 26 patients with resection of multiple mets consistent with 26 similar patients with resected single mets**
- **Median survival at 1, 2, and 5 years was similar**
  - **Median: 14 months vs 14 months**
  - **1 year: 55 vs 50%**
  - **2 years: 32 vs 30%**
  - **5 years: 11 vs 166%**

Bindal, et al. *J Neurosurg.* 1993;79:210.

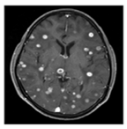
Early RTOG Brain Met Trials

Fractionation, schedule and dose are unimportant

Year	N	Gy / week	MS
71-73	227	40 / 4	16
	233	40 / 3	18
	217	30 / 3	18
	233	30 / 2	21
73-76	447	20 / 1	15
	228	30 / 2	15
	227	40 / 3	18
76-79	156	30 / 2	18
	153	50 / 4	17

WBRT: Strategies to minimize neurocognitive decline?

- **RTOG 0614:** phase III randomized, placebo-controlled study
- Placebo vs. Memantine 20 mg daily within 3 days of starting WBRT 37.5 Gy and continued for 24 weeks



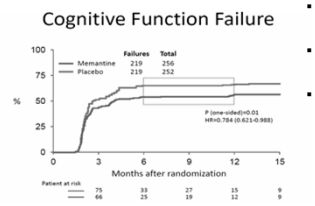
Cognitive domain	Measure
Memory	Hopkins Verbal Learning Test-Revised
Processing speed	Trail making test Part A
Executive function	Trail making test Part B, controlled oral word association
Global function	Mini-mental status examination
Cognitive function (self-report)	Medical outcomes scale – cognitive function scale
Quality of life	Fact-Br

MRI, Cognitive Assessment and QOL at Baseline, 8, 16, 24 and 52 weeks

Lauck NNI, et al. RTOG 0614. Presented at ASTRO 2012.
Brown PD, et al. Int J Rad Oncol Biol Phys 2012; 84 (3S): S1-S2.

Outcomes: RTOG 0614

- Primary endpoint: Reduced the decline in HVLT-R DR by 0.9 **(P=.059)** at 24 weeks



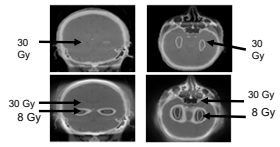
- 17% reduced relative risk of cognitive decline **(p=.01)**
- Delayed time to cognitive decline **(p=.01)**
- Reduced the rate of decline in cognitive, executive, and global function as well as processing speed **(p<.01)**

Lauck NNI, et al. RTOG 0614. Presented at ASTRO 2012.

Hippocampal Sparing during WBRT

Whole-brain radiotherapy

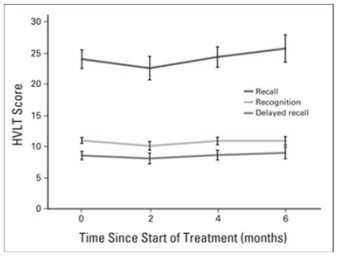
Hippocampal sparing whole-brain radiotherapy using intensity-modulated radiotherapy



- Preserve neurogenic fate of hippocampal neural stem cells.
- Preserve memory function after brain irradiation

Courtesy of Vinay Gondi (AAN 2019)

Hippocampal Sparing: RTOG 0933



Whole brain radiation
No evidence of neuro-cognitive decline
No increase in metastases in the hippocampus

Gondi JCO 2014

NRG-CC001: Phase III Trial Memantine and WBRT with or without Hippocampal Sparing in Patients with Brain Metastases

Basic Eligibility: Brain Mets 5mm outside hippocampus; KPS≥70; MRI scan

Brain Metastasis → Stratify (RPA, Prior Therapy) → Randomize
- WBRT + Memantine
- Hippocampal Sparing WBRT + Memantine

Sample Size: 518 patients

Primary endpt: Time to cognitive failure--HVLT-R, COWA, and TMT A and B

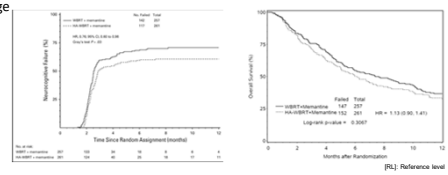
Basic Statistical Design:
Cognitive fxn failure Monthly HR = 0.129; Overall HR = 0.65 388 analyzable pts.

NRG ONCOLOGY™

NRG CC001: Primary Endpoint

- Hippocampal sparing prevents cognitive toxicity
  - 26% relative risk reduction
  - Effect of treatment persists regardless of age

Variable	HR	95% CI	*p* value
Treatment arm (HA-WBRT+Mem vs. WBRT+Mem[RL])	**0.74**	**0.58-0.95**	**0.020**
Age (≤61 vs. >61[RL])	**0.60**	**0.46-0.79**	**0.0002**
RPA Class* (I vs. II[RL])	1.35	0.97-1.86	0.072
Prior radiosurgery* (No vs. Yes[RL])	0.81	0.62-1.08	0.15
Prior surgery* (No vs. Yes[RL])	1.1	0.84-1.44	0.49



[RL]: Reference level

NRG ONCOLOGY™

Brown PD et al JCO 2020

Rationale for Radiosurgery

If surgery works, so should radiosurgery

- Spherical / pseudospherical
- Most <4 cm
- Generally non-infiltrative
- Grey-White location ("non-eloquent")
- Improved local control = better survival
- Need higher doses for local control
- Potential dose-response relationship

RTOG 9508: Phase III Trial

Enrollment: 1/96-6/01: 331 pts

Arm 1: WBRT + SRS: 164

≤ 2 cm	24 Gy
2.1 – 3.0 cm	18 Gy
3.1 – 4.0 cm	15 Gy

Arm 2: WBRT (37.5 Gy) alone: 167

Stratification:

1. **Number of brain metastases (1 vs 2 - 3)**
2. **Extracranial mets (none vs present)**

15 & 24% of 1 & 2-3 brain met pts randomized to RS did not receive it

Based on RTOG Phase I 9005
Shaw E. *Int J Radiat Oncol Biol Phys.* 200;47: 291-298.

RTOG 9508: Patient Characteristics

Trait	WBRT	+RS
Lung Cancer	63%	64%
RPA I	73%	72%
Primary controlled	75%	77%
Brain only met	31%	32%
Single brain met	56%	56%

RTOG 9508: Subset Analysis

Selected subsets benefit from radiosurgery

Survival Analyses	WBRT & SRS	WBRT	*P*-value
Overall	6.5 mos	5.7 mos	0.13
Solitary brain met	6.5 mos	4.9 mos	0.04
1-3 mets & Age < 50	9.9 mos	8.3 mos	0.04
1-3 mets & NSCLC	5.9 mos	3.9 mos	0.05
1-3 mets & RPA Class 1	11.6 mos	9.6 mos	0.05

Sperduto, ASTRO 2002.

Stereotactic Radiosurgery +/- Whole Brain Radiation

- JROSG 99-1
  - Patients with 1-4 brain mets
  - SRS (n = 67) vs SRS + WBRT (n = 65)
  - OS 8.0 vs 7.5 months
  - Met recurrence 76% vs 47% at 12 months
  - SRS alone salvaged with WBRT
  - Function improved with SRS + WBRT using MMSE

Aoyama et al Int J Radiat Oncol Biol Phys 2007

Stereotactic Radiosurgery +/- Whole Brain Radiation

- MD Anderson Study
  - Patients with 1-3 brain mets
  - SRS (n = 30) vs SRS + WBRT (n = 28)
  - Survival shorter with SRS alone, higher incidence of distant brain mets (73% vs 27%)
  - However, neurocognitive decline more prominent by HVLT at 4 months post treatment with SRS + WBRT

Chang et al Lancet Oncol 2009

Stereotactic Radiosurgery +/- Whole Brain Radiation

- EORTC 22952-26001
  - SRS or surgical resection (n= 179) vs focal treatment + WBRT (n = 180)
  - No difference in duration of functional preservation or overall survival
  - Decreased intracranial relapse with combination treatment

Kocher et al J Clin Oncol 2011

Adjuvant WBRT After SRS

	#	Local Control	Distant Brain Control	Median OS
EORTC SRS	199	69%	52%	10.9 m
+WBRT		**81%**	**67%**	**10.9m**
JAPAN SRS	132	73%	36%	8m
+WBRT		**89%**	**58%**	**7.5m**
MDACC SRS	58	67%	45%	15.2m
+WBRT		**100%**	**73%**	**15.7m**

No improvement in overall survival

Kocher JCO 2010
Aoyama JAMA 2006
Chang Lancet Oncol 2009

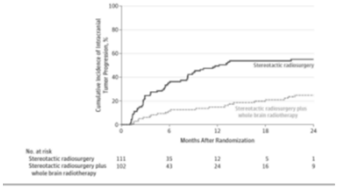
JAMA

Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases
A Randomized Clinical Trial

2016;316:406

- 213 pts with 1-3 brain metastases randomized to SRS or SRS+WBRT

Figure 2. Cumulative Incidence of Brain Tumor Progression (Local and/or Distant) After Correcting for the Competing Risk of Survival According to Treatment Group



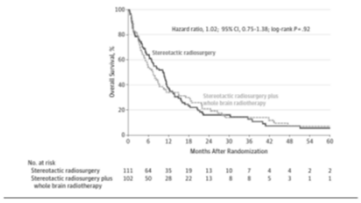
JAMA

Effect of Radiosurgery Alone vs Radiosurgery With Whole Brain Radiation Therapy on Cognitive Function in Patients With 1 to 3 Brain Metastases
A Randomized Clinical Trial

2016;316:406

- Less cognitive deterioration at 3 months after stereotactic radiosurgery alone (64%) than after SRS + WBRT (92%), (P=0.007)
- Less cognitive deterioration at 12 months after stereotactic radiosurgery alone (60%) than after SRS + WBRT (94.4%), (P=0.04)
- **In patients with 1 to 3 brain metastases, SRS alone may be the preferred strategy**

Figure 3. Kaplan-Meier Estimates of Overall Survival According to Treatment Group

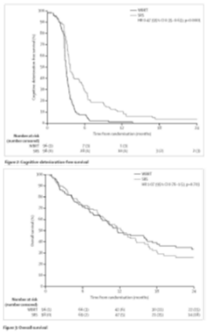


Stereotactic Radiosurgery +/- Whole Brain Radiation

- No clear winner or standard of care
- If only focal treatment provided (surgery or SRS) careful follow up is required
- Outcomes may be best with focal treatment with single or solitary metastases

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial

- 194 patients randomized to post-op SRS or WBRT
- Cognitive-deterioration-free survival was longer in patients assigned to SRS (median 3·7 m) than in patients assigned to WBRT (median 3·0 m) [hazard ratio [HR] 0·47; p<0·0001)
- Cognitive deterioration at 6 months less with SRS (52%) than those who received WBRT (85%) p<0·00031)
- No difference in median overall survival
- After resection of a brain metastasis, SRS should be considered one of the standards of care as a less toxic alternative to WBRT



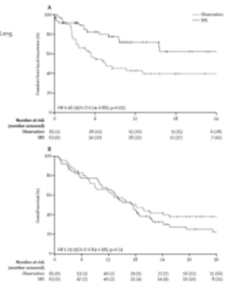
Metastatic Disease to the Brain, Spine, Carcinomatous Meningitis

Mark Gilbert, MD

Tuesday, August 18, 2020

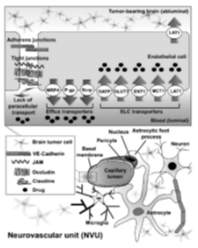
Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial

Lancet Oncol 2017



- 132 patients were randomized to the observation or post-op SRS
- 12-month freedom from local recurrence was 43% in the observation group and 72% in the SRS group (hazard ratio 0·46 p=0·015)
- SRS of the surgical cavity in patients who have had complete resection of 1-3 brain metastases significantly lowers local recurrence compared with that noted for observation alone

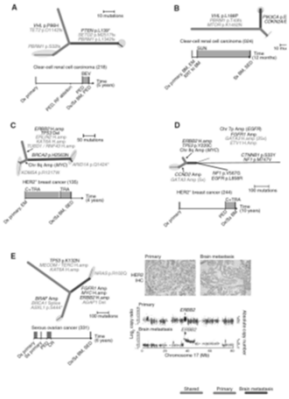
Medical Therapies For Brain Metastases



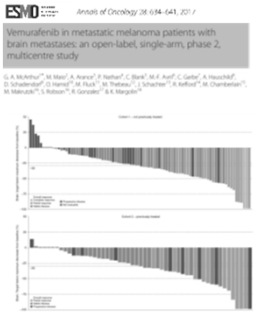
Kim et al., Pharm Res 2018;35:177

- Blood-brain barrier
- Pathogenesis of brain metastases
- Lack of effective chemotherapy agents
- Extensive prior treatment
- Concurrent systemic disease
- Measurement of response/efficacy

Cancer Discovery 2015

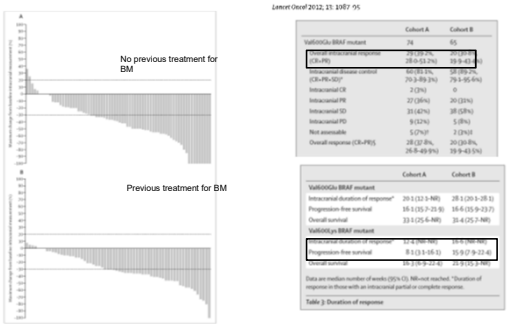


- **53% of brain metastases have genetically distinct molecular drivers compared to primary tumor**
- Little intralesional heterogeneity
- Molecular drivers in different metastases in the same patient are relatively similar
- Evidence of upregulation of PI3Kinase and CDK pathways



- 146 patients were treated
  - Cohort 1 (untreated)-90
  - Cohort 2 (previously treated)-56
- **Intracranial BORR:**
  - Cohort 1 by IRC was **18% (2 CRs, 14 PRs)**
- **Median PFS** (brain only, investigator-assessed) was **3.7** months in cohort 1 and 4.0 months in cohort 2
- **Median OS** was 8.9 months in cohort 1 and 9.6 months in cohort 2

Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial



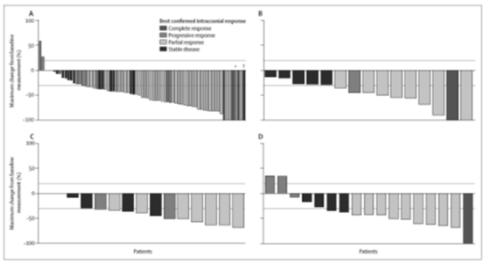
Dabrafenib plus trametinib in patients with BRAF^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Lancet Oncol 2017; 18: 863-73

- Multicenter, multicohort, open-label phase II study
- Dabrafenib 150mg bid and trematinib 2mg qd
  - Group A (76pt) : BRAFv600E +ve, asymptomatic melanoma BM, no previous local brain therapy, ECOG 0 or 1
    - **Overall intracranial response (CR+PR=58%)**
  - Group B (16 pt): BRAFv600E +ve, asymptomatic melanoma BM, previous local brain therapy, ECOG 0 or 1
    - **Overall intracranial response (CR+PR=56%)**
  - Group C (16 pt): BRAFv600D/K/R +ve, asymptomatic melanoma BM, with or without previous brain therapy, ECOG 0 or 1
    - **Overall intracranial response (CR+PR=44%)**
  - Group D (17 pt): BRAFv600D/E/K/R +ve, symptomatic melanoma BM, with or without previous brain therapy, ECOG 0,1 or 2
    - **Overall intracranial response (CR+PR=59%)**

Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Lancet Oncol 2017; 18: 863-73



Dabrafenib plus trametinib in patients with *BRAF*^{V600}-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial

Lancet Oncol 2017; 18: 863-73

	Cohort A (n=76)	Cohort B (n=16)	Cohort C (n=16)	Cohort D (n=17)
Intracranial duration of response				
Events	29/44 (66%)	6/9 (67%)	4/7 (57%)	8/10 (80%)
Median (95% CI; months)	6·5 (4·9-10·3)	7·3 (3·6-12·6)	8·3 (1·3-15·0)	4·5 (2·8-5·9)
Response at 6 months	63% (45-76)	73% (28-93)	67% (19-90)	13% (1-43)
Extracranial duration of response				
Events	16/42 (38%)	0/7	6/12 (50%)	4/7 (57%)
Median (95% CI; months)	10·2 (5·8-NE)	NE (NE-NE)	4·9 (3·0-NE)	5·9 (1·8-NE)
Response at 6 months	69% (50-82)	100% (100-100)††	40% (10-70)	48% (8-81)

- Intracranial response appears to be shorter than extracranial response
- ? Upregulation of PI3K pathway
- Potentially combinations of MAPKi and PI3Ki maybe beneficial

NSCLC (EGFR mutated)

Table 2. Intracranial response rates in patients treated with TKI with brain metastasis

Reference	Drug	Study	Line of treatment	Number of patients with brain metastases	Response rate %	Survival months
Kim et al. (2009)	Gefitinib or Erlotinib	Case series	First line	23	70	OS = 18.8
Hotta et al. (2004)	Gefitinib	Case series	Prior chemotherapy exposure	14	43	
Porta et al. (2011)	Erlotinib	Case series	Some patients had prior WBRT exposure	69	82	OS = 12.9
Park et al. (2012)	Gefitinib or Erlotinib	Phase II	Some patients had prior chemotherapy exposure	28	83	OS = 15.9
Wu et al. (2013)	Erlotinib	Phase II	Prior chemotherapy exposure	48	58	PFS = 15.2
Iuchi et al. (2013)	Gefitinib followed by sequence Erlotinib	Phase II	First line	41	88	OS = 21.9
Hoffknecht et al. (2015)	Afatinib	Efficacy from compassionate usage program	Prior chemotherapy and TKI exposure	100	35	–
Mok et al. (2017)	Osimertinib	Subgroup analysis from RCT	Prior TKI exposure	93	–	PFS = 8.5
Yang et al. (2017)	Icotinib	Phase III	First-line comparison of WBRT and chemo versus Icotinib	85	65	PFS = 10
	Dacomitinib	To date, to our knowledge, there are no data with regards to intracranial efficacy. Recent phase III trials have not reported intracranial outcomes or have excluded patients with brain metastasis in their design. ARCHER 1009/1050.				

TKI, tyrosine kinase inhibitor; OS, overall survival; WBRT, whole brain radiotherapy; PFS, progression-free survival; RCT, randomized controlled trial.

Ullahannan et al. Ann Oncol 28: 2923–2931, 2017

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT 2018;36:2702-2709

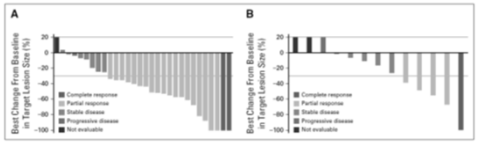
CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non–Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3)

- Osimertinib is a EGFR-TKI selective for both EGFR-TKI–sensitizing and EGFR T790M–resistance mutations with good BBB penetration.
- Patients with asymptomatic, stable CNS metastases were randomly assigned 2:1 to osimertinib 80 mg once daily or platinum-pemetrexed.
- Preplanned sub-group analysis was conducted in patients with measurable and/or non-measurable CNS lesions on baseline brain scan by blinded independent central neuroradiological review.
- Primary objective for this analysis was CNS objective response rate (ORR).
- Of 116/419 patients had CNS lesions, including 46 patients with measurable CNS lesions.

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT 2018;36:2702-2709

CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non–Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3)

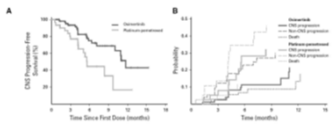
- Pt with measurable lesions:
  - CNS ORR was:
    - **70% with osimertinib**
    - **31% with platinum-pemetrexed**
    - **(odds ratio, 5.13; 95% CI, 1.44 to 20.64; P = .015)**



JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT 2018;36:2702-2709

CNS Efficacy of Osimertinib in Patients With T790M-Positive Advanced Non–Small-Cell Lung Cancer: Data From a Randomized Phase III Trial (AURA3)

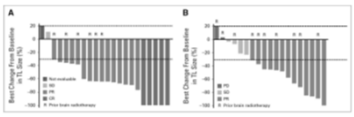
- Median CNS duration of response in patients with measurable and/or nonmeasurable CNS lesions was:
  - 8.9 months for osimertinib
  - 5.7 months for platinum-pemetrexed
- Median CNS progression-free survival was:
  - 11.7 months for osimertinib
  - 5.6 months for platinum-premetrexed (HR, 0.32; 95% CI, 0.15 to 0.69; P = .004)



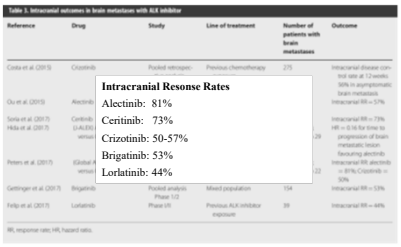
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT 2018 (epub)

CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

- **CNS ORR were 91% with osimertinib** and **68%with EGFR-TKI** in patients with ≥ one measurable CNS lesion (odds ratio, 4.6; 95% CI, 0.9 to 34.9; P = .066)
- CNS ORR was 66% for osimertinib and 43% for EGFR-TKI in patients with measurable and/or nonmeasurable CNS lesions (OR, 2.5; 95% CI, 1.2 to 5.2; P = .011) treated with osimertinib and standard EGFR-TKIs, respectively.



NSCLC (ALK+)



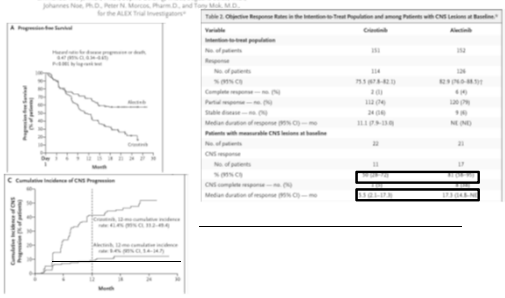
Intracranial Resonse Rates
Alectinib: 81%
Ceritinib: 73%
Crizotinib: 50-57%
Brigatinib: 53%
Lorlatinib: 44%

Ulahannan et al. Ann Oncol 28: 2923–2931, 2017

The NEW ENGLAND JOURNAL of MEDICINE

Alectinib versus Crizotinib in Untreated *ALK*-Positive Non–Small-Cell Lung Cancer

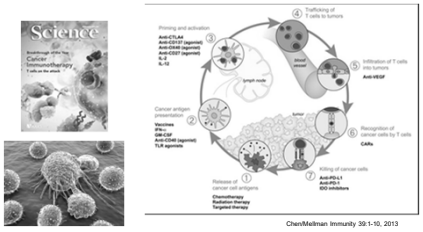
2017;377:829-38



Lapatinib and Capecitabine For Brain Metastases

Study	N	Prior RT	CNS ORR	TTP/PFS
Lin et al CCR 2009	50	100%	20%	3.6 mo
Boccardo et al, ASCO 2008 (LEAP)	138	NR	18%	Median time on study 2.8 mo
Sutherland et al, Br J Ca 2010 (LEAP)	34	94%	21%	5.1 mo
Metro et al, Ann Oncol 2011	22	86%	32%	5.1 mo
Lin et al, J Neuro-Oncol 2011	13	100%	38%	NR
Bachelot et al, Lancet Oncol 2013	45	0%	66%	5.5 mo

Immunotherapy Strategies For Brain Metastases



Chen/Mellman Immunity 39:1-10, 2013

THE LANCET Oncology 2012;13:459

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

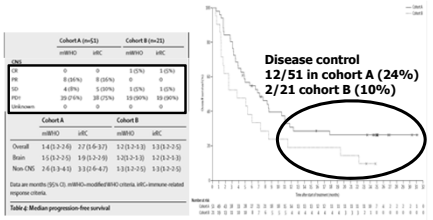
- 72 patients with melanoma and brain metastases enrolled into 2 cohorts:
  - **Cohort A** (51 pt) were **neurologically asymptomatic and not receiving corticosteroid** treatment at study entry
  - **Cohort B** (21 pt) were **symptomatic and on a stable dose of corticosteroids**.
- Patients were to receive four doses of 10 mg/kg intravenous ipilimumab, one every 3 weeks.
- Individuals who were clinically stable at week 24 were eligible to receive 10 mg/kg intravenous ipilimumab every12 weeks
- Primary endpoint was the proportion of patients with disease control, defined as CR, PR or SD after 12 weeks

Metastatic Disease to the Brain, Spine, Carcinomatous Meningitis

Mark Gilbert, MD

Tuesday, August 18, 2020

Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial



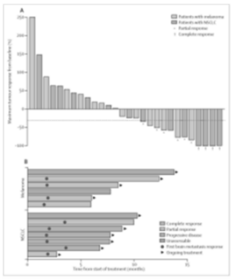
Disease control
12/51 in cohort A (24%)
2/21 cohort B (10%)

Margolin K. Lancet Oncol. 2012 May;13(5):459-65

2016;17:976

THE LANCET Oncology

Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial



Response was achieved in:

- **4 (22%) of 18 patients with melanoma**
- **6 (33%) of 18 patients with NSCLC**
- Responses were durable

The NEW ENGLAND JOURNAL of MEDICINE

2018;379:722-730

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

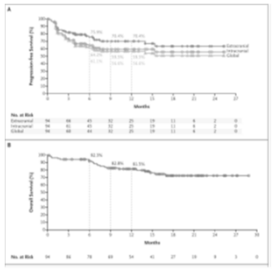


Table 2. Response to Treatment.

Variable	Intracranial (N = 94)	Extracranial (N = 94)	Global (N = 94)
Best overall response — no. (%)*			
Complete response	24 (26)	7 (7)	8 (9)
Partial response	28 (30)	40 (43)	40 (43)
Stable disease for ≥6 mo	2 (2)	6 (6)	5 (5)
Progressive disease	31 (33)	28 (30)	33 (35)
Could not be evaluated†	9 (10)	13 (14)	8 (9)
Objective response‡			
No. of patients	52	47	48
Percent of patients (95% CI)	55 (45–66)	50 (40–60)	51 (40–62)
Clinical benefit§			
No. of patients	54	53	53
Percent of patients (95% CI)	57 (47–68)	56 (46–67)	56 (46–67)

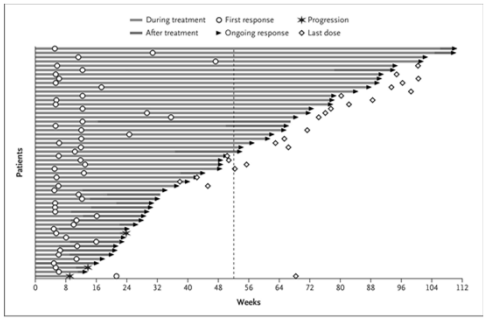
- **26% CR, 30% PR, SD for at least 6 months 2%**
- 57% intracranial benefit
- Extracranial clinical benefit 56%
- 55% Gr ¾ adverse events; 7% CNS

Responses are durable

Median PFS > 1yr

Extracranial PFS> intracra

ICI (Ipi/Nivo)Treatment for Melanoma Brain Metastases



High response rate
Durable responses

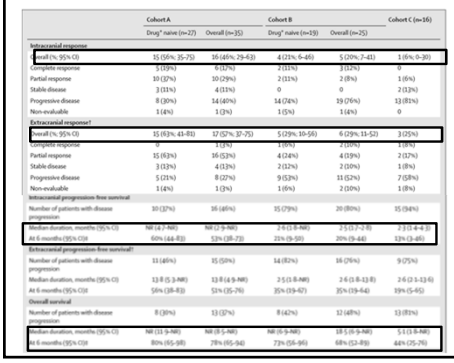
Margolin et al NEJM 2018

Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study

Lancet Oncol 2018

- Asymptomatic brain metastases with no previous local brain therapy were randomly assigned to:
  - **Cohort A (nivolumab plus ipilimumab)**
  - **Cohort B (nivolumab)**
- Patients with brain metastases in whom local therapy had failed, or who had neurological symptoms, or leptomeningeal disease
  - **Cohort C : (nivolumab)**
- Patients in cohort A received intravenous nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg every 3 weeks for four doses, then nivolumab 3 mg/kg every 2 weeks
- Patients in cohort B or cohort C received intravenous nivolumab 3 mg/kg every 2 weeks.
- Primary endpoint was intracranial response from week 12

Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study



	Cohort A	Cohort B	Cohort C (n=16)
	Drug-naive (n=27)	Overall (n=35)	Drug-naive (n=19)	Overall (n=25)	
Intracranial response					
Overall (%, 95% CI)	15 (56%; 35–75)	16 (46%; 29–63)	4 (21%; 6–46)	5 (20%; 7–41)	1 (6%; 0–30)
Complete response	5 (19%)	6 (17%)	2 (11%)	3 (12%)	0
Partial response	10 (37%)	10 (29%)	2 (11%)	2 (8%)	1 (6%)
Stable disease	3 (11%)	4 (11%)	0	0	2 (13%)
Progressive disease	8 (30%)	14 (40%)	14 (74%)	19 (76%)	13 (81%)
Non-evaluable	1 (4%)	1 (3%)	1 (5%)	1 (4%)	0
Extracranial response†					
Overall (%, 95% CI)	15 (63%; 41–81)	17 (52%; 37–75)	5 (29%; 10–56)	6 (29%; 11–52)	3 (25%)
Complete response	0	1 (3%)	1 (6%)	1 (10%)	1 (8%)
Partial response	15 (63%)	16 (53%)	4 (24%)	4 (19%)	2 (17%)
Stable disease	3 (13%)	4 (13%)	2 (12%)	2 (10%)	1 (8%)
Progressive disease	5 (21%)	8 (27%)	9 (53%)	11 (52%)	7 (58%)
Non-evaluable	1 (4%)	1 (3%)	1 (6%)	2 (10%)	1 (8%)
Intracranial progression-free survival					
Number of patients with disease progression	10 (37%)	16 (46%)	15 (79%)	20 (80%)	15 (94%)
Median duration, months (95% CI)	NR (4·7–NR)	NR (2·9–NR)	2·6 (1·8–NR)	2·5 (1·7–7·9)	2·3 (1·4–4·3)
At 6 months (95% CI)‡	60% (44–81)	53% (38–73)	25% (9–59)	20% (9–44)	13% (3–46)
Extracranial progression-free survival†					
Number of patients with disease progression	11 (48%)	15 (50%)	14 (82%)	16 (76%)	9 (75%)
Median duration, months (95% CI)	13·8 (5·3–NR)	13·8 (4·9–NR)	2·5 (1·8–NR)	2·6 (1·8–13·8)	2·6 (2·1–13·6)
At 6 months (95% CI)‡	56% (38–83)	51% (35–76)	35% (19–67)	35% (19–64)	19% (5–65)
Overall survival					
Number of patients with disease progression	8 (30%)	13 (37%)	8 (42%)	12 (48%)	13 (81%)
Median duration, months (95% CI)	NR (11·9–NR)	NR (8·5–NR)	NR (6·9–NR)	18·5 (6·9–NR)	5·1 (1·8–NR)
At 6 months (95% CI)‡	85% (65–98)	78% (65–94)	73% (56–95)	68% (52–89)	44% (25–76)

Treatment-related grade 3/4 AEs occurred in **54% (combination)** and **15% (nivolumab)** of patients, and 26% and 5% of patients, respectively, discontinued due to an AE.

Summary of Results of Immune Checkpoint Blockade for Melanoma

Checkpoint inhibitor	ORR
Ipilimumab	**16%** (Margolin, Lancet Oncol 2012)
Pembrolizumab	**22%** (Goldberg, Lancet Oncol 2016)
Nivolumab	**20%** (Long; Lancet Oncol 2018)
Nivolumab + Ipilimumab	**56%** (Tawbi; NEJM 2018) **46-56%** (Long; Lancet Oncol 2018)

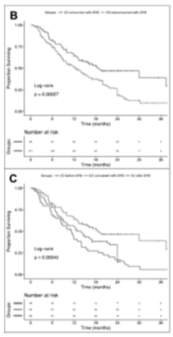
- **Summary**
  - Response rates for TKI and immunotherapeutic agents are both high
  - Onset of response faster for TKI
  - Duration of response longer for immunotherapies
- **Ongoing Studies**
  - Combination of TKI + immunotherapy
    - e.g pembrolizumab with dabrafenib and trimetanib
  - Combination of bevacizumab (avastin) with immunotherapy
  - Immunotherapy + RT


Radiotherapy and Oncology

Systematic Review

Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: An international meta-analysis of individual patient data

Eric J. Lehrer, Jennifer Peterson, Paul D. Brown, Jason P. Sheehan, Alfredo Quiñones-Hinojosa, Nicholas G. Zaorsky, Daniel M. Trifiletti

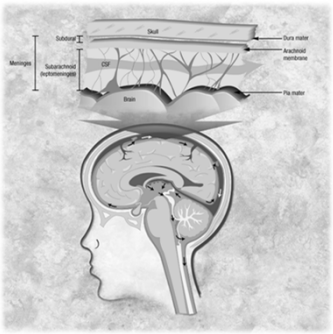


- **534 melanoma, NSCLC, renal cancer brain met**
- **Concurrent immune checkpoint inhibitor + SRS 1yr OS of 65%**
- **Non concurrent SRS and immune checkpoint inhibitor, 1 yr OS 52%**
- **Concurrent SRS+ immune checkpoint appears to produce better outcome**

Summary

- Recent studies support radiosurgery for 3 or fewer metastases and administering radiosurgery to the tumor bed after resection of a limited number of lesions
- Growing evidence of therapeutic benefit of targeted therapies and immunotherapies for brain metastases, especially for melanoma, EGFR mutated NSCLC, NSCLC with ALK fusion, and to a lesser extent HER2+ breast cancer
- Optimal combinations of targeted agents and immunotherapies, and with RT remained to be defined
- As more pts are treated with TKI and IO in first line, role at recurrence also evolving
- Need for more randomized trials focused on brain metastases

Diagnosis and Management of Neoplastic Meningitis



Infiltration of malignant cells into the CSF, the meninges, and the entire neuraxis

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Neoplastic Meningitis: Frequency by Neoplasm

Neoplasm	Frequency (%)
Overall (Autopsy)	5-8
Breast	5-10
Lung	10-15
Melanoma	17-25
GI	1-9
Primary brain	3-32
NHL (non HIV)	7-15
NHL (HIV)	30-40
Hodgkin's	2
Leukemias	5-15

7,000-9,000/ year clinically, but 5% cancers = 40,000/yr

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Pathogenesis of Neoplastic Meningitis

- Hematogenous dissemination
  - Through the choroid plexus
- Via retrograde growth along peripheral nerve sheaths
- Direct "spillage" from intracranial tumor mass
  - Important for PCNSL, non-Hodgkin's lymphoma with brain metastases
  - Very high (> 40%) incidence with posterior fossa metastases

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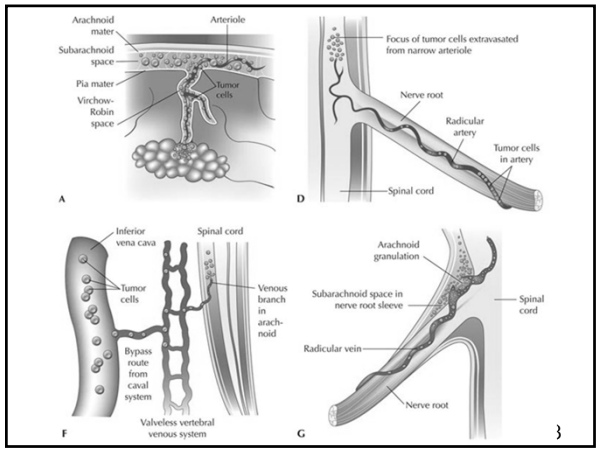

Signs and Symptoms of Neoplastic Meningitis

- General
  - Altered cognitive function or level of consciousness
  - Headache/nausea vomiting
  - Seizures
- Focal
  - Cranial or peripheral nerve palsies- skull base or cauda equina
    - ➢**effect of gravity**
  - Neurologic signs from development of masses

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Prognosis of Neoplastic Meningitis

- Untreated: 1 month median survival
- Supportive care: 2 month median survival
- Prognosis dependent upon underlying cancer histology
  - Melanoma 2-4 months
  - Lung cancer 2-4 months
  - Breast cancer 4-6 months
  - Lymphoma 6-8 months (some long term survival)
  - Leukemia 6-8 months (some long term survival)

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Prognostic Factors in Neoplastic Meningitis[1]

- Performance status*
- Presence of fixed neurologic deficits
- Underlying tumor type
  - Melanoma, lung vs breast vs lymphoma, leukemia
- Presence or absence of encephalopathy*
  - 10 wk vs 24 wk survival (1)
- Extent of systemic disease
- Compartmentalization of CSF flow*

***may be a related to disease burden**

1 Reviewed in Kim Current Treat Option in Onc 2001 2:517
2 Chamberlain Neurology 2004, 63:2159

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Diagnostic Testing for Neoplastic Meningitis

- Imaging
  - Brain MRI
    - ➢**Subarachnoid enhancement**
    - ➢**Intraventricular or sulcal nodules**
  - Spine MRI
    - ➢**Sugar coating**
  - Brain CT
  - CT myelography
    - ➢**nerve root clumping**
    - ➢**nerve root nodules**

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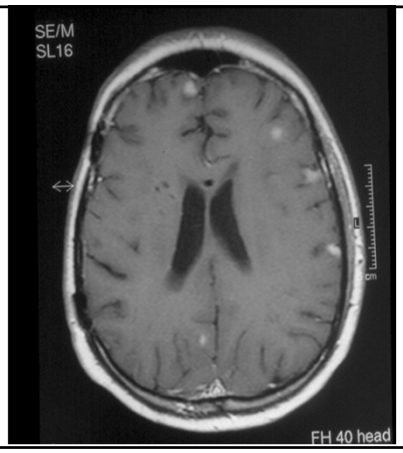

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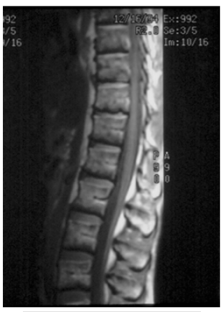
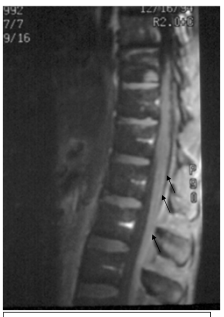
MRI Evidence of Leptomeningeal Cancer



Spine MRI: Pre-contrast



Spine MRI: Post-contrast

Arrows show sugar coating enhancement

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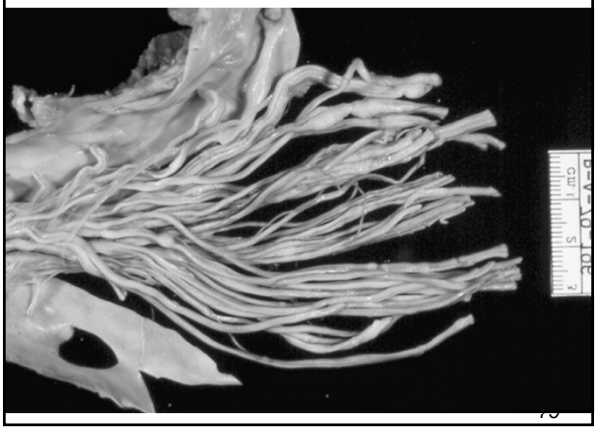

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Diagnostic Testing for Neoplastic Meningitis

- Cerebrospinal fluid
  - "gold standard" for diagnosis
  - variable sensitivity
  - may require 3-5 samples for definitive diagnosis (positive cytology); more difficult with lymphoma
  - completely normal CSF = 97% likelihood of no CSF disease

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CSF in Leptomeningeal Cancer

- Parameters: Opening pressure, Cell count, Glucose, Protein, Cytology

	Initial	Subsequent
Pressure > 160 mm	50	71
Cells > 5 mm3	57	72
Protein > 50 mg/dl	81	89
Glucose < 40 mg/dl	31	41
Positive cytology	54	91
All normal parameters	3	1

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Diagnostic Testing for Neoplastic Meningitis

- CSF Markers
  - Immunoglobulin
    - **Ig index (helpful in myeloma and some B cell lymphomas)**
    - **beta2-microglobulin: not specific, ? Utility in determining response to treatment**
- Flow cytometry
  - Looking for a clonal population of cells
- Molecular biologic studies:
  - T cell receptor or Ig gene rearrangement: still investigationa
- Cell-free DNA
  - Sensitivity and specificity to be determined

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Treatment Concepts

- LMD is a diffuse process
  - Focal therapies such as regional radiation are palliative only
- LMD can result in localized tumor masses
  - Not effectively treated by intrathecal chemotherapy
- LMD can cause abnormalities in CSF flow

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Treatment of LMD

- Treatment modalities
  - Radiotherapy
    - **Used mostly for bulky, symptomatic disease**
    - **Craniospinal radiation can be used for lymphoma/leukemia but with severe effects on bone marrow**
    - **Ongoing investigations of intrathecal injection of ^{125}I providing local delivery of radiotherapy**
  - Systemic chemotherapy
    - **Small number of agents achieve adequate CSF concentrations**
      - **MTX, ARA-C, thioTEPA, ?temozolomide, ?procarbazine**

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Systemic Chemotherapy Treatment of Neoplastic Meningitis

- Few systemic agents achieve adequate CSF levels
  - Methotrexate: when given at 8 gms/m2, cytotoxic levels were achieved and maintained longer in CSF c/w intrathecal delivery (1)
  - Ara-C: good penetration of CSF, limited scope of tumors (leukemia, lymphoma)
  - ThioTEPA: good penetration of CSF, but very myelosuppressive at required systemic dosing
  - Temozolomide: recent study of CSF PK post oral administration revealed a CSF to serum AUC ratio of 1:5 (20% of serum level)(2)
  - Anecdotal reports of trastuzamab(3) and capecitabine(4)

1Glantz JCO 1988, 16:1561
2Ostermann in press
3Baculi JCO 2001, 19:3297
4Giglio J Neuro-Onc 2003, 65:167

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Direct treatment of CSF

- Intrathecal
  - Requires repeated lumbar punctures or lumbar reservoir
  - LPs associated with pain, 15% miss rate and potential for arachnoiditis and scarring
  - LP avoids need for surgical procedure
  - ?implications for drug delivery into lateral ventricles

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Direct treatment of CSF

- Intraventricular
  - ØRequires procedure to place the reservoir
  - ØRequires confirmation of normal CSF flow
  - ØOnce placed, treatment is easy
  - ØLess concern regarding missing CSF
  - ØImproved pharmacology

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Determination of CSF Flow Kinetics

- Evaluate for compartmentalization of flow
  - Non-communicating
  - Communicating
- Confirm placement of ventricular catheter
- Assure treatment delivery
- Reduce neurotoxicity

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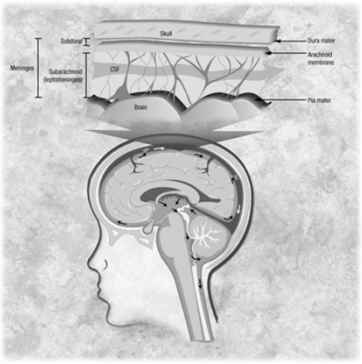

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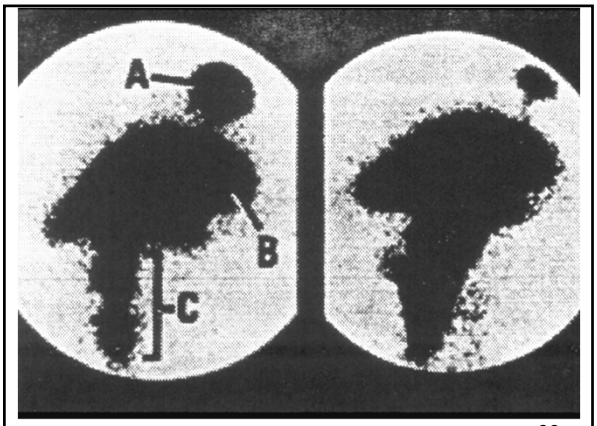

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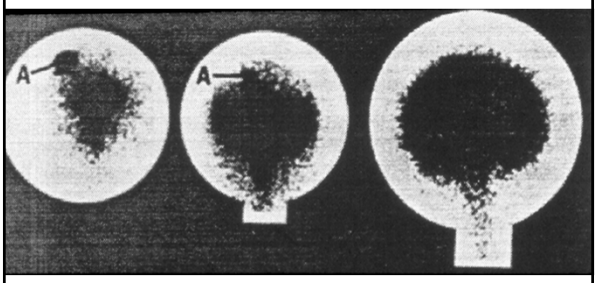

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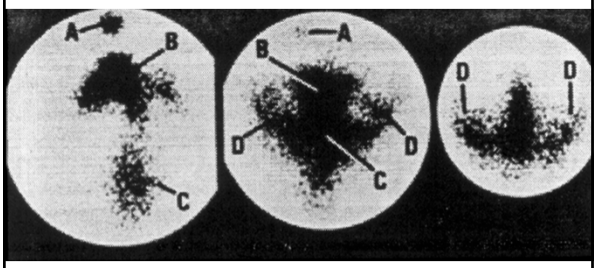

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Treatment of Neoplastic Meningitis

- Intrathecal or intraventricular chemotherapy
  - Mainstay of treatment
  - Limited number of agents
    - **Methotrexate**
    - **Ara-C**
    - **thioTEPA**
    - **encapsulated Ara-C (Depocyt)**
  - Route of administration

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Other Experimental Intrathecal Agents

- Alpha Interferon
  - Anecdotal reports in melanoma, larger series (n = 22) showed modest benefit (1)
- Rituximab
  - Good efficacy in small series for B-cell lymphoma (2)
- Trastuzumab
  - Anecdotal reports of efficacy (3)
- Topotecan
  - Phase I data demonstrates good tolerance(4), phase II studies underway
- Monoclonal antibodies with radiolabel or toxins
  - Few clinical trials(5), many animal studies

1Chamberlain Cancer 2002, 94:2675
2Schulz Haematologica. 2004 89:753
3Laufman Clin Breast Cancer 2001, 19:3297
4Blaney JCO 2003, 21:143
5Coakham J Neuro-onc 1998, 38:225

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Future Directions of Treatment of Neoplastic Meningitis

- The incidence of neoplastic meningitis is increasing, mandating new treatment strategies.
- Intrathecal chemotherapy has had only a modest impact on outcomes in most studies,
- The future may involve novel approaches such as gene therapy or immunotherapy, however conventional cytotoxic chemotherapy remains the most common approach.
- Advances will require a combination of novel treatment approaches and early diagnosis so that patients with good performance status and lower tumor burden are treated.
  - Clinical experience confirms the lack of benefit in treating patients with high disease burden or poor performance status.

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Endocrine Malignancies

Ann Gramza, MD

August 18, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

55 – Endocrine Malignancies

Ann Gramza, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

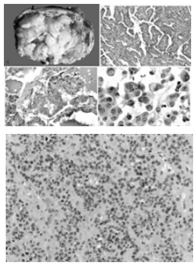
- **None**

Outline

- Thyroid Malignancies
  - Differentiated thyroid cancer (papillary and follicular)
  - Medullary thyroid cancer
  - Anaplastic thyroid cancer
- Adrenocortical carcinoma
- Pheochromocytoma/paraganglioma

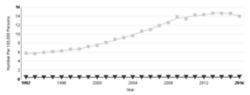
Thyroid Malignancies

- Cancers of Follicular Epithelial Cells
  - Differentiated Thyroid Cancer
    - Papillary Thyroid Carcinoma
    - Follicular Thyroid Carcinoma
    - Hürthle Cell Carcinoma
  - Poorly Differentiated Thyroid Cancer
    - Derived from Follicular or Papillary Thyroid Carcinomas?
  - Undifferentiated Thyroid Cancer
    - Anaplastic Thyroid Carcinoma
- Cancer of Parafollicular (C) Cells
  - Medullary Thyroid Carcinoma



Thyroid Cancer Epidemiology

Estimated New Cases in 2019	52,070
% of All New Cancer Cases	3.0%
Estimated Deaths in 2019	2,170
% of All Cancer Deaths	0.4%



Percent Surviving 5 Years
98.2%
2009-2015

- Thyroid Cancer is the most common endocrine malignancy
  - **Papillary Thyroid Cancer** most common thyroid cancer
- age- and gender-adjusted incidence has increased faster than that of any other malignancy
  - 23,500 cases in 2005
  - 64,300 cases estimated in 2016
  - 52,070 cases estimated in 2019
- Prevalence is high and increasing
  - 2004: 366,000 men and women alive with history of thyroid cancer
  - 2016: 822,242

SEER Cancer Stat Facts: Thyroid Cancer. National Cancer Institute. Bethesda, MD.

Incidence and Death Rates

SEER Cancer Stat Facts: Thyroid Cancer. National Cancer Institute. Bethesda, MD.

Thyroid Malignancies

Tumor type	Prevalence	Age	Distant Metastases	Survival rate (5yr)
Papillary thyroid carcinoma	**85-90%**	20-50	5-7%	>90%
Follicular thyroid carcinoma	**<10%**	40-60	20%	>90%
Poorly differentiated thyroid carcinoma	Rare-7%	50-60	30-80%	50%
Undifferentiated thyroid carcinoma	2%	60-80	20-50%	1-17%
Medullary thyroid carcinoma	3%	30-60	15%	30-80%

Nature Reviews. April 2006, p.292-306.

Thyroid Cancer AJCC Staging

Stage	Follicular or Papillary*		Medullary	Anaplastic
	<55yo	≥55yo	Any age	Any age
I	M0	T1-2N0	T1N0	
II	M1	T1-2N1 T3	T2-3N0	
III		T4a	T1-T3N1a	
IVa		T4b	T1-T3N1b T4a	T1-T3aN0
IVb		M1	T4b	T1-T3aN1 or >T3a
IVc			M1	M1

*The most advanced a patient <55 yo can be is stage II

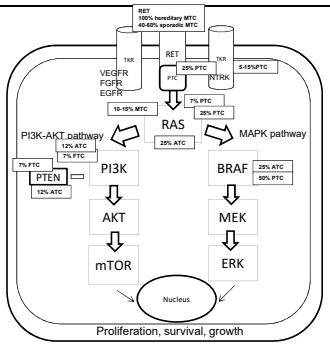
Thyroid Cancer Stage Distribution

Histologic Subtype	I (%)	II (%)	III (%)	IV (%)	Unknown (%)	Total
Papillary	**46.9**	14.4	10.3	2.1	16.4	**34,794**
Follicular	**41.2**	26.7	6.9	7.2	17.9	**5271**
Hurthle Cell	**20.8**	35.1	9.3	5.7	29	**1310**
Undifferentiated/Anaplastic	0	0	0	100	0	741
Medullary	16.5	29.6	26.9	11	16	1550
Total	51.5	16.8	10.3	4.8	16.6	
Cases	22,486	7335	4491	2091	7263	43,666

50% of Differentiated Thyroid Cancers are Stage I

CANCER December 15, 1998 / Volume 83 / Number 12

Thyroid Cancer Signaling

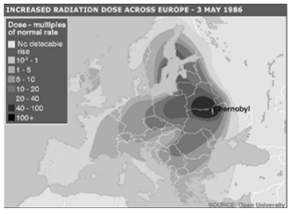


Differentiated Thyroid Cancer

(Papillary and Follicular)

Differentiated Thyroid Cancer (DTC) Risk Factors

- Radiation exposure
  - Survivors of atomic fall-out
  - Children exposed to external beam radiation
  - Children living in Chernobyl (nuclear accident)
  - Younger age at exposure: Higher risk
    - Controversial whether exposure after age 15 confers increased risk



Differentiated Thyroid Cancer (DTC) Risk Factors

Genetic

- Component of several inherited syndromes:
  - Familial adenomatous polyposis
    - Gardner's syndrome
    - Turcot syndrome
  - Cowden syndrome
  - Carney complex
- "Familial nonmedullary thyroid carcinoma"
  - 10-fold increased risk of thyroid cancer in relatives of thyroid cancer patients (case control study, n = 339)
  - Swedish retrospective analysis (n=1953 cases)
    - Familial risk: 3-fold if a parent has DTC, 6-fold if sibling has DTC, 11-fold if female has a sister diagnosed with DTC

Pal T; J Clin Endocrinol Metab 2001

Hemminki K; J Clin Endocrinol Metab 2005

Clinical Presentation and Prognosis

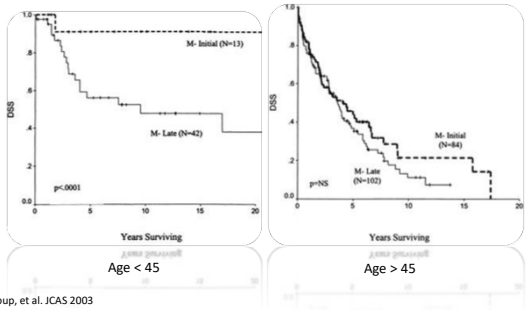
- Most patients present with asymptomatic thyroid nodule
  - More advanced patients can present with local symptoms
- One of the least morbid solid tumors
- Disease-related mortality < 10% at 10 years
- Prognostic factors
  - Age, tumor size, invasion, metastases
  - PET avidity
  - Males > 45 years old
- Regional lymph node metastasis does not correlate with overall survival—does correlate with local recurrence
  - 33-61% of patients with PTC have clinically apparent cervical lymph node involvement at dx
- Distant mets at dx: 43-90% of patients will die of thyroid cancer

Disease Specific Survival By Stage

Stage	N	10-yr Disease Specific Survival
I	7736	99.5
II	441	94.7
III	707	94.1
IV	600	67.7

THYROID
Volume 26, Number 3, 2016

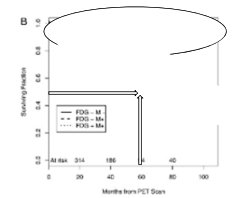
Age and Prognosis



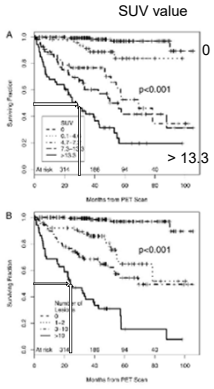
Age < 45 Age > 45

Shoup, et al. JCAS 2003

PET and Prognosis



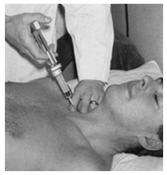
SUV and number of PET-avid lesions influences prognosis in differentiated thyroid cancer



Robbins, et al. JCEM, Feb 2006, 91 (2): 498-505

Diagnosis

- FNA is standard diagnostic procedure when a thyroid nodule is found
- Most thyroid nodules are benign
  - 5-10% chance of malignancy
  - Higher rate of cancer in:
    - Men
    - Age < 20 or > 70
    - History of childhood neck radiation:
      - 33-37% chance malignancy
    - Enlarging nodule
    - Fixed nodule/vocal cord paralysis
    - h/o Graves' disease
    - Family h/o PTC, MTC, MEN 2
  - Up to 90% of women > 70 and up to 60% men > 80 have nodular goiter



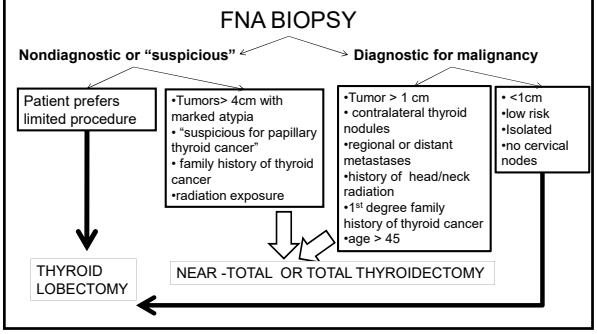
FNA RESULTS

FNA result	N	%
Benign	526	87.7
Malignant	28	4.7
Suspicious for malignancy	10	1.6
Insufficient material	36	6
Total	600	100

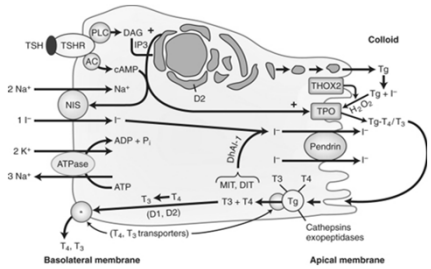
Binesh F, Pak J Med Sci 2008;24(3):382-5.

What is the appropriate surgical management?

American Thyroid Association Management Guidelines THYROID vol 16, 2006



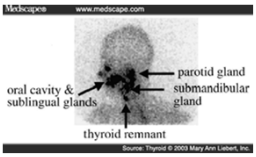
Thyroid Follicular Cell



Postoperative treatment and surveillance are based on differentiated thyroid cancer maintaining characteristics of normal thyroid follicular cells

Postoperative Radioiodine

- Goals:
  - Eliminate post-surgical thyroid remnant
    - Decrease local recurrence
    - Facilitate long-term surveillance with RAI (radioiodine) scans and/or stimulated thyroglobulin measurements
  - Destroy micrometastatic disease



- No prospective studies have been done to determine which patients benefit
- Requires TSH stimulation
  - Can be done by stopping thyroid hormone replacement and allowing endogenous TSH levels to rise
  - For low risk patients, can give rhTSH (thyrotropin)

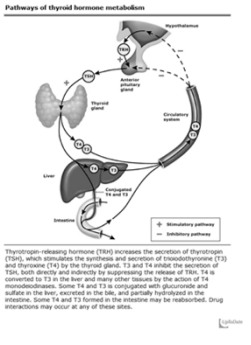
Postoperative Radioiodine

- Not recommended for low-risk disease
  - < 1cm, unifocal, etc.
- Recommended for select intermediate-risk patients
  - Microscopic invasion, aggressive histology, N1
- Routinely recommended for high-risk disease
  - Distant metastases, N1 > 3 cm, residual disease, etc.

Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016; 26:1.

TSH Suppression Therapy

- Differentiated thyroid cancer cells express the thyrotropin receptor on the cell membrane
  - Responds to TSH stimulation
    - Increases rates of cell growth
- Use supratherapeutic doses of LT4
  - TSH suppression to < 0.1mU/L may improve outcomes in high risk patients
  - TSH 0.1-0.5 is appropriate for low risk patients
  - TSH suppression can be reduced after 5 years
- Adverse effects of TSH suppression—subclinical thyrotoxicosis:
  - Exacerbation of angina, increased risk of atrial fibrillation, increased risk of osteoporosis in post menopausal women



Management of Recurrent Disease

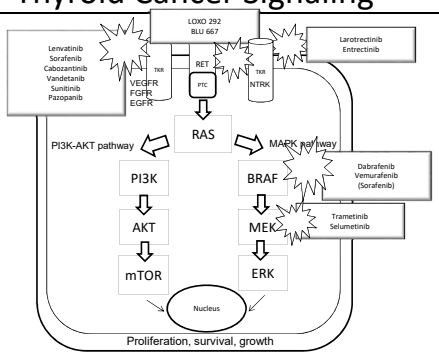
- Surgical resection if limited disease
  - +/- RAI therapy depending on uptake, prior dose
- If more extensive disease:
  - RAI if uptake on iodine scan
    - NOTE: IV contrast SHOULD NOT BE GIVEN for CT scans if RAI is still a potential option
    - Treatment of choice, can result in CR
      - Young patients, small pulmonary nodules
  - External beam radiotherapy
  - Bisphosphonates
  - Systemic therapy
  - Observation

RAI-Refractory Thyroid Cancer

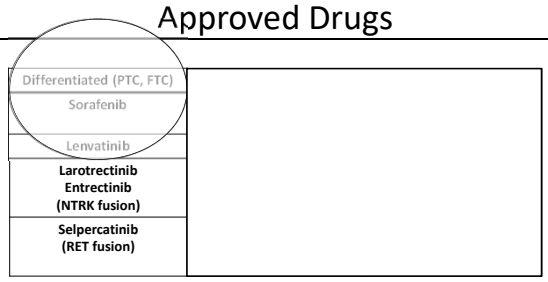
- Distant metastases in 10-15% DTC patients
- 35-50% metastatic thyroid cancers lose iodine concentrating ability
- RAI rarely results in complete remission
  - Young women with small volume disease (lungs)
- PET avidity is inversely proportional to RAI uptake
- Standard chemotherapy had disappointing response rates, significant toxicity

Shimaoka, et al. Cancer 56, 1985

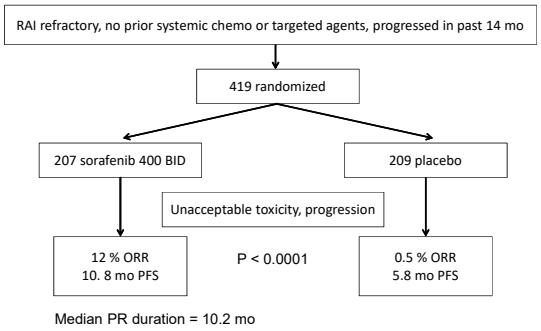
Thyroid Cancer Signaling



Approved Drugs



Sorafenib vs. Placebo in Locally Advanced or Metastatic DTC



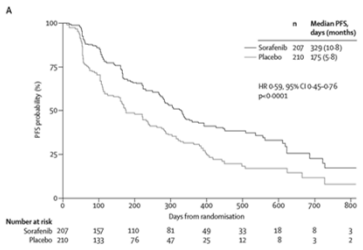
Histologic Subtypes

Histology by central review*	Sorafenib N (%)	Placebo N (%)
Papillary	118 (57)	119 (57)
Follicular, oncocytic (Hurthle cell)	37 (18)	37 (18)
Follicular, non-Hurthle cell	13 (6)	19 (9)
Poorly differentiated	24 (12)	16 (8)
Well-differentiated	2 (1)	1 (0.5)
Non-thyroid	0	1 (0.5)
Medullary	0	1 (0.5)
Oncocytic carcinoma	2 (1)	0
Carcinoma, NOS	0	3 (1.4)
Missing/non-diagnostic	13 (6)	14 (7)

*all had DTC by investigator review

Brose, et al. Lancet. 2014 Apr 23.

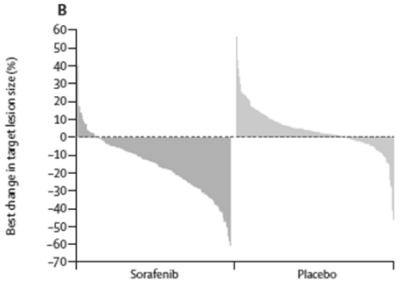
Sorafenib in DTC Progression Free Survival



FDA approved Nov 2013 for the treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment.

Brose, et al. Lancet. 2014 Apr 23.

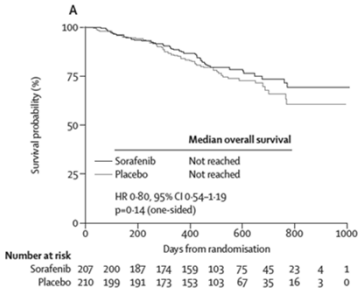
Best Response



PR + SD ≥ 6 months = 54% P<0.0001 34%

Brose, et al. Lancet. 2014 Apr 23.

Sorafenib in DTC Overall Survival



150 (71%) of placebo patients crossed over to sorafenib

Brose, et al. Lancet. 2014 Apr 23.

Adverse Events

	Sorafenib		Placebo	
	Any %	**Grade 3/4 %**	**Any %**	**Grade 3/4 %**
Any AE	99	-	88	-
SAE	37	-	26	-
Hand-foot	76	20/0	10	-
Diarrhea	69	5/0.5	15	1/0
Alopecia	67	-	8	-
Rash or desquamation	50	5/0	12	-
Fatigue	50	5/0.5	25	1/0
Weight loss	47	6/0	14	1/0
Hypertension	41	10/0	12	2/0

Brose, et al. Lancet. 2014 Apr 23.

Lenvatinib in patients with ^{131}I-refractory differentiated thyroid cancer

- VEGFR1-3, FGFR1-4, PDGFRβ, RET, KIT inhibitor
- Randomized 2:1, double blind, placebo controlled study
- RAI refractory, PD within 13 mo.
- 392 patients, 54% PTC
- Crossover permitted after progression (83%)
- 392 patients

N Engl J Med 2015; 372:621-630

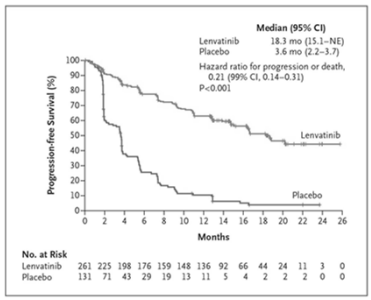
Lenvatinib vs. Placebo - Efficacy

Efficacy	**Lenvatinib (n=261)**	**Placebo (n=131)**
ORR	169 (65%)	2 (2%)
CR	4 (2%)	0
PR	165 (63%)	2 (2%)
SD > 23 weeks	40 (15%)	39 (30%)
PD	18 (7%)	52 (40%)
Median time to response (mo)	2 (1.9-3.5)	-
Median duration of response	30 months	-
Median PFS (mo)	18.3	3.6
Deaths % p = 0.10	27%	36%

Median OS = Not Evaluable

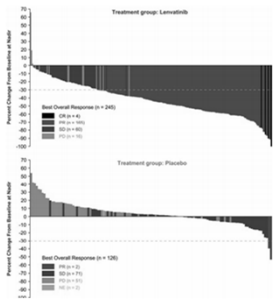
Lenvima package insert 2015

Lenvatinib vs. Placebo - Progression-Free Survival



N Engl J Med 2015; 372:621-630

Analysis of Overall Tumor Shrinkage



N Engl J Med 2015; 372:621-630

Lenvatinib vs. Placebo - Adverse Events

Adverse Event	Lenvatinib 24mg N=261 All Grades %	Grades 3-4 %	Placebo N=131 All Grades %	Grades 3-4 %
hypertension	73	44	16	4
diarrhea	67	9	17	0
Fatigue/asthenia	67	11	35	4
Arthralgia/myalgia	62	5	28	3
Decreased appetite	54	7	18	1
Weight loss	51	13	15	1
nausea	47	2	25	1
Hand/foot	32	3	1	0
Rash	21	0.4	3	0

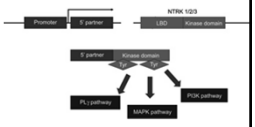
Lenvima package insert 2015

Approved Drugs

Differentiated (PTC, FTC)	
Sorafenib	
Lenvatinib	
Larotrectinib Entrectinib (NTRK fusion)	
Selpercatinib **(RET fusion)**	

NTRK Fusions

- Somatic chromosomal rearrangements involving *NTRK1*, *NTRK2*, or *NTRK3* genes occur in ~1% of all solid cancers
- TRK proteins activate MAPK, PI3K, PLC pathways
  - Fusions result in constitutive activation and cell transformation, growth, proliferation
- Papillary thyroid cancer:
  - *NTRK1* fusion < 12%
  - >15% in Italian population, < 10% in others
  - *ETV6-NTRK3* radiation associated



Onco Targets Ther. 2019; 12: 3171–3179.

TRK Inhibitors - Larotrectinib

EFFICACY BY SOLID TUMOR TYPE

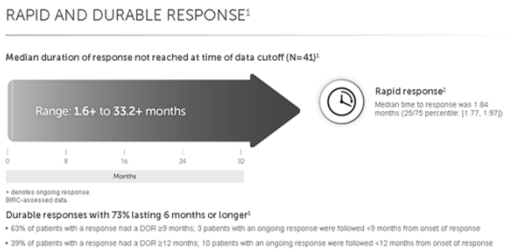
Response rates in various tumor types (as assessed by a BIRC,* N=55)[1]

Tumor Type	Patients (N=55)	ORR* %	ORR* 95% CI	DOR* Range (months)
Salivary gland	12	83%	(52%, 98%)	7.7, 27.9+
Soft tissue sarcoma	11	91%	(59%, 100%)	3.6, 33.2+
Infantile fibrosarcoma	7	100%	(59%, 100%)	1.4+, 10.2+
Thyroid	5	100%	(48%, 100%)	3.7, 27.0+
Lung	4	75%	(19%, 99%)	8.2, 20.3+
Melanoma	4	50%	NA*	1.9, 17.5+*
Colon	4	25%	NA	5.6*
Gastrointestinal stromal tumor	3	100%	(29%, 100%)	9.5, 17.3
Cholangiocarcinoma	2	SD,* NE*	NA	NA
Appendix	1	SD	NA	NA
Breast	1	PD*	NA	NA
Pancreas	1	SD	NA	NA

+ denotes ongoing response.
*BIRC, blinded independent review committee; DOR, duration of response; NA, not applicable due to small numbers or lack of response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; SD, stable disease.
*Observed values at data cutoff, not a range.

https://www.hcp.vitrakvi-us.com/about-vitrakvi/efficacy/

TRK Inhibitors - Larotrectinib



https://www.hcp.vitrakvi-us.com/about-vitrakvi/efficacy/

TRK Inhibitors – Entrectinib

Table 8: Efficacy Results for Patients with Solid Tumors Harboring *NTRK* Gene Fusions

Efficacy Parameter	ROZLYTREK N = 54
Overall Response Rate (95% CI)	57% (43, 71)
Complete Response	7.4%
Partial Response	50%
Duration of Response*	**N = 31**
Range (months)	2.8, 26.0+
% with duration ≥ 6 months	68%
% with duration ≥ 9 months	61%
% with duration ≥ 12 months	45%

Response duration were based on additional 5 months' follow-up after the primary analysis of ORR.
* Observed DOR
+ denotes ongoing response

Table 9: Efficacy by Tumor Type

Tumor Type	Patients N = 54	ORR		DOR Range (months)
		%	95% CI	
Sarcoma	13	46%	19%, 75%	2.8, 15.1
Non-small cell lung cancer	10	70%	35%, 93%	1.9*, 20.1*
Salivary (MASC)	7	86%	42%, 100%	2.8, 16.5*
Breast cancer	6	83%	36%, 100%	4.2, 14.8*
Thyroid cancer	5	20%	NA	7.9
Colorectal cancer	4	25%	NA	4.8*
Neuroendocrine cancers	3	PR	NA	5.6*
Pancreatic cancer	3	PR, PR	NA	7.1, 12.9
Gynecological cancers	2	PR	NA	20.3*
Cholangiocarcinoma	1	PR	NA	9.3

* Censored
MASC: mammary analogue secretory carcinoma; NA = not applicable; PR = partial response.

rozlytrek_prescribing.pdf

Approved Drugs

Differentiated (PTC, FTC)
Sorafenib
Lenvatinib
Larotrectinib Entrectinib (NTRK fusion)
Selpercatinib (RET fusion)

Selpercatinib – RET Fusion Thyroid Cancer

- 27 patients with RET fusion-positive thyroid cancer refractory to RAI (18 previously treated with sorafenib, lenvatinib, or both; 9 systemic therapy naïve)
- 160 mg po BID
- Tumor Types:
  - PTC = 78%
  - PDTC = 11%
  - ATC = 7%
  - Hurthle Cell = 4%

Selpercatinib – RET Fusion Thyroid Cancer

Table 13 Efficacy Results in LIBRETTO-001 (*RET* Fusion-Positive Thyroid Cancer)

	RETEVMO Previously Treated (n = 19)	RETEVMO Systemic Therapy Naïve (n = 8)
Overall Response Rate[1] (95% CI)	79% (54%, 94%)	100% (63%, 100%)
Complete response	5.3%	12.5%
Partial response	74%	88%
Duration of Response		
Median in months (95% CI)	18.4 (7.6, NE)	NE (NE, NE)
% with ≥ 6 months[2]	87	75

[1]Confirmed overall response rate assessed by BICR.
[2] Based on observed duration of response
NE = not estimable

FDA approved May 2020

https://uspl.lilly.com/retevmo/retevmo.html#pi

Selpercatinib Toxicity

Table 5 Adverse Reactions (≥ 15%) in Patients Who Received RETEVMO in LIBRETTO-001

Adverse Reaction	RETEVMO (n = 702) Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal		
Dry Mouth	39	0
Diarrhea[1]	37	3.4[1]
Constipation	25	0.6[1]
Nausea	23	0.6[1]
Abdominal pain[2]	23	1.9[2]
Vomiting	15	0.3[2]
Vascular		
Hypertension	35	18
General		
Fatigue[3]	35	2[3]
Edema[4]	33	0.3[4]
Skin		
Rash[5]	27	0.7[5]
Nervous System		
Headache[6]	23	1.4[6]
Respiratory		
Cough[7]	18	0
Dyspnea[8]	16	2.3
Investigations		
Prolonged QT interval	17	4[9]
Blood and Lymphatic System		
Hemorrhage[10]	15	1.9

[1]Diarrhea includes diarrhea, defecation urgency, frequent bowel movements, and anal incontinence
[2]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, gastrointestinal pain
[3]Fatigue includes fatigue, asthenia, malaise.
[4]Edema includes edema, edema peripheral, face edema, eye edema, eyelid edema, generalized edema, localized edema, lymph edema, scrotal edema, peripheral swelling, scrotal swelling, swelling, swelling face, eye swelling, peripheral swelling
[5]Includes rash, rash erythematous, rash macular, rash maculopapular, rash morbilliform, rash pruritic
[6]Headache includes headache, sinus headache, tension headache
[7]Includes cough, productive cough
[8]Includes dyspnea, dyspnea exertional, dyspnea at rest
[9]Hemorrhage includes epistaxis, hematuria, hemoptysis, contusion, rectal hemorrhage, vaginal hemorrhage, ecchymosis, hematochezia, petechiae, traumatic hematoma, anal hemorrhage, blood blister, blood urine present,

Table 6 Select Laboratory Abnormalities (≥ 20%) Worsening from Baseline in Patients Who Received RETEVMO in LIBRETTO-001

Laboratory Abnormality	RETEVMO[1] Grades 1-4 (%)	Grades 3-4 (%)
Chemistry		
Increased AST	51	8
Increased ALT	45	9
Increased glucose	44	2.2
Decreased albumin	42	0.7
Decreased calcium	41	3.8
Increased creatinine	37	1.0
Increased alkaline phosphatase	36	2.3
Increased total cholesterol	31	0.1
Decreased sodium	27	7
Decreased magnesium	24	0.6
Increased potassium	24	1.2
Increased bilirubin	23	2.0
Decreased glucose	22	0.7
Hematology		
Decreased leukocytes	43	1.6
Decreased platelets	33	2.7

[1]Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available, which ranged from 675 to 692 patients.

https://uspl.lilly.com/retevmo/retevmo.html#pi

DTC Summary

- Papillary thyroid cancer is the most common type
- Main risk factors: radiation as a child and family history
- Mainstay of treatment is surgery, often followed by RAI ablation and TSH suppression
- Distant metastases can sometimes be eradicated with RAI therapy
- IV contrast should not be given to patients who are potential candidates for RAI (if needed quickly)

DTC Summary – RAI refractory disease

*Sorafenib AND lenvatinib are approved for treatment of locally recurrent or metastatic, progressive differentiated thyroid carcinoma (DTC) refractory to radioactive iodine treatment (not tested head to head)

*Sorafenib and lenvatinib improved PFS, but not OS, therefore, timing of therapy and discussion of risks and benefits with patients is imperative

*For patients with TRK fusions, larotrectinib or entrectinib are options

*For patients with RET fusions, selpercatinib is now approved as an option

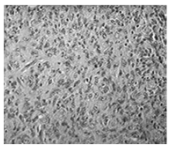
Anaplastic Thyroid Cancer

Anaplastic Thyroid Cancer

- **Rare**
  - incidence: 1-2 cases/million annually
  - 2-5% of all thyroid cancer (600-1000 patients in US/year)
- **Aggressive**
  - Median survival 3-6 months
  - 90% with regional/distant metastases at diagnosis
- **Lethal**
  - Nearly 100% disease-specific mortality
  - Papillary thyroid cancer has ≤ 10% disease-specific mortality

Clinical Presentation

- **Symptoms**
  - Related to neck mass in most patients
    - Pain, compression of airway, dyspnea, dysphagia, hoarseness, cough
  - Constitutional symptoms can occur
- **Diagnosis**
  - FNA or core biopsy
  - Imaging studies
    - CT of neck and chest
    - FDG PET



Staging

- All ATC is Stage IV
- In 2003, AJCC revised the staging:
  - IVA: tumor intrathyroidal (surgically resectable)
  - IVB: tumor extrathyroidal (not surgically resectable)
  - IVC: distant metastases
- Stage Distribution in a retrospective series (n=100):
  - Stage IVA: 11%
  - Stage IVB: 31%
  - Stage IVC: 58%

AJCC 6th Edition
Sugino, et al. Thyroid 2011

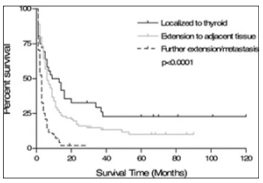
Prognosis

- "good" prognostic factors
  - Disease confined to the thyroid
  - Local or regional metastases (rather than distant)
  - Tumor size < 6 cm
- "bad" prognostic factors
  - Male
  - Older age
  - Dyspnea
  - Tumor > 6 cm
  - Distant mets at diagnosis

Pichardo-Lowden, et al
Thyroid 2009; 19:775-778

Kebebew, et al. Cancer 2005;103:1330-1335

Survival by Extent of Disease



- Retrospective review
- SEER Database (1983-2002)
- 261 patients
- included those eligible for surgical resection who lived at least one month (omitted 203 patients)

Extent	Median Survival	2-year Survival %	5-year Survival %
Confined to thyroid	9 months	33	23
Local extension	6 months	16	10
Distant mets	3 months	2	---

Chen, et al. Am J Clin Oncol 2008; 31:460-464

National Cancer Database Review

- 2742 patients
- diagnosed with ATC between 1998-2008
- Older age and omission of treatment were associated with greater mortality
- Mean age: 70 + 12.3 years
- 62% women

National Cancer Database Review

Treatment	Yes (median survival)	No (median survival)
Total thyroidectomy	6.2 mo.	2.3 mo.
Radiation	5 mo.	1.8 mo.
Chemotherapy	5.9 mo.	2.3 mo.

2003-2008 (n = 699)	Median Survival
Stage IVA	9 mo
Stage IVB	4.8 mo
Stage IVC	3 mo

Goals of Therapy

- Quality of life
- Symptom management
- End of life care
- Prevent asphyxiation?
  - death most often caused by airway compromise (50-60%)
- No therapy has been shown to clearly improve overall survival
  - No adequately powered randomized trials
  - Selection bias

Surgery

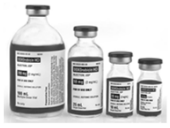
- Usually recommended for disease confined to the thyroid or if locoregional disease is surgically resectable
  - Intrathyroidal: total thyroidectomy
  - Locally advanced: depends on extent of disease – total thyroidectomy, lobectomy

Radiation Therapy

- Up to 80% of patients may respond, but most will recur locally
- Hyperfractionated accelerated radiation therapy (>40 Gy) may improve local control
  - Retrospective study of 47 patients
  - 6 month PFS = 94% vs. 65% for palliative (<40 Gy)
  - No survival benefit
- Concurrent chemoradiotherapy
  - Several small series claim potential improved local control and survival compared to historical controls
  - No definitive data regarding survival or local control
    - Selection bias
    - No proven benefit to doxorubicin, cisplatin, taxane, or combination thereof

Wang et al. Cancer (2006) 107 (8)

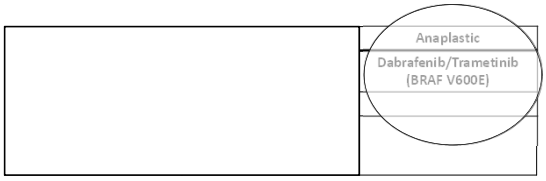
Chemotherapy—Advanced Disease



- Doxorubicin used most commonly
  - Poor response rates
  - No improved survival
- Paclitaxel appears to have most activity
  - 20 patients with advanced disease
    - 120-140mg/m2 CIV over 96hrs q 3 weeks
    - 53% response rate
    - Median survival responders: 32 weeks
    - Median survival non responders: 10 weeks

Ain, et al. Thyroid (2000): 10 (7)

Approved Drugs



Dabrafenib and trametinib in patients with V600E-mutated ATC

- 16 patients with BRAF V600E mutated ATC
  - All had prior radiation
  - 6 had prior systemic therapy
  - Median age 72

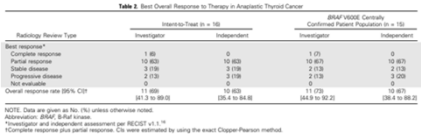


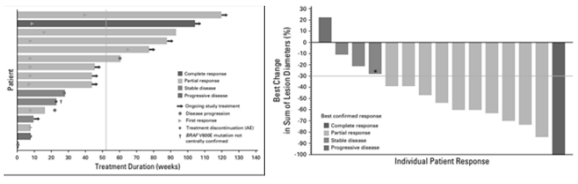
Table 2. Best Overall Response to Therapy in Anaplastic Thyroid Cancer

Radiology Review Type	Intent-to-Treat (n = 16)		*BRAF* V600E Centrally Confirmed Patient Population (n = 15)	
	Investigator	Independent	Investigator	Independent
Best response*				
Complete response	1 (6)	0	1 (7)	0
Partial response	10 (63)	10 (63)	10 (67)	10 (67)
Stable disease	3 (19)	3 (19)	2 (13)	2 (13)
Progressive disease	2 (13)	3 (19)	2 (13)	3 (20)
Not evaluable	0	0	0	0
Overall response rate (95% CI)†	11 (69) [41.3 to 89.0]	10 (63) [35.4 to 84.8]	11 (73) [44.9 to 92.2]	10 (67) [38.4 to 88.2]

NOTE. Data are given as No. (%) unless otherwise noted.
Abbreviation: *BRAF*, B-Raf kinase.
*Investigator and independent assessment per RECIST v1.1.[16]
†Complete response plus partial response. CIs were estimated by using the exact Clopper-Pearson method.

J Clin Oncol 36:7-13. © 2017

Swimmers and Waterfalls



J Clin Oncol 36:7-13. © 2017

Anaplastic Thyroid Cancer - Current Management Summary

- BRAF TESTING!!!!
- Dabrafenib and trametinib combination therapy for BRAFV600E mutated ATC
- Surgery, radiation, and chemotherapy may improve survival for patients with local disease
- Adjuvant radiation and/or chemotherapy may improve survival for patients with locally advanced disease
- Radiation alone with hyperfractionation may achieve local control, but patients are likely to relapse
- Multimodality therapy may improve local control and prevent asphyxiation
  - Does not improve survival
  - Toxicities
- Chemotherapy alone may provide a response
  - Short duration
- No standard therapeutic recommendations, can consult the American Thyroid Association Guidelines or NCCN guidelines
- Clinical trials

Medullary Thyroid Cancer

Medullary Thyroid Cancer

- Neuroendocrine tumor of the parafollicular (C cells)
- Produce calcitonin
- 80% are sporadic
- 20% are familial: MEN type 2 syndromes
- Sporadic MTC presents 50s-60s
- Familial MTC (MEN2) presents younger (30s)
  - Children with MEN 2B undergo thyroidectomies in infancy
  - Children with MEN 2A undergo thyroidectomies by ages 5 or 6

Medullary Thyroid Cancer

- Clinical presentation:
  - Thyroid nodule
  - 50% have cervical lymph node involvement
  - 15% have symptoms—dysphagia, hoarseness
  - 5% have distant metastases
  - Systemic symptoms:
    - Secretes calcitonin: diarrhea, facial flushing
    - Can secrete corticotrophin (ACTH): Cushing's syndrome

Inherited MTC
Autosomal Dominant Syndromes

MEN 2A	MEN 2B	FMTC (Familial Medullary Thyroid Cancer)
MTC (100%)	MTC (100%)	MTC
pheochromocytoma	pheochromocytoma	
Primary parathyroid hyperplasia (hyperparathyroidism)	Mucosal neuromas	
RET C634R	RET M918T	RET exon 11

Inherited MTC

- Kindred can be screened for medullary thyroid cancer with calcitonin levels
  - Screening of MEN 2A families found 80% of cases—most had no thyroid abnormalities on exam
- Kindred are now screened for point mutations in the RET proto-oncogene
  - Allows for earlier diagnosis and prophylactic thyroidectomies

Clinical Evaluation

- CTs of neck, chest, abdomen, pelvis
- Bone scan
- PET/CT imaging controversial—can often miss metastases
- Serum calcium level
- 24 hour excretion of metanephrines, norepinephrine, and epinephrine
- RET mutation
- Calcitonin level

Prognosis

- Postoperative calcitonin doubling time:
  - < 6 months: 10 yr. survival = 8%
  - 6-24 months: 10 yr. survival = 37%
  - > 2 yrs: 10 yr. survival = 100%
- Age at diagnosis:
  - < 40: 10 yr. survival = 65%
  - > 40: 10 yr. survival = 50%
- RET M918T mutation

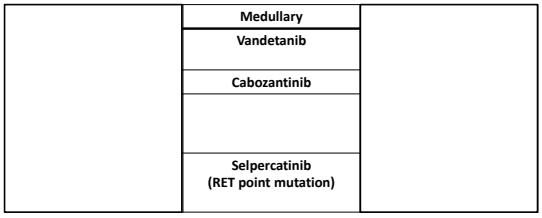
Treatment of Medullary Thyroid Cancer

- Cured only by complete resection of tumor and lymph node mets
- Total thyroidectomy
  - Up to 30% have bilateral or multifocal disease
- Start thyroxine (T4) immediately post-op
  - Maintain euthyroid state
  - C-cells are not TSH responsive
  - No role for radioiodine
- Measure serum calcitonin and CEA 6 months after surgery
  - Detect residual disease
  - If undetectable, 5% 5-yr recurrence rate

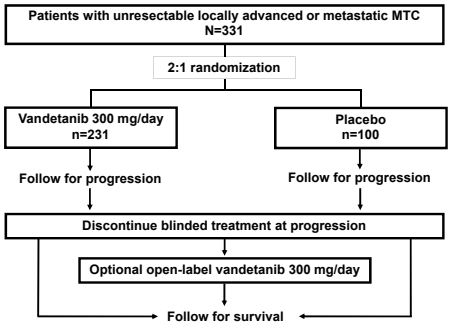
Residual/Recurrent MTC

- Surgical resection
- Radiation?
  - No prospective data
  - May prolong disease progression interval
- Chemotherapy
  - Not effective
- **Vandetanib** and **Cabozantinib** approved for advanced, progressive or symptomatic disease regardless of RET mutation
- **Selpercatinib** approved for RET mutant MTC

Approved Drugs

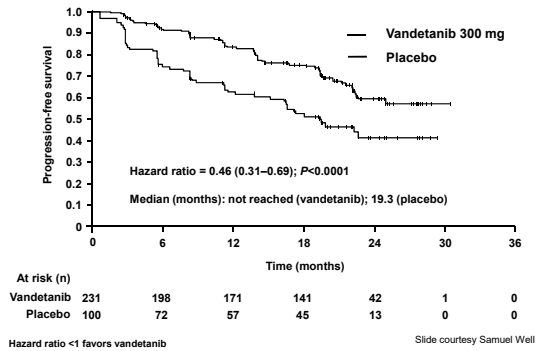


Vandetanib in MTC Study Design



Slide courtesy Samuel Wells, MD

PFS (primary endpoint)



Hazard ratio <1 favors vandetanib

Slide courtesy Samuel Wells, MD

Objective Tumor Assessments

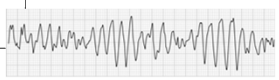
	Vandetanib 300 mg (n=231)	Placebo (n=100)
ITT analysis*		
Objective response rate	45% (104)	13% (13)
Odds ratio (95% CI)	5.48 (2.99–10.79), P<0.0001	
Excluding open-label scans		
Objective response rate	44% (101)	1% (1)
Odds ratio (95% CI)	76.91 (16.68–1366), P<0.0001	

- 24 patients randomized to placebo received open-label therapy before progression according to central read
  - 12 (50%) had an objective tumor response
- Objective responses were durable; median duration of response not reached at 24 months of follow-up

Odds ratio >1 favors vandetanib
***Including all scans until progression according to central read**

Vandetanib Toxicities

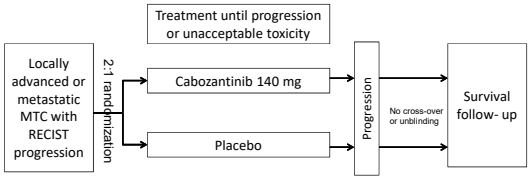
Black Box Warning: QT prolongation. Torsades de pointes and sudden death have been reported.



Most Common toxicities

Adverse Event	**Vandetanib 300mg N = 231**		**Placebo N=99**	
	All Grades	Grade 3-4	All Grades	Grade 3-4
Diarrhea/Colitis	57 %	26 %	27 %	2 %
Rash	53 %	5 %	12 %	0
Dermatitis Acneiform/Acne	35 %	1 %	7 %	0
Nausea	33 %	1 %	16 %	0
Hypertension	33 %	9 %	5 %	1 %

An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline



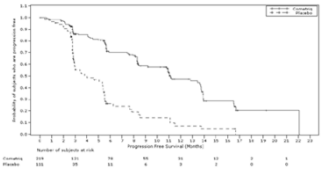
An international, double-blind, randomized, placebo-controlled phase III trial (EXAM) of cabozantinib (XL184) in medullary thyroid carcinoma (MTC) patients with documented RECIST progression at baseline

	Cabozantinib	**Placebo**
Median PFS (months)	11.2	4
1 year PFS	47.3%	7.2%
HR (95% CI)	0.28 (0.19, 0.40)	

	PR rate
Cabozantinib	27%
Placebo	0

P < 0.0001

Figure 1: Progression-Free Survival



Cabozantinib package insert

Cabozantinib Toxicity

MedDRA System Organ Class/ Preferred Terms	Cabozantinib (n=214)		Placebo (n=109)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
GASTROINTESTINAL DISORDERS				
Diarrhea	63	16	33	2
Stomatitis[2]	51	5	6	0
Nausea	43	1	21	0
Oral pain[3]	36	2	6	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	41	9	28	3
Asthenia	21	6	15	1
INVESTIGATIONS				
Decreased weight	48	5	10	0
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	46	5	16	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PPES[4]	50	13	2	0
Hair color changes/ depigmentation, graying	34	0	1	0

WARNING: PERFORATIONS AND FISTULAS, and HEMORRHAGE

See full prescribing information for complete boxed warning.

- **Perforations and Fistulas: Gastrointestinal perforations occurred in 3% and fistula formation in 1% of COMETRIQ-treated patients. Discontinue COMETRIQ in patients with perforation or fistula. (5.1)**
- **Hemorrhage: Severe, sometimes fatal, hemorrhage including hemoptysis and gastrointestinal hemorrhage occurred in 3% of COMETRIQ-treated patients. Monitor patients for signs and symptoms of bleeding. Do not administer COMETRIQ to patients with severe hemorrhage. (5.2)**

Cabozantinib package insert

Selpercatinib

- Subset global Ph 1/2 trial Libretto-001 trial
- Included patients with RET-mutated MTC who were treated with prior cabozantinib or vandetanib (N=55) or treatment naïve (N=88)

Table 11 Efficacy Results in LIBRETTO-001 (RET-Mutant MTC Previously Treated with Cabozantinib or Vandetanib)

	RETEVMO (n = 55)
Overall Response Rate[1] (95% CI)	69% (55%, 81%)
Complete response	9%
Partial response	60%
Duration of Response	
Median in months (95% CI)	NE (19.1, NE)
% with ≥ 6 months[2]	76

[1] Confirmed overall response rate assessed by BICR.
[2] Based on observed duration of response
NE = not estimable

Table 12 Efficacy Results in LIBRETTO-001 (Cabozantinib and Vandetanib-naïve RET-Mutant MTC)

	RETEVMO (n = 88)
Overall Response Rate[1] (95% CI)	73% (62%, 82%)
Complete response	11%
Partial response	61%
Duration of Response	
Median in months (95% CI)	22.0 (NE, NE)
% with ≥ 6 months[2]	81

[1] Confirmed overall response rate assessed by BICR.
[2] Based on observed duration of response
NE = not estimable

https://uspl.lilly.com/retevmo/retevmo.html#pi

MTC Summary

- Hereditary or sporadic neuroendocrine tumor
  - MEN 2 syndromes – germline RET mutations
  - Sporadic - ~ 50% somatic RET mutations
- Can present with systemic symptoms related to hormone production
- Surgery is the mainstay of therapy
- RAI and TSH suppression are NOT effective treatments for MTC
- Advanced progressive or symptomatic disease not amenable to surgical resection can be treated with vandetanib or cabozantinib regardless of whether there is a RET mutation
  - Must institute cautiously given the often indolent nature of the malignancy and potential toxicities – no overall survival benefit
- Selective RET inhibitor selpercatinib is now approved for RET mutated MTC

Adrenal Tumors

Adrenocortical Carcinoma

Pheochromocytoma

ACC Epidemiology

- Rare: 1-2 cases/million/year
- Bimodal age distribution
  - < 5 or 40-50
- Tumor of the adrenal cortex
  - Tumors of adrenal medulla = pheochromocytoma
- Can be “functioning” or “non-functioning”

ACC Clinical Presentation

- ~ 60% functioning/secretory
  - Adrenal hormone secretion
    - Cortisol: Cushing’s syndrome (most common ~45%)
    - Aldosterone: hypertension, hypokalemia
    - Androgen or estrogen: Virilization or feminization
- Patients with non-functioning tumors present with incidental finding or tumor-related symptoms
- Diameter of adrenal mass is predictive of malignancy
  - Most adrenal adenomas are <4 cm, most ACCs are >4 cm in diameter when discovered

ACC Pathogenesis

- Most cases are sporadic
- Inherited syndromes:
  - Li-Fraumeni (TP53 mutation): breast cancer, sarcoma, brain tumor, ACC
  - Beckwith-Wiedemann (chromosome 11p15): Wilms’ tumor, neuroblastoma, hepatoblastoma, ACC
  - MEN 1 (MEN1 gene): parathyroid, pituitary, pancreatic neuroendocrine tumors, adrenal adenoma, ACC
  - SBLA syndrome (unknown cause): sarcoma, breast, lung, ACC, others

ACC Diagnosis

- Hormonal evaluation
- Rule out pheochromocytoma with plasma or urine metanephrines and catecholamines
  - Particularly prior to bx of an adrenal lesion
    - High rate of complications with pheo bx
- PET-CT has sensitivity of 100% and specificity of 98% for differentiating carcinoma from adenoma
- FNA not helpful to distinguish adrenal adenoma from carcinoma
    - Useful to distinguish adrenal met from primary adrenal lesion

ACC Staging

Most treatment studies use European Network for The Study of Adrenal Tumors ENSAT staging (differentiates resectable Stage IV from Stage IV with distant disease)

Stage	Description	TNM	5-yr survival
Stage I	Confined to adrenal gland, tumor ≤ 5 cm	T1N0M0	82%
Stage II	Same as I, but tumor > 5 cm	T2N0M0	61%
Stage III	Any size but at least one RF: Infiltration Tumor thrombus Positive LNs	 T3 T4 N1	50%
Stage IV	Distant Metastases	M1	13%

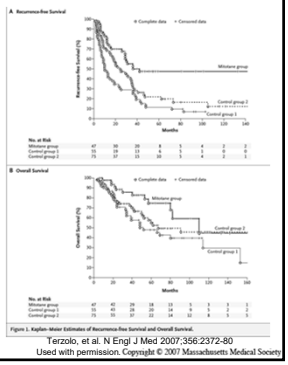
Fassnacht, et al. Cancer. 2009;115(2):243

ACC Primary Treatment

- Surgery: preferred treatment if possible for stage I-III
  - Open adrenalectomy with lymphadenectomy
  - Incomplete resection with maximum debulking may help relieve symptoms in patients with hormone-secreting tumors
- Unresectable or incomplete resection
  - Mitotane: adrenocorticolytic
    - Main benefit is reduce symptoms
    - Decreases symptoms in ~75% of patients
    - ~33% response rate
    - Does not prolong survival – median survival 6.5 months

ACC Adjuvant Therapy - Mitotane

- Data for adjuvant mitotane is conflicting
  - Rare cancer, few trials
- Retrospective trial: Stage I, II, III disease
  - Mitotane:
    - RFS = 42 mo
    - OS = 110 mo
  - Control groups:
    - RFS = 10 and 25 mo (p<0.001 and 0.005)
    - OS = 52 and 67 mo (p = 0.01 and 0.1)

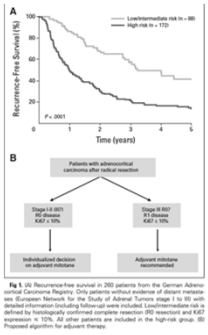


Terzolo, et al. N Engl J Med 2007;356:2372-80

*

Considerations for Mitotane Use

- Mitotane levels must be monitored!!!
  - Therapeutic at 14-20 mcg/ml
  - Toxicities:
    - Weakness, somnolence, confusion, lethargy, headache
    - Anorexia, nausea, diarrhea
    - Ataxia, vertigo, dysarthria
- ADIUVO trial for low to intermediate risk ACC (I-III, R0 resection, Ki67 <10)

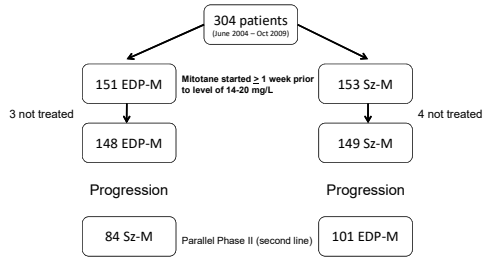


Adjuvant therapy in patients with adrenocortical carcinoma: a position of an international panel: JCO 2010.

ACC Adjuvant Therapy -- Radiation

- No prospective data, retrospective data that it improves local control, not survival
- NCCN guidelines suggest for localized, high grade tumors to "consider RT to tumor bed"
- German ACC registry:
  - recommend adjuvant RT for: microscopically incomplete (R1 or R2) or uncertain (Rx) margin, and stage III disease
  - Considered for tumor > 8 cm with invasion (not thrombus) and Ki67 > 10%, or spillage
- RT can also be used for metastatic sites as needed

FIRM-ACT Trial Treatment



EDP-M = Etoposide 100mg/m2 IV days 2,3,4; Doxorubicin 40mg/m2 day 1; Cisplatin 40mg/m2 days 3,4; oral mitotane continuously
Sz-M = streptozocin 1g IV days 1-5 (cycle 1) then 2g day 1 each cycle; oral mitotane continuously

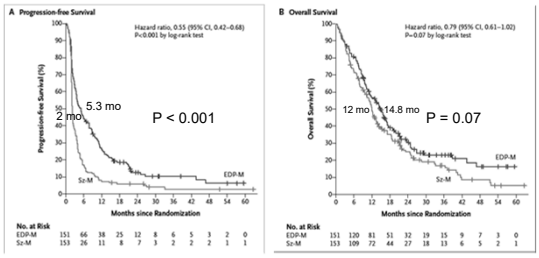
Fassnacht, et al. N Engl J Med 2012; 366:2189-2197

Best Overall Response (RECIST)

Variable	EDP-M	Sz-M	P value
Type of response n (%)			
Complete response	2 (1.3)	1 (0.7)	
Partial response	23 (21.8)	13 (8.5)	
Stable disease (≥ 8 weeks)	53 (35.1)	34 (22.2)	
Progressive disease	43 (28.5)	88 (57.5	
Did not receive treatment	3 (2.0)	4 (2.6)	
Not evaluable	17 (11.3)	13 (8.5)	
Objective response	35	14	
% (95% CI)	23.2 (16.7-30.7)	9.2 (5.1-14.9)	< 0.001
Disease control (CR + PR + SD)	88	48	
% (95% CI)	58.3 (50.0-66.2)	31.4 (24.1-39.4)	< 0.001

Fassnacht, et al. N Engl J Med 2012; 366:2189-2197

Progression-Free Survival and Overall Survival



26.1% of EDP-M patients had no progression at 12 months
7.2% of Sz-M patients had no progression at 12 months

Fassnacht, et al. N Engl J Med 2012; 366:2189-2197

*

Controlling hormonal excess

- Mitotane – adrenocorticolytic
- Metyrapone – inhibits last step of cortisol biosynthesis (off-label use)
- Ketoconazole – inhibits 1st step of cortisol biosynthesis (off-label use)

ACC Summary

- 60% present as functioning tumors
  - Most commonly Cushing's syndrome +/- virilism
- Diagnosis made by CT characteristics, hormone levels
- Surgery is only chance of cure
  - Stage I-III
  - Debulking for symptom control
- Mitotane is often used in the adjuvant setting and for metastatic disease +/- other systemic therapy
  - Improves adrenocortical hormone-related sx
  - Can have objective tumor responses
- FIRM-ACT trial showed that EDP-M had higher anti-tumor efficacy than Sz-M as first line therapy
  - No overall survival advantage

Pheochromocytoma

- Arises from the chromaffin cells of the adrenal medulla
- Paraganglioma is considered an "extra-adrenal pheochromocytoma"
  - Arises from the sympathetic ganglia
  - Produces catecholamines
  - Treated the same as pheochromocytoma
- Associated with hereditary syndromes in about 40% of cases: VHL, MEN2, NF1

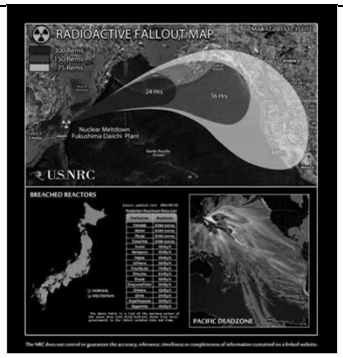
Pheochromocytoma

- Symptoms occur in ~50% of patients and are often paroxysmal
- Classic Triad: episodic headache, sweating, tachycardia
- 85-95% will have hypertension
- Approximately 10% are malignant and 10% are multiple
- Diagnosis: measure urine and plasma fractionated metanephrines and catecholamines

Pheochromocytoma - treatment

- Surgical resection is mainstay of treatment
  - Laparoscopic appropriate if performed by experienced surgeon
  - Preoperative control of blood pressure and alpha and beta-adrenergic blockade to prevent intraoperative hypertensive crisis
- Metastatic disease:
  - I^{131} attached to MIBG (iobenguane I-131) if takes up MIBG on scan
  - Octreotide
  - CVD (cyclophosphamide, vincristine, dacarbazine)
  - Lutathera (^{177}Lu-DOTATATE) in a clinical trial, not FDA approved for pheo/paraganglioma

QUESTIONS?



56

Renal Cell Cancer

Dean F. Bajorin, MD, FACP

August 19, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

56 – Renal Cell Cancer

Dean Bajorin, MD, FACP

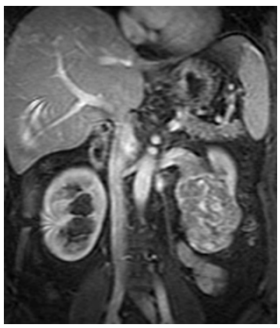
Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultancy: Novartis, Merck, Merck Sharpe and Dome, Fidia Farmaceutici, Bristol-Myers Squibb, Astra Zeneca, Dragonfly and Pfizer
- Honoraria: Novartis, Merck, Merck Sharpe and Dome, Fidia Farmaceutici, Bristol-Myers Squibb, Astra Zeneca, Dragonfly and Pfizer
- Research Funding: Novartis, Merck, Merck Sharpe and Dome, Fidia Farmaceutici, Bristol-Myers Squibb, Astra Zeneca, Dragonfly and Pfizer

Renal Cortical Tumors
Epidemiology

- Malignant tumors of the kidney account for 2% of all cancers in USA each year.
- Median age at diagnosis is 66 years and median age at death is 70 years.
- Autopsy incidence is ~ 2-5%.
- Incidental tumor detection: 70%
- Median tumor size: 3.5 cm
- 30-40% of patients will present with or eventually develop metastatic disease.



Renal Cortical Tumors

Renal cortical tumors account for 90% of solid renal masses.

Benign renal masses: angiomyolipoma, hemorrhagic cyst, cystic nephroma, AVM, leiomyoma, oncocytoma

Other malignant renal tumors include:

- **TCCa of renal pelvis**
- **Wilm's tumor (children and adults)**
- **Metastatic tumors (rare)**
- **Renal or peri-renal sarcoma**
- **Lymphoma**

Associated Risk Factors

Smoking (2X risk, history in 20-30% of patients)

Obesity (particularly women): linear relation w/ body weight

Hypertension

Unopposed estrogen therapy

Occupational exposure to: petroleum products, heavy metals, asbestos

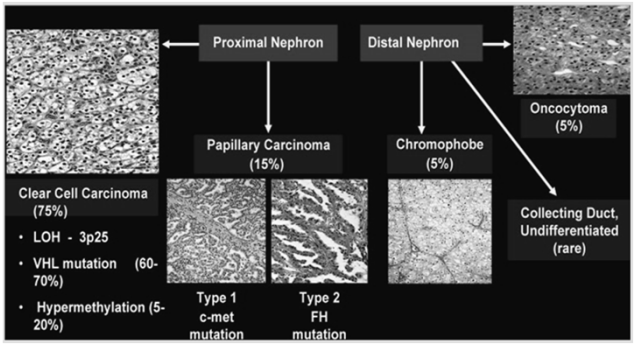
? Carcinogenic effects of chronic kidney disease (CKD).

Renal Cortical Tumors:
1997 Heidelberg Classification

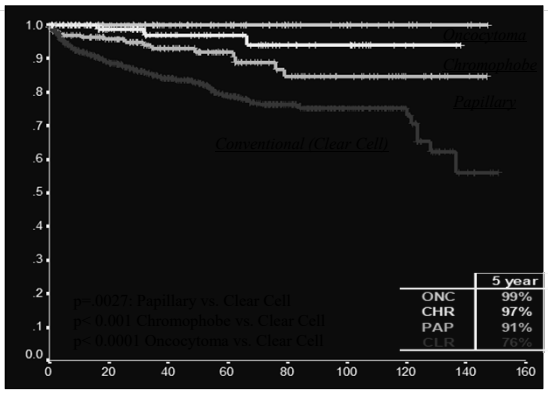
- **Benign Parenchymal Neoplasms**
  - Metanephric Adenoma
  - Metanephric adenofibroma
  - Papillary renal cell adenoma
  - *Renal Oncocytoma
- **Malignant Parenchymal Neoplasms**
  - *Conventional (Clear Cell)
  - *Papillary
  - *Chromophobe
  - Collecting duct carcinoma
    - Medullary carcinoma of the kidney
  - Unclassified

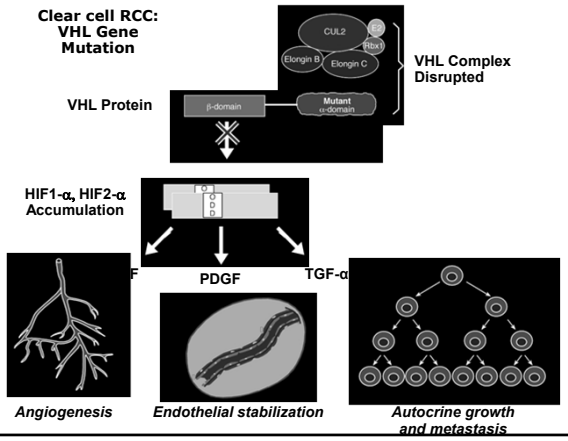
Kovacs, G., Akhtar, M., and Beckwith, B. J.: The Heidelberg Classification of renal cell tumors. J Pathol, 183: 131, 1997

Genetic Findings in RCT Subtypes



Progression Free Probability by Histological Subtype





Genetic Findings in RCT Subtypes

Histological Subtype	%	Genetic/ Molecular Defects	Associated Syndromes
Conventional Clear Cell	75	**LOH 3p Mutation of 3p25 (VHL)**	**Von Hippel-Lindau** Sporadic RCC Hereditary RCC
Papillary 1	5	C-Met Gene mutation 7q31	Hereditary Papillary (HPRCC)
Papillary 2	10	Fumarate hydratase 1q42	Sporadic Papillary
Chromophobe	5	Birt-Hogg Dube 17p11	Birt-Hogg Dube
Oncocytoma	9.7	Birt-Hogg Dube 17p11	Familial Oncocytoma Birt-Hogg Dube
Collecting Duct	0.4	-18, -Y	Renal Medullary Carcinoma

*Zambrano N., Histopathology and Molecular Genetics of Renal Tumors J. Urol, Oct 1999

Von Hippel Lindau Syndrome

- Autosomal dominant mutation in 3p25 (VHL)
- 40% VHL patients have RCC with retinal and CNS findings usually preceding discovery of renal involvement
- Multicentric, bilateral renal involvement in ~ 75% patients
- MSKCC: 5 VHL patients / 2002 RCC patients operated on between 1989 and 2005
- Renal cancer and renal insufficiency are now the leading cause of death in VHL

Choyke PL, Glenn GM, McClellan M, et al. Radiology, 1995, 146:629-42.

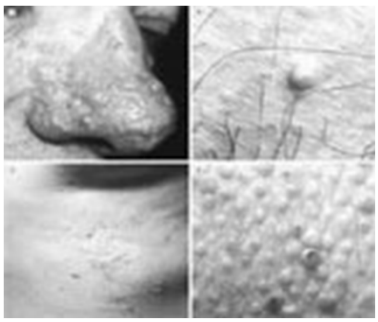
Von Hippel Lindau Syndrome

VHL: Familial multiple cancer syndrome
- Hemangiomas
- Hemangioblastomas (brain, spinal cord, retina)
- Pheochromocytomas
- Pancreatic carcinomas
- Epididymal cysts
- RCC (40% of VHL patients)
- Renal cysts multiple/bilateral (49-85%)

Birt-Hogg-Dubé Syndrome (BHD)

- Hereditary hair follicle tumors located on face and neck
- Kidney tumors of multiple tumor histologies develop in 20-30% of patients (chromophobe commonest)
- Bilateral, multi-focal renal tumors (chromophobe, oncocytoma, clear cell)
- Lung cysts occur in 90%
- Spontaneous pneumothorax (20%)
- Genetic linkage analysis places the BHD on chromosome 17.
- FLCN gene (folliculin- ?tumor suppressor)

Birt-Hogg-Dubé Syndrome



BHDSyndrome.org; Courtesy of Urologic Oncology Branch, NCI, NIH

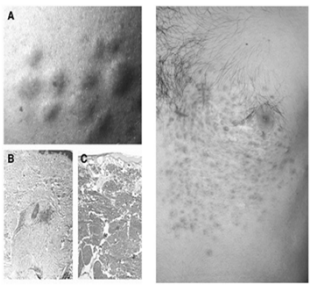
Hereditary Syndromes: Clinical Features

Hereditary Papillary Renal Cell Carcinoma (HPRC)
Risk of bilateral, multifocal papillary RCC
Patients develop papillary RCC (type 1)
Mutations in c-MET

Hereditary Leiomyomatosis Renal Cell Carcinoma (HLRCC)
Uterine leiomyomas (more common) or leiomyosarcoma (rare)
Cutaneous nodules (leiomyomas)
Type 2 papillary RCC, frequently solitary, aggressive
Germline mutation in gene recently identified is fumarate hydratase (FH) codes for a Krebs cycle enzyme

Cutaneous Leiomyomas

Found on both extremity and trunk Isolated or disseminated in distribution. may be painful



http://www.vhl.org/hlrcc

When to refer for Genetic Counseling? ACMG Practice Guidelines

• RCC with clear cell histology, if any of the following criteria are met:	VHL, OMIM 193300; BHD, OMIM 135150
–dx at age <50	
–Bilateral or multifocal tumors	
–≥1 close relative with clear cell RCC	
• RCC with papillary type 1 histology	HPRC, OMIM 605074
• RCC with papillary type 2 histology	HLRCC, OMIM 605839, 150800
• RCC with collecting duct histology	HLRCC, OMIM 605839, 150800
• RCC with tubulopapillary histology	HLRCC, OMIM 605839, 150800
• RCC with BHD-related histology (chromophobe, oncocytoma, oncocytic hybrid)	BHD, OMIM 135150
• Urothelial carcinoma (or transitional cell carcinoma) and 2 additional cases of any LS-associated cancer (Table 6) in the same person or in relatives	LS, OMIM 120435, 120436
• RCC and 2 additional Cowden syndrome criteria (Table 4) in the same person	Cowden, OMIM 158350
• Angiomyolipomas of the kidney and one additional TSC criterion (Table 8) in the same person	TSC, OMIM 191100

OMIM - Online Mendelian Inheritance in Man
https://www.omim.org

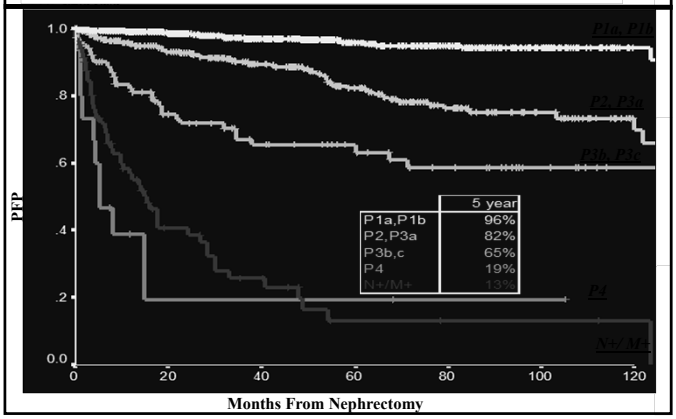
Hampel et al. Genetics in Medicine 2014

Renal Cell Carcinoma Primary Tumor (T) AJCC/UICC Staging

pTxPrimary tumor cannot be assessed
pTo No evidence of primary tumor
pT1 Tumor 7 cm or less confined to kidney
pT1a 4 cm or less
pT1b > 4 cm but not greater than 7 cm
pT2 > 7 cm but confined to kidney
pT3 Tumor involves major veins, adrenal, or perinephric tissue but not beyond Gerota's fascia
pT3a adrenal or perinephric tissue
pT3b renal vein or vena cava below diaphragm
pT3c vena cava above diaphragm
pT4 Beyond Gerota's fascia.

TNM Classification of Malignant Tumours, Sixth Ed, UICC, 2002 p. 193 – 196.

Progression Free Probability by Pathological Stage

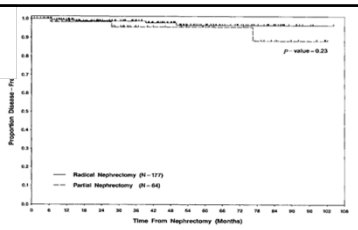


Changing Landscape Leads to Expansion in Partial Nephrectomy

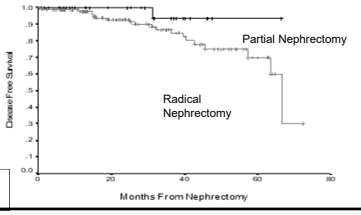
- 70% of tumors now discovered incidentally.
- New concerns for long term renal health of patients subjected to radical nephrectomy.
- Partial nephrectomy is equally effective to radical nephrectomy for tumors of 7cm or less.
- Small but real risk (5%) of contralateral tumor formation in patient's lifetime.

Expansion of Surgery to Partial Nephrectomy

Disease-Free Survival
Partial and Radical Nephrectomy:
Tumors 4cm or less



Conventional (Clear Cell)
tumors 4 to 7cm
in greatest diameter.



McKiernan et al. Urology 59:816–820, 2002
Dash et al, BJU, 97:939, 2006

Impact on Renal Function Partial compared to Radical Nephrectomy *(N=662)*

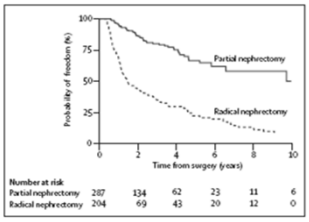


Figure 2: Probability of freedom from new onset of GFR lower than 60 mL/min per 1·72 m², by operation type

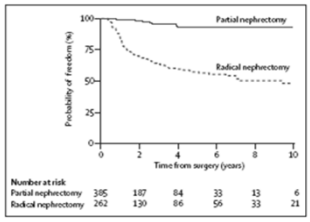


Figure 3: Probability of freedom from new onset of GFR lower than 45 mL/min per 1·72 m², by operation type

Huang et al. Lancet Oncol 2006; 7: 735–40

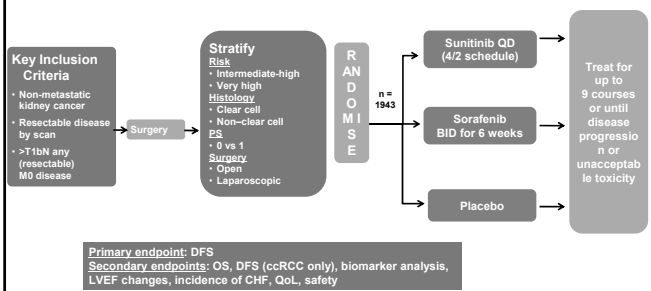
RCC: Does Adjuvant Therapy impact Survival?

Author	Trial	Number	Benefit?
Pizzocaro	IFN vs Surveillance	264	No
Porzolt	IFN vs Surveillance	270	No
Messing	IFN vs Surveillance	283	No
Clark	HD-IL-2 vs surveillance	69	No
Atzpodien	IL-2, IFN & 5-FU vs surveillance	200	No
Aitchison	IL-2, IFN & 5-FU vs surveillance	309	No
Wood	HSP vaccine vs surveillance	818	No

Adjuvant Randomized Phase III trials with modern TKI's:

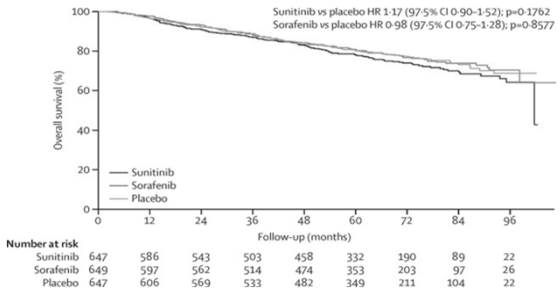
ASSURE – Sorafenib vs Sunitinib vs placebo - NB
S-TRAC – Sunitinib- FDA approved based on benefit
PROTECT – Pazopanib- NB
ATLAS – Axitinib –terminated early by DSMC-NB (Annals Oncol 2018)
SORCE – Sorafenib- no benefit (1 yr vs 3 yrs vs surveillance) (ESMO 2019)

Adjuvant Sorafenib vs Sunitinib vs Placebo Phase III ASSURE Trial (ECOG E2805)



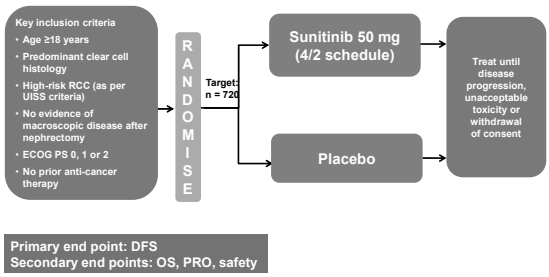
Hass NB et al., 2015 ASCO Annual Meeting

ASSURE – no difference in disease-free survival was seen between treatment arms



Haas NB, et al. *Lancet* 2016; 387:2008-16

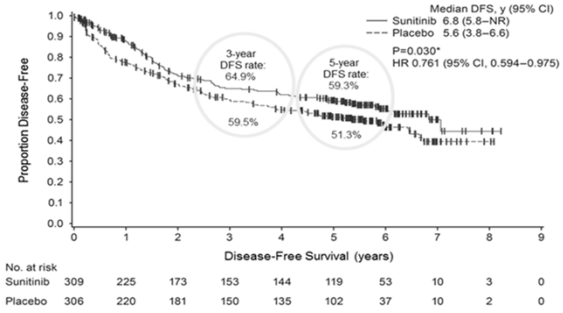
Phase III S-TRAC trial – adjuvant sunitinib vs. placebo



Primary end point: DFS
Secondary end points: OS, PRO, safety

Ravaud et al. Presented at: 2016 ESMO Annual Meeting

S-TRAC - superior disease-free survival for sunitinib-treated patients



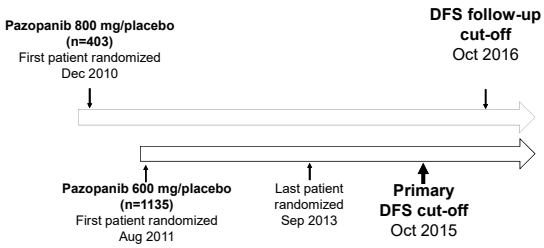
Ravaud A et al. ESMO 2016
Ravaud A et al. *N Engl J Med* 2016 Oct 9

ASSURE & S-TRAC – subtle differences

	S-TRAC	ASSURE (sunitinib arm)
Numbers total	615	1294
Sponsor	Pfizer	ECOG, SWOG, CLGB, NCI
T-stages(n) - T1-2 - T3-4	 - 615 (100%)	 469 (36.3%) 824 (63.7%)
Histology - Clear cell - Non clear-cell	 99.0% 1%	 79% (=1021 patients) 21%
Completion of 1 year sunitinib (%)	55,6%	59%
Discontinuation of therapy in the sunitinib arm - total - AE	 44.4% 28.1%	 Full dose: 193/438 (44%)[s] Reduced: 65/191 (34%) Total: 258/629 (41%)
Starting dose sunitinib at 50 mg/d	306 (100%)	438/647 (67.7%)

Adapted from Bex A, ESMO Annual Meeting 2016

Adjuvant Pazopanib (PROTECT)



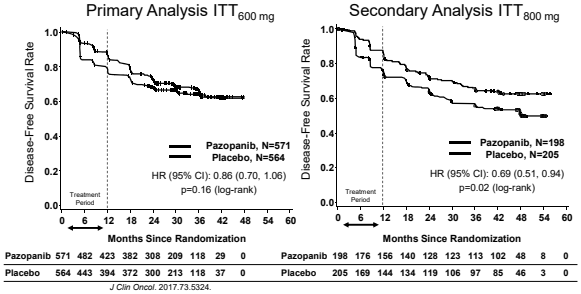
J Clin Oncol 2017

Randomized phase III trial of adjuvant pazopanib versus placebo after nephrectomy in patients with locally advanced renal cell carcinoma (RCC) (PROTECT)

	ITT 600		ITT 800		ITT ALL	
	Pazopanib	Placebo	Pazopanib	Placebo	Pazopanib	Placebo
	N = 571	N = 564	N = 198	N = 205	N = 769	N = 769
DFS—Primary analysis, HR (95% CI)	0.862 (0.699, 1.063); p = 0.165*		0.693 (0.510, 0.943)		0.802 (0.675, 0.954)	
DFS—Follow up analysis, HR (95% CI)	0.936 (0.769, 1.140)		0.663 (0.491, 0.895)		0.842 (0.714, 0.993)	
DFS rate at 3 years, % (95% CI)	67 (62, 71)	64 (60, 68)	66 (58, 72)	56 (48, 62)	66 (63, 70)	62 (58, 65)
DFS rate at 5 years, % (95% CI)	NA	NA	61 (53, 68)	48 (40, 55)	58 (53, 62)	54 (48, 58)

Motzer et al. ASCO 2017

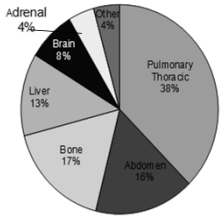
Adjuvant Pazopanib (PROTECT)



J Clin Oncol. 2017.73.5324.

Metastatic RCC

Patterns of Metastases: Organ Sites

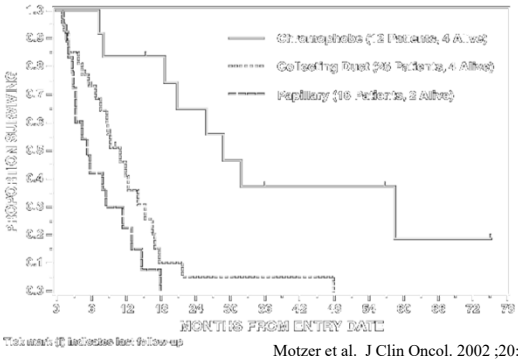


Prognostic Factors: Cytokine era, Prior to TKI's

	p-value	Risk Ratio
LDH (>1.5 x nl)	0.00001	2.5
Hemoglobin (< Normal)	0.00001	1.7
Corrected Calcium (>10)	0.00001	1.7
Karnofsky Perf. Status (< 80)	0.00001	1.5
Nephrectomy (None)	0.001	1.4

J Clin Oncol 17: 2530, 1999

Non-Clear Cell Histology: Survival by Cell Type



Motzer et al. J Clin Oncol. 2002 ;20:2376-81.

RCC: Treatment Options for Metastatic Disease

Metastectomy
Nephrectomy in Metastatic Disease
Tyrosine Kinase Inhibitor Therapy
Checkpoint Blockade Therapy

Renal Cell Carcinoma Surgical Resection of Metastasis

- 278 Patients with recurrent RCC 1980-1993.
  - 141 (51%) underwent curative metastasectomy
  - 70 (25%) underwent non-curative resection
  - 67 (24%) received non-surgical treatment
- Variables:
  - Site and number of metastatic deposits
  - Performance status of the patient
  - Disease-free interval from treatment of primary tumor to diagnosis of metastatic disease.

Kavolus et al J Clin Oncol. 1998 16:2261-6.

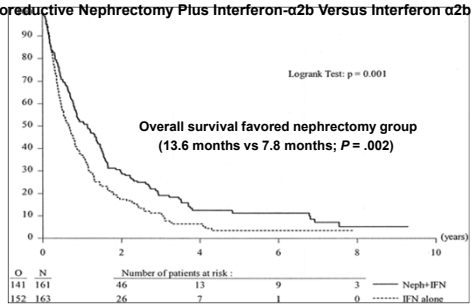
Renal Cell Carcinoma Surgical Resection of Metastasis

	Five-year Survival
Surgical Resection (n=141)	
Non-curative	14%
Curative intent	44%
Solitary (n=94)	
Lung Only	50%
Brain	18%
Non-surgical therapy (n=67)	11%
Prognostic factors	
DFI > 12 ms	55% vs 9%
Solitary vs multiple	54% vs 29%
Age < 60 yrs	49 vs 35%

Kavolus et al J Clin Oncol. 1998 16:2261-6.

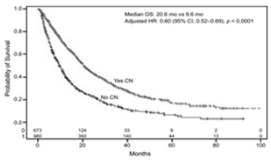
Debulking nephrectomy: Prospective trial of Pre-treatment Nx from the cytokine era

Cytoreductive Nephrectomy Plus Interferon-α2b Versus Interferon α2b Alone



Flanigan et al. *J Urol.* 2004;171:1071-1076

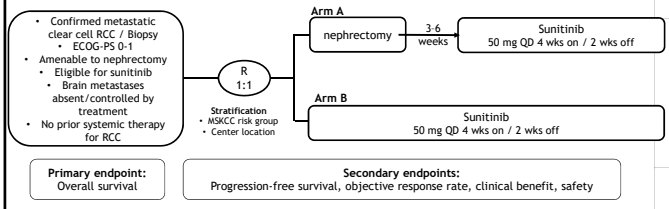
Debulking Nephrectomy: retrospective data from the targeted era – IMDC cohort (n=1,633)



IMDC RF	No CN OS, mo (n)	CN OS, mo (n)	p value
0	insufficient number to compare		
1	22.5 (n = 72)	30.4 (n = 178)	0.002
2	10.2 (n = 143)	20.2 (n = 253)	<0.001
3	10.0 (n = 113)	15.9 (n = 106)	<0.001
4	5.4 (n = 103)	6.0 (n = 67)	0.166
5	3.6 (n = 36)	2.8 (n = 14)	0.504
6	insufficient number to compare		

Heng et al., *Eur Urol* 2014 Oct;66(4):704-10

CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study



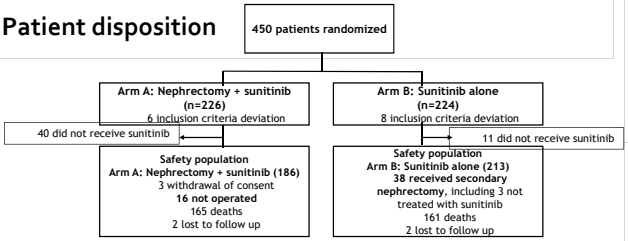
Primary endpoint: Overall survival

Secondary endpoints: Progression-free survival, objective response rate, clinical benefit, safety

The study was designed to have 80% power at a 1-sided significance level of 5% (risk alpha)
Non-inferiority margin of HR: upper 95% CI ≤1.20 for sunitinib alone

Arnaud Méjean et al. ASCO 2018 and NEJM

Patient disposition



- From Sept. 2009 to Sept. 2017, 450 patients were enrolled
- Second interim analysis, cutoff Sept. 9, 2017: 326 events had occurred
- Median follow-up 50.9 months
- Based on overall survival results, the Steering Committee decided to stop the trial and considered this interim analysis as final

Arnaud Méjean et al. ASCO 2018 and NEJM

Patient characteristics

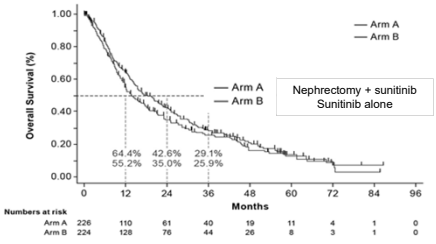
Characteristic	Arm A: Nephrectomy + sunitinib (N = 226)	Arm B: Sunitinib alone (N = 224)
Median age (range), years	63 (33–84)	62 (30–87)
Male sex, n (%)	169 (75)	167 (75)
MSKCC score, n (%)		
Intermediate	**125 (56)**	**131 (59)**
Poor	**100 (44)**	**93 (41)**
Missing	**1**	**0**
ECOG PS, n (%)		
0	**130 (57)**	**122 (54)**
1	**96 (42)**	**102 (45)**

Arnaud Méjean et al. ASCO 2018 and NEJM

Overall survival (ITT)

Median follow-up 50.9 months (range 0.0-86.6)

HR 95%CI = 0.89 (0.71-1.10)
Non inferiority study ≤1.20



Median OS, months (95% CI)	Arm A: Nephrectomy + Sunitinib (n = 226)	Arm B: Sunitinib alone (n = 224)	HR (95% CI)
Overall	13.9 (11.8–18.3)	18.4 (14.7–23.0)	0.89 (0.71–1.10)
MSKCC intermediate risk	**19.0 (12.0–28.0)**	**23.4 (17.0–32.0)**	**0.92 (0.6–1.24)**
MSKCC poor risk	**10.2 (9.0–14.0)**	**13.3 (9.0–17.0)**	**0.86 (0.62–1.17)**

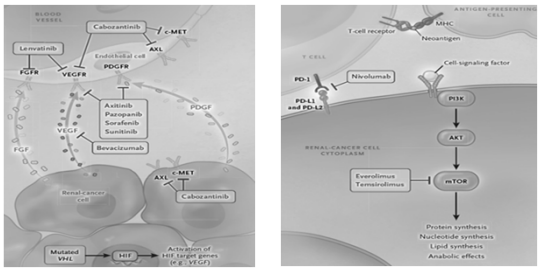
RCC: rIL-2 High-dose Bolus

Author	Patients	CR (%CR+PR)
Atkins	71	4 (17%)
Fyfe	255	12 (14%)
Yang	65	2 (20%)
Rosenberg	149	10 (20%)
Rosenberg	48	4 (21%)
Taneja	28	1 (18%)
Bukowski	41	1 (15%)
Abrams	16	0
All	**673**	**34 (17%)**

*Approved due to durable CR's

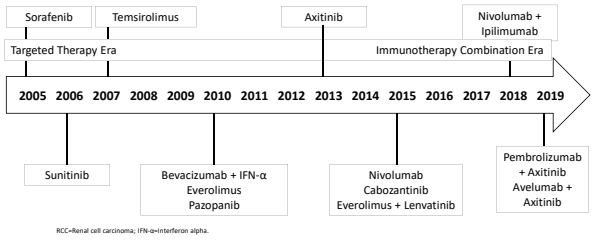
J Urol 163: 308, 1999

Overview – Targeted therapies for advanced renal cell cancer



adapted from N Engl J Med 2017;376:354-366

Treatment Landscape for Metastatic RCC



RCC=Renal cell carcinoma; IFN-α=interferon alpha.

Poor Risk Factors in Advanced Untreated RCC

MSKCC Criteria	
Karnofsky Performance Status	<80%
Time from diagnosis to treatment with IFN-α	<12 months
Hemoglobin	<LLR
LDH	>1.5 x ULR
Corrected serum calcium	>10.0 mg/dL

IFN = interferon; KPS = Karnofsky PS; LDH = lactate dehydrogenase;
LLR = lower limit of laboratory's reference range;
MSKCC = Memorial Sloan-Kettering Cancer Center;
ULR = upper limit of laboratory's reference range.
IIMDC (International Metastatic RCC Database Consortium)

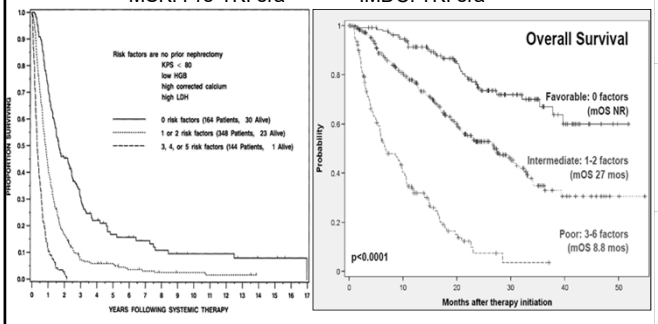
IMDC Criteria	
Karnofsky Performance Status	<80%
Time from diagnosis to treatment with TKI	<12 months
Hemoglobin	<LLR
Neutrophils	> ULR
Platelets	> ULR
Corrected serum calcium	>10.0 mg/dL

Risk Group by No. of Risk Factors	
Favorable	0
Intermediate	1 or 2
Poor	3-5

Motzer RJ et al. *J Clin Oncol.* 2002;20:289-296 Heng DY, et al. *J Clin Oncol.* 2009;27:5794-5799

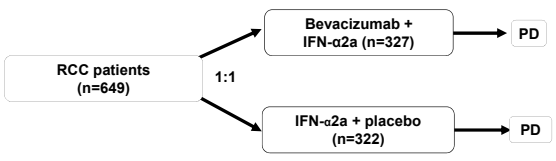
Improved Survival with the Targeted Therapies

MSK: Pre-TKI era IMDC: TKI era



J Clin Onc 1999,2002 and 2009

IFN +/- bevacizumab 1st-Line Treatment

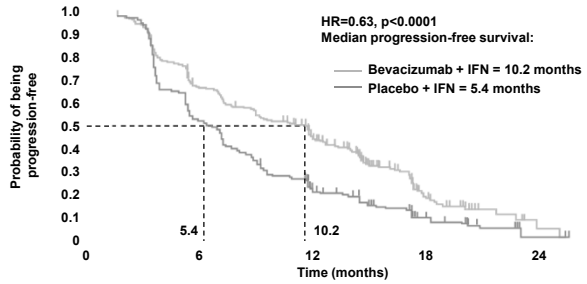


Response	IFN + placebo (n=289)	Bevacizumab + IFN (n=306)
Overall response rate (%)*	13	31
Complete response	2	1
Partial response	11	30

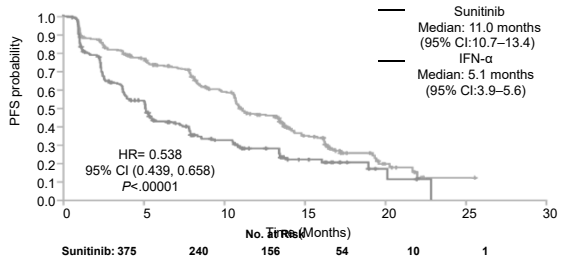
p<0.0001

Escudier et al. J Clin Oncol 2010; 28 , 2144

Progression-free survival (investigator assessed)



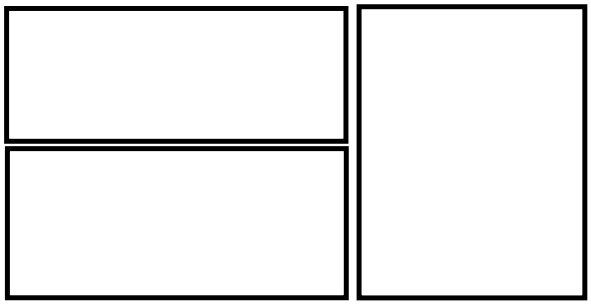
Sunitinib vs Interferon-α (Study 1034)



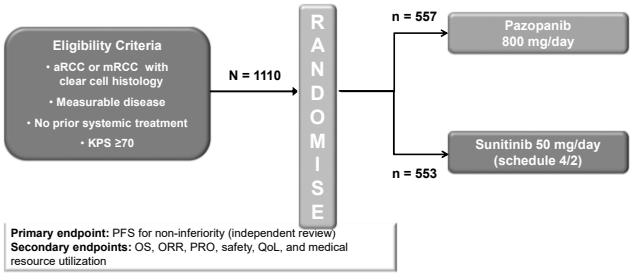
PFS by on central review

N Engl J Med. 2007;356:115–124

Sunitinib Skin Adverse Events:
Palmar - Plantar Erythrodysesthesia (21%) and Mucositis (43%)



COMPARZ: Phase III Non-Inferiority Trial of Pazopanib vs Sunitinib: Study Design



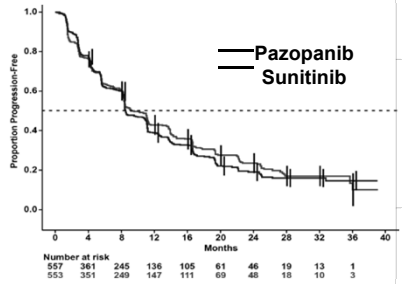
Primary endpoint: PFS for non-inferiority (independent review)
Secondary endpoints: OS, ORR, PRO, safety, QoL, and medical resource utilization

KPS, Karnofsky performance status; QoL, quality of life.

Motzer RJ et al. *N Engl J Med.* 2013;369:722-731.

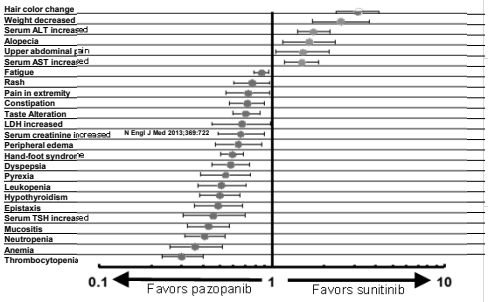
Pazopanib versus Sunitinib (COMPARZ) Progression-free Survival (independent review)

	N	Median PFS (95% CI)
Pazopanib	557	8.4 mo (8.3, 10.9)
Sunitinib	553	9.5 mo (8.3, 11.1)
HR (95% CI) = 1.047 (0.898,1.220)		



Pazopanib vs Sunitinib - Relative Risk in Adverse Events (COMPARZ)

AE occurrence ≥10% in either arm; 95% CI for RR does not cross 1



N Engl J Med 2013;369:722

Phase III: Temsirolimus vs IFN in Advanced RCC

- **626 patients with mRCC with poor-risk features**

Stratification by:

Geographic Regions:
- WEU + AU + CA (22%)
- US (30%)
- EEU + Other (48%)

Nephrectomy:
- Yes (67%)
- No (33%)

R A N D O M I Z E

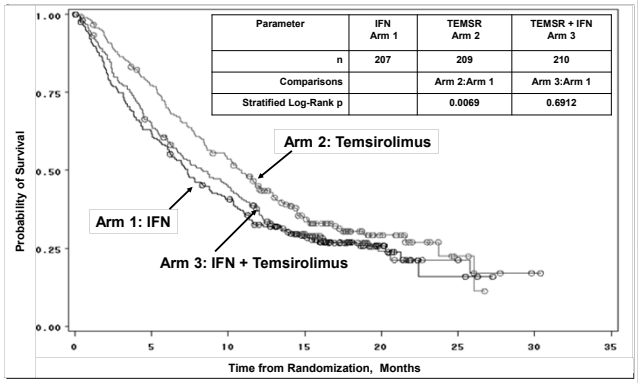
IFN: escalating to 18 MU SC TIW — n = 207

TEMSR: 25 mg IV QW — n = 209

TEMSR: 15 mg IV QW + **IFN:** 6 MU TIW — n = 210

Hudes et al. NEJM. 2007 356(22):2271-81

Overall Survival by Treatment Arm



1st-line Targeted Treatment of RCC

STUDY	n	ORR (%)	Median PFS (months) vs. IFN-α	Final Median OS (months) vs IFN-α
Sunitinib vs.IFN-α[1]	750	47 vs 12*	11 vs 5* *P*<.001	26.4 vs 21.8 *P* = .051
Bev + IFN-α vs IFN-α[2]	649	31 vs 12	10.4 vs 5.5 *P*<.0001	23.3 vs 21.3 *P* = .1291
Bev + IFN-α vs IFN-α[3]	732	25.5 vs 13.1	8.4 vs 4.9 *P*<.0001	18.3 vs 17.4 *P* =.069
Sorafenib vs IFN-α[4] (Phase II)	189	5.2 vs 8.7	5.7 vs. 5.6* *P* = .504	NA
Pazopanib vs.placebo[5]	233	30 vs 3	11.1 vs 2.8 *P*<.0000001	NA
Temsirolimus vs IFN-α[6]	626	8.6 vs 4.8	5.5 vs 3.1* *P*<.001	10.9 vs 7.3 *P* = .0069
Tivozanib vs Sorafenib	517	33vs 24	11.9 vs 9.1 P< 0.042	pending
Pazopanib vs Sunitinib (non-inferiority design)	1110	31 vs 24	8.4 vs 9.5 NS	28.3 vs 29.1 P=0.245

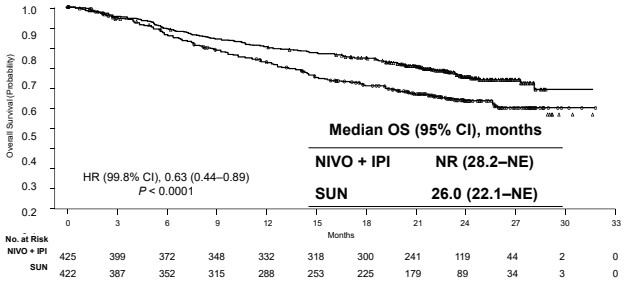
1. Motzer RJ, et al. *J Clin Oncol*. 2009; 27:3584–3590; 2. Escudier B, et al. *J Clin Oncol*. 2009;27(Suppl. 15S):5020 (Abstract); 3. Rini B, et al. *J Clin Oncol*. 2009;27(Suppl. 15S):LBA5019 (Abstract); 4. Escudier B, et al. *J Clin Oncol*. 2009;27:1280–1289; 5. Sternberg CN, et al. *J Clin Oncol*. 2010;28:1061–1068; 6. Hudes G, et al. *N Eng J Med*. 2007;356:2271–2281.

Chekmate 214: Nivo/IPI vs Sunitinib ORR and PFS by Risk Categories

	Intermediate and Poor Risk N = 847		Favorable Risk N = 249[a]	
Outcome	NIVO + IPI N = 425	SUN N = 422	NIVO + IPI N = 125	SUN N = 124
Confirmed ORR,[a] % (95% CI)	42 (37–47)	27 (22–31)	29 (21–38)	52 (43–61)
	P < 0.0001		*P* = 0.0002	
Median PFS (95%)	11.6 (8.7-15.5)	8.4 (7.0-10.8)	15.3 (9.7–20.3)	25.1 (20.9–NE)
	P=0.033		*P < 0.0001*	
Median OS	Not Reached (28.2-NE)	26 (22.1-NE)	*Not reported*	

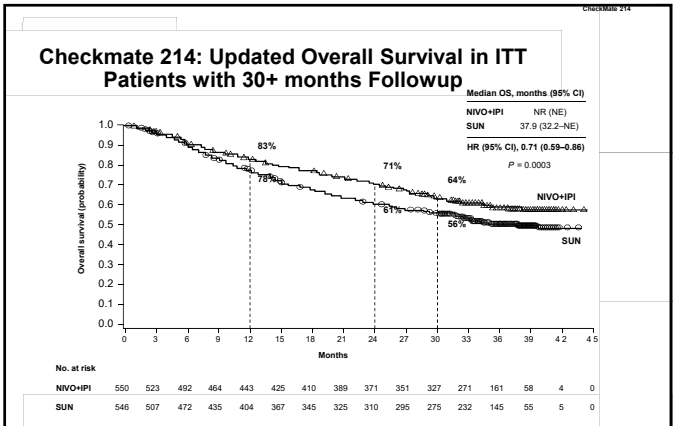
ESMO 2017

Nivo/IPI vs Sunitinib OS: IMDC intermediate/poor risk



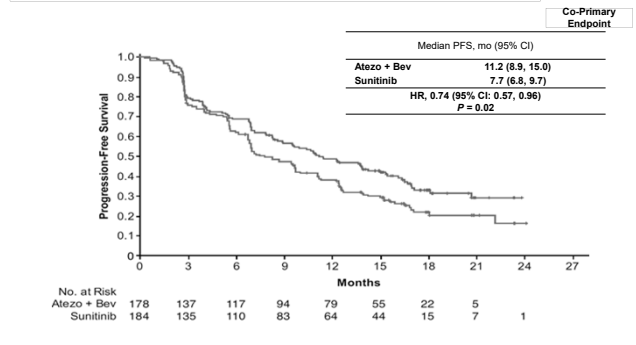
ESMO 2017

Checkmate 214: Updated Overall Survival in ITT Patients with 30+ months Followup



Tannir NM, et al. GU Ca Symp 2019. Abstract 547; Motzer RJ, et al. *Lancet Oncol*. 2019; 20: 1370–85.

Phase 3 Trial of Atezo + Bev vs Sunitinib; Progression-Free Survival in PD-L1+

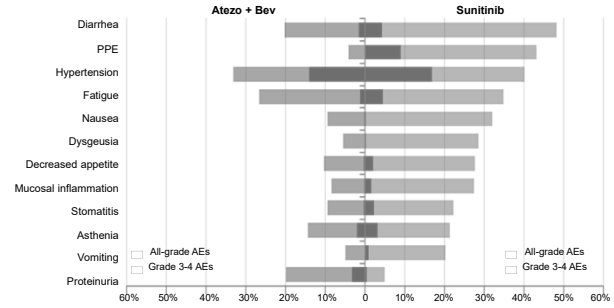


PFS assessed by investigators. Minimum follow-up, 12 mo. Median follow-up, 15 mo.
The PFS analysis passed the pre-specified *P* value boundary of alpha = 0.04. GU ASCO 2018

Atezo + Bev vs Sunitinib Treatment-related AEs

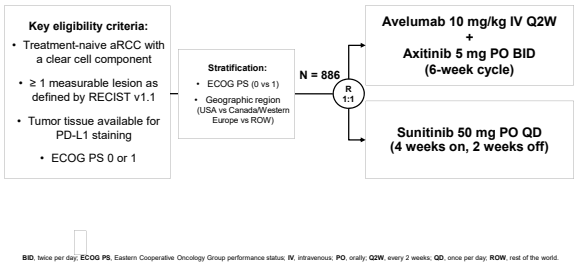
≥ 20% frequency in either arm and > 5% difference between arms

Secondary Endpoint



- PPE, palmar-plantar erythrodysesthesia. GU ASCO 2018

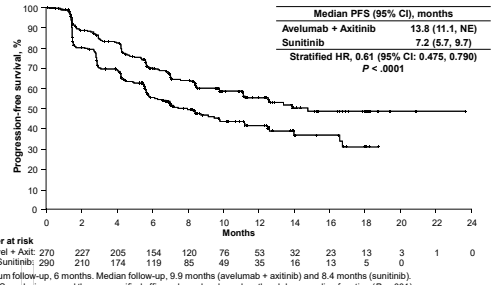
JAVELIN Renal 101: study design



BID, twice per day; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **IV**, intravenous; **PO**, orally; **Q2W**, every 2 weeks; **QD**, once per day; **ROW**, rest of the world.

PFS per IRC in the PD-L1+ group

Primary endpoint

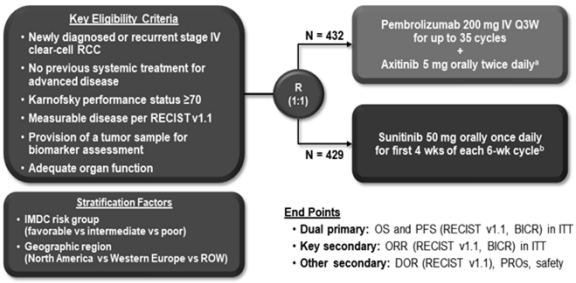


Minimum follow-up, 6 months. Median follow-up, 9.9 months (avelumab + axitinib) and 8.4 months (sunitinib).
The PFS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (*P* = .001).

NE, not estimable.

Powles KN426 ASCO-GU 2019

KEYNOTE-426 Study Design



[a]Axitinib dose could be increased to 7 mg, then 10 mg, twice daily if safety criteria were met; dose could be reduced to 3 mg, then 2 mg, twice daily to manage toxicity.
[b]Sunitinib dose could be decreased to 37.5 mg, then 25 mg, once daily for the first 4 wks of each 6-wk cycle to manage toxicity.
BICR, blinded independent central radiologic review; DOR, duration of response; PROs, patient-reported outcomes; ROW, rest of world.
KEYNOTE-426 is a randomized, open-label, phase 3 study (ClinicalTrials.gov identifier NCT02853331).

Powles KN426 ASCO-GU 2019

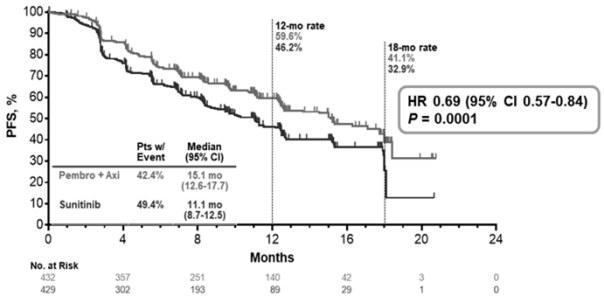
Baseline Characteristics

	Pembrolizumab + Axitinib N = 432	Sunitinib N = 429
Age, median (range)	62 yrs (30-89)	61 yrs (26-90)
Male	308 (71.3%)	320 (74.6%)
Region of enrollment		
North America	104 (24.1%)	103 (24.0%)
Western Europe	106 (24.5%)	104 (24.2%)
Rest of world	222 (51.4%)	222 (51.7%)
IMDC risk category		
Favorable	138 (31.9%)	131 (30.5%)
Intermediate	238 (55.1%)	246 (57.3%)
Poor	56 (13.0%)	52 (12.1%)
Sarcomatoid features	51/285 (17.9%)	54/293 (18.4%)
PD-L1 CPS ≥1[a]	243/410 (59.3%)	254/412 (61.7%)
≥2 metastatic organs	315 (72.9%)	331 (77.2%)
Previous nephrectomy	357 (82.6%)	358 (83.4%)

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay. CPS = combined positive score = number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
Data cutoff date: Aug 24, 2018.

Powles KN426 ASCO-GU 2019

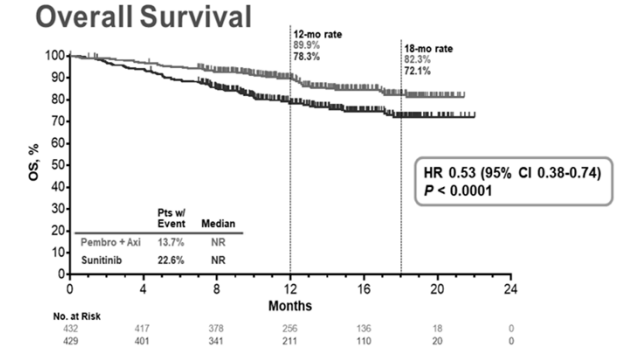
Progression-Free Survival



Data cutoff date: Aug 24, 2018.

Powles KN426 ASCO-GU 2019

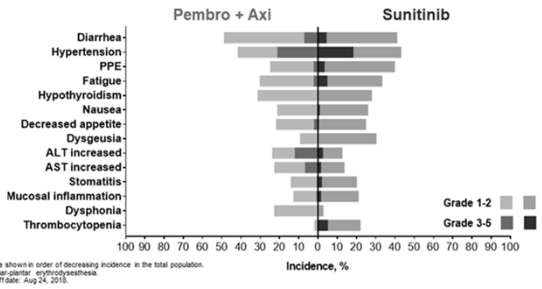
Overall Survival



Data cutoff date: Aug 24, 2018.

Powles KN426 ASCO-GU 2019

Treatment-Related Adverse Events: Incidence ≥20%



Events are shown in order of decreasing incidence in the total population.
PPE, palmar-plantar erythrodysesthesia.
Data cutoff date: Aug 24, 2018.

1L Combination Therapy Trials

Variable	Nivolumab + Ipilimumab CheckMate 214[1] n=1096	Pembrolizumab + Axitinib Keynote 426[2] n=861	Avelumab + Axitinib Javelin 101[3] n=886
IMDC Risk Group			
Favorable	23%	31%	21%
Intermediate	61%	56%	62%
Poor	17%	13%	16%
PD-L1 Expression ≥1%	24% (Dako PD-L1 28-8; Tumor)	60% (Agilent Tech PD-L1 22C3; CPS)	63% (Ventana PD-L1 SP263; Immune)
Primary Endpoint	ORR, PFS, OS in Int/Poor (IRC)	OS, PFS (IRC)	OS, PFS in PD-L1+ (IRC)

IMDC=International Metastatic RCC Database Consortium; PD-L1=Programmed Death Ligand 1; CPS=Combined positive score; ORR=Objective response rate; PFS=Progression-free survival; OS=Overall survival; Int=Intermediate; IRC=Independent review committee.

1. Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277–1290. 2. Rini BI, et al. *N Engl J Med.* 2019;380:1116-27; 3. Motzer RJ, et al. *N Engl J Med.* 2019; 380:1103-15.

Patients With Intermediate-/Poor-Risk mRCC

Keynote 426[1]	Intermediate/Poor Risk Pembro+Axi (n=294)	Intermediate/Poor Risk Sunitinib (n=298)
ORR*	55.8%	29.5%
P value	-	
CR	4.8%	0.7%
Median PFS, months	12.6	8.2
Hazard Ratio (95% CI)	0.67 (0.53-0.85)	
P value	-	
12-month OS	87%	71%
Hazard Ratio (95% CI)	0.52 (0.37-0.74)	
P value	-	

CheckMate 214[2]	Intermediate/Poor Risk Nivo+Ipi (n=425)	Intermediate/Poor Risk Sunitinib (n=422)
ORR*	42%	27%
P value	<0.001	
CR	9%	1%
Median PFS, months	11.6	8.4
Hazard Ratio (99.1% CI)	8.2 (0.64-1.05)	
P value	0.03	
12-month OS	80%	72%
Hazard Ratio (99.8% CI)	0.63 (0.44-0.89)	
P value	<0.001	

*Per blinded independent radiology review committee by RECIST version 1.1.
Pembro+Axi=Pembrolizumab + axitinib; Nivo+Ipi=Nivolumab + ipilimumab; ORR=Objective response rate; CR=Complete response; PFS=Progression-free survival; CI=Confidence interval; OS=Overall survival.

1. Rini BI, et al. *N Engl J Med.* 2019;380:1116-1127; 2. Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277–1290.

Patients With Favorable-Risk mRCC

Keynote 426	Favorable Risk Pembro+Axi (n=138)	Favorable Risk Sunitinib (n=131)
ORR*	66.7%	49.6%
P value	-	
CR	-	-
Median PFS, months	17.7	12.7
Hazard Ratio (95% CI)	0.81 (0.53-1.24)	
P value	-	
12-month OS	95%	94%
Hazard Ratio (95% CI)	0.64 (0.24-1.68)	
P value	-	

CheckMate 214	Favorable Risk Nivo+Ipi (n=125)	Favorable Risk Sunitinib (n=124)
ORR*	29%	52%
P value	<0.001	
CR	11%	6%
Median PFS, months	15.3	25.1
Hazard Ratio (95% CI)	2.18 (1.29-3.68)	
P value	<0.001	
12-month OS	94%	96%
Hazard Ratio (99.8% CI)	1.45 (0.51-4.12)	
P value	0.27	

*Per blinded independent radiology review committee by RECIST version 1.1.
Pembro+Axi=Pembrolizumab + axitinib; Nivo+Ipi=Nivolumab + ipilimumab; ORR=Objective response rate; CR=Complete response; PFS=Progression-free survival; CI=Confidence interval; OS=Overall survival.

1. Rini BI, et al. *N Engl J Med.* 2019;380:1116-1127; 2. Motzer RJ, et al. *N Engl J Med.* 2018;378(14):1277–1290.

Selected 2nd line Studies

AXIS: Phase III study of Axitinib vs. Sorafenib

Advanced RCC (N=723)
- Clear cell component
- Progression after **one** prior treatment with sunitinib, bevacizumab/IFN, temsirolimus **or cytokines**

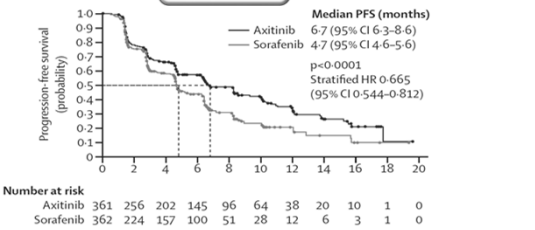
Randomization 1:1
No cross-over allowed

Axitinib n=361

Sorafenib n=362

Primary endpoint:
- PFS by independent review committee

Tumor assessments were conducted at 6 and 12 weeks, and every 8 weeks thereafter



Rini BI, et al. *Lancet*. 2011;378:1931-9.

METEOR: Phase III Cabozantinib vs Everolimus

Advanced RCC (N=650)
- Clear cell component
- Progression on or within 6 months of prior VEGFR TKI
- **No limit to the number of prior therapies**

Cabozantinib

Randomization 1:1
No crossover allowed

Everolimus

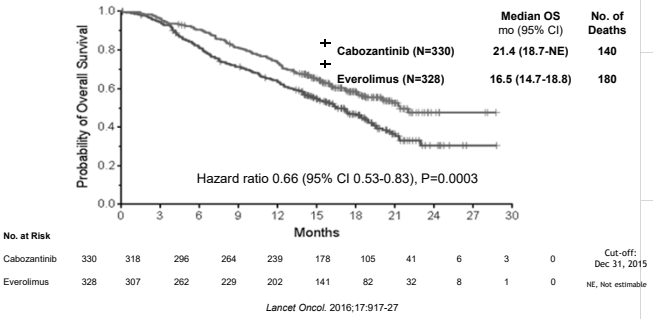
Primary Endpoint: PFS

Tumor assessment by RECIST 1.1 every 8 weeks

Treatment until loss of clinical benefit or intolerable toxicity

[1]Choueiri TK, et al. *N Engl J Med*. 2015;373:1814-1823
[2]Choueiri TK et al. *Lancet Oncol* 2016;7:917–927

Overall Survival for Cabozantinib vs Everolimus (METEOR)



Lancet Oncol. 2016;17:917-27

Selected Treatment-Emergent Adverse Events

Event	Cabozantinib (n = 331)		Everolimus (n = 322)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any adverse event	100	74	99	65
Diarrhea	74	11	27	2
Fatigue	56	9	45	7
Nausea	50	4	27	< 1
Decreased appetite	46	2	33	< 1
Palmar-plantar erythrodysesthesia syndrome	42	9	6	< 1
Hypertension	37	15	7	3
Vomiting	31	2	14	< 1
Weight decreased	31	2	12	0
Constipation	25	< 1	18	< 1
Dysgeusia	24	0	9	0

Choueiri TK, et al. *NEJM*. 2015;373:1814-1823.

Values: % of patients

Study 205: Phase II Lenvatinib+Everolimus

Advanced RCC following progression on 1 prior VEGF-targeted therapy

1:1:1 Randomization

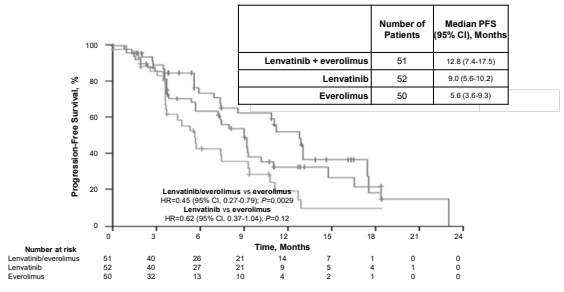
- **Lenvatinib** (24 mg/d) n = 51
- **Lenvatinib** (18 mg/d) **Everolimus** (5 mg/d) n = 52
- **Everolimus** (10 mg/d) n = 50

Primary End Point
- PFS: lenvatinib ± everolimus vs everolimus

Secondary End Points
- PFS: lenvatinib + everolimus vs lenvatinib
- OS, ORR, disease control rate, stable disease, clinical benefit rate[2]

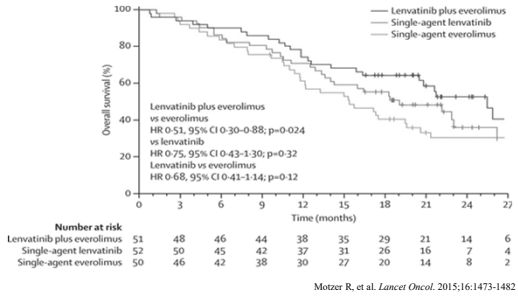
Motzer RJ, et al. *Lancet Oncol*. 2015;16(15):1473-1482.

Lenvatinib/Everolimus Phase II Study: PFS (Independent Radiologic Review)



Motzer R, et al. *Lancet Oncol*. 2015;16:1473-1482

Lenvatinib/Everolimus Phase II Study: Overall Survival in the Post-hoc Updated Analysis



Motzer R, et al. *Lancet Oncol*. 2015;16:1473-1482

CheckMate 025: Phase III Nivolumab vs. Everolimus

Advanced RCC (N=822)
- clear cell component
- 1-2 prior anti-angiogenic therapies
- Max 3 total prior lines

1:1 randomization

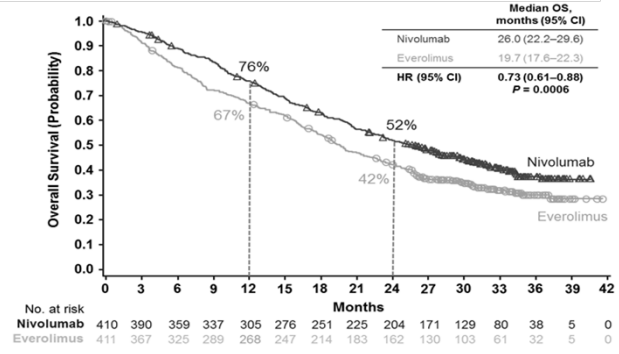
- Nivolumab
- Everolimus

Primary Endpoint: OS

Tumor assessments were conducted every 8 weeks for the first year

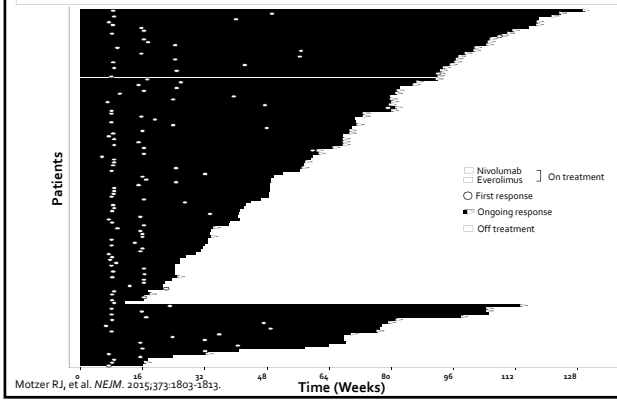
Study therapy continued if clinical benefit and acceptable side effect profile were seen

CheckMate 025: Overall Survival



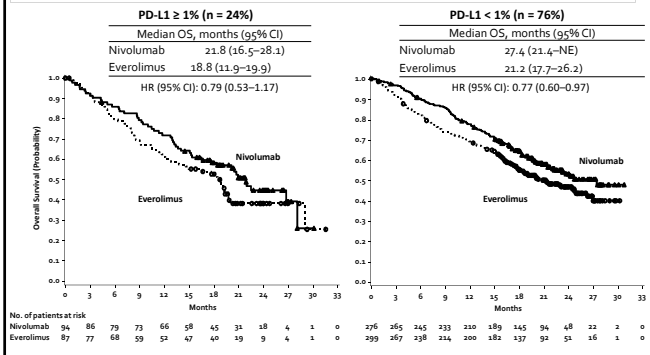
Plimack ER, et al. 15th Intl Kidney Cancer Symposium. Nov 2016, Miami, FL.

Response Characteristics



Motzer RJ, et al. *NEJM*. 2015;373:1803-1813.

Overall Survival by PD-L1 Expression



Motzer RJ, et al. *NEJM*. 2015;373:1803-1813.

CheckMate 025 - Safety Summary

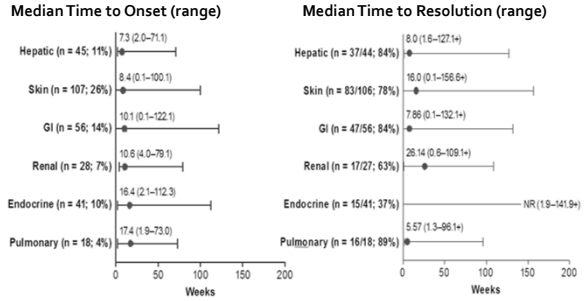
	Nivolumab N = 406		Everolimus N = 397	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Treatment-related AEs, %	79	**19**	88	**37**
Treatment-related AEs leading to discontinuation, %	8	5	13	7
Treatment-related deaths, n	0		2[a]	

[a] Septic shock (1), bowel ischemia (1).

- 44% of patients in the nivolumab arm and 46% of patients in the everolimus arm were treated beyond progression

Motzer RJ, et al. *NEJM*. 2015;373:1803-1813.

Time to Onset and Resolution of Treatment-related Select AEs with Nivolumab



Time to resolution based on the time to onset of the AE (not at the start of treatment)
+ indicates a censored value; GI: gastrointestinal; NR: not reached

Plimack ER, et al. 15th Intl Kidney Cancer Symposium. Nov 2016, Miami, FL.

	AXIS[1,2]	CheckMate 025[3,4]	METEOR[5,6]	Study 205[7]
Phase	Phase III	Phase III	Phase III	Phase II
PFS	AXI: 6.7 mo SOR: 4.7 mo	NIV: 4.6 mo EVE: 4.4 mo	CAB: 7.4 mo EVE: 3.8 mo	LEN/EVE: 14.6 mo LEN: 7.4 mo EVE: 5.5 mo
Tumor responses	CR: 0% vs 0% PR: 19% vs 9% SD: 50% vs 54% PD: 22% vs 21%	CR: 1% vs 1% PR: 24% vs 5% SD: 34% vs 55% PD: 35% vs 28%	CR: 0% vs 0% PR: 21% vs 5% SD: 62% vs 62% PD: 14% vs 27%	CR: 2% vs 0% vs 0% PR: 41% vs 27% vs 6% SD: 41% vs 52% vs 62% PD: 4% vs 6% vs 24%
OS	AXI: 20.1 mo SOR: 19.2 mo HR 0-96 (0-80–1-17)	NIV: 25.0 mo EVE: 19.6 mo HR 0.73 (0.57-0.93)	CAB: 21.4mo EVE 16.5mo HR 0.66 (0.53-0.83)	LEN/EVE: 25.5 mo LEN: 19.1 mo EVE: 15.4 mo HR 0.51 (0.3-0.88)
PFS/OS by prior therapy	PFS 1 prior TKI: 4.8 vs 3.4 mo	OS 1 prior anti-VEGF (any): 23.6 vs 19.9 mo 2 prior anti-VEGF (any): NE vs 18.4 mo	PFS Prior SUN: 9.1 vs 3.7 mo	PFS 1 prior TKI: LEN/EVE: 14.6 mo LEN: 7.4 mo EVE: 5.5 mo

References: 1. Rini BI et al. *Lancet*. 2011;378(9807):1931-1939. **2.** Motzer RJ et al. *Lancet Oncol*. 2013;14(6):552-562.. 3. Motzer RJ et al. *N Engl J Med*. 2015;373(19):1803-1813. 4. Motzer RJ et al. Poster presented at: 2016 Genitourinary Cancers Symposium. *J Clin Oncol* 34, 2016 (suppl 2S; abstr 498). 5. Choueiri TK et al. *N Engl J Med*. 2015;373(19):1814-1823. 6. Escudier B et al. Poster presented at: 2016 Genitourinary Cancers Symposium. *J Clin Oncol* 34, 2016 (suppl 2S; abstr 499). 7. Motzer RJ et al. *Lancet Oncol*. 2015;16(15):1473-1482.

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY

Risk	Preferred regimens	Other recommended regimens	Useful under certain circumstances
Favorable[a]	• Axitinib + pembrolizumab • Pazopanib • Sunitinib	• Ipilimumab + nivolumab • Cabozantinib (category 2B) • Axitinib + avelumab	• Active surveillance[b] • Axitinib (category 2B) • High-dose IL-2[c]
Poor/ intermediate[a]	• Ipilimumab + nivolumab (category 1) • Axitinib + pembrolizumab (category 1) • Cabozantinib	• Pazopanib • Sunitinib • Axitinib + avelumab	• Axitinib (category 2B) • High-dose IL-2[c] • Temsirolimus[d]

SUBSEQUENT THERAPY FOR CLEAR CELL HISTOLOGY

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Cabozantinib (category 1) • Nivolumab (category 1) • Ipilimumab + nivolumab	• Axitinib (category 1) • Lenvatinib + everolimus (category 1) • Axitinib + pembrolizumab • Everolimus • Pazopanib • Sunitinib • Axitinib + avelumab (category 3)	• Bevacizumab or biosimilar[e] (category 2B) • Sorafenib (category 2B) • High-dose IL-2 for selected patients[c] (category 2B) • Temsirolimus[d] (category 2B)

[a] See Risk Models to Direct Treatment (IMDC criteria) (KID-D).
[b] Rini BI, Dorff TB, Elson P, et al. Active surveillance in metastatic renal-cell carcinoma: a prospective, phase 2 trial. Lancet Oncol 2016;17:1317-1324.
[c] Patients with excellent performance status and normal organ function.
[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[e] Biosimilar options include: bevacizumab-awwb.

KID-C

PRINCIPLES OF SYSTEMIC THERAPY FOR RELAPSE OR STAGE IV DISEASE

SYSTEMIC THERAPY FOR NON-CLEAR CELL HISTOLOGY[f]

Preferred regimens	Other recommended regimens	Useful under certain circumstances
• Clinical trial • Sunitinib	• Cabozantinib • Everolimus	• Axitinib • Bevacizumab or biosimilar[e] • Erlotinib • Lenvatinib + everolimus • Nivolumab • Pazopanib • Bevacizumab or biosimilar[e] + erlotinib for selected patients with advanced papillary RCC including hereditary leiomyomatosis and renal cell cancer (HLRCC) • Bevacizumab or biosimilar[e] + everolimus • Temsirolimus[d] (category 1 for poor-prognosis risk group; category 2A for other risk groups)

[d] The poor risk model used in the global ARCC trial to direct treatment with temsirolimus included at least 3 of the following 6 predictors of short survival: <1 year from the time of diagnosis to start of systemic therapy, Karnofsky performance status score 60–70, hemoglobin <LLN, corrected calcium greater than 10 mg/dL, LDH >1.5 times the ULN, and metastasis in multiple organs. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med 2007;356:2271-2281.
[e] Biosimilar options include: bevacizumab-awwb.
[f] For collecting duct or medullary subtypes, partial responses have been observed with cytotoxic chemotherapy (carboplatin + gemcitabine, carboplatin + paclitaxel, or cisplatin + gemcitabine) and other platinum-based chemotherapies currently used for urothelial carcinomas. Oral targeted therapies generally do not produce responses in patients with renal medullary carcinoma. Outside of clinical trials, platinum-based chemotherapy regimens should be the preferred therapy for renal medullary carcinoma.

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Prostate Cancer

Jeanny B. Aragon-Ching, MD, FACP

August 19, 2020

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Bladder Cancer

Dean F. Bajorin, MD, FACP

August 19, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

58 – Bladder Cancer

Dean Bajorin, MD, FACP

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Consultancy: Novartis, Merck, Merck Sharpe and Dome, Fidia Farmaceutici, Bristol-Myers Squibb, Astra Zeneca, Dragonfly and Pfizer
- Honoraria: Novartis, Merck, Merck Sharpe and Dome, Fidia Farmaceutici, Bristol-Myers Squibb, Astra Zeneca, Dragonfly and Pfizer
- Research Funding: Novartis, Merck, Merck Sharpe and Dome, Fidia Farmaceutici, Bristol-Myers Squibb, Astra Zeneca, Dragonfly and Pfizer

Bladder (Urothelial) Cancer Epidemiology and Pathobiology (1)

Peak incidence 7th decade; Male to Female ratio of 3:1
Caucasians ~ twice as African Americans, rare in Asians

Risk factors: smoking (2-4 fold risk over non-smokers), 2-naphthylamine, 4-aminobiphenyl, benzidine and benzene.

Occupations at risk: aluminum workers, dry cleaners, manufacturers of preservatives and polychlorinated biphenyls, and pesticide applicators.

Arylamines, also carcinogenic, are metabolically activated to electrophilic compounds by N-hydroxylation in the liver by cytochrome P-450 IA2 and detoxified by N-acetylation.

Occupations with higher exposure to arylamines include workers in the dye, rubber or leather manufacturing industries, thought to be at higher risk

Bladder Cancer Epidemiology and Pathobiology (2)

Histology: 90-95% urothelial (transitional cell) carcinomas; 5% squamous cell cancer, 2% adenocarcinoma, 1% small cell. Mixed histologies are common.

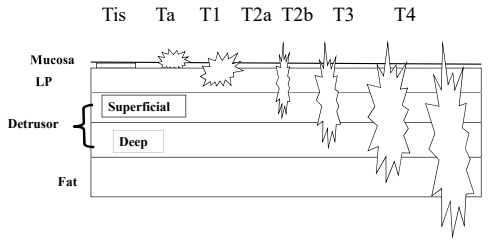
Schistosoma haematobium infection enhances formation of carcinogenic N nitroso compounds and results in an increased risk of both squamous and transitional cell carcinomas of the bladder.

Patients with chronic indwelling catheters at higher risk for SCC of bladder

Cyclophosphamide can increase the risk of bladder cancer nine-fold and phenacetin-containing compounds have been implicated in the development of renal pelvis and ureteral tumors.

Presentation: Stage I ~ 75%
Stage II/III ~ 20%
Stage IV ~ 5%

TNM Staging System
Treatment of NMIBC "superficial" disease



Favorable	Unfavorable
Ta	T1
Low grade	High grade
No dysplasia	CIS
Long tumor-free interval	Short tumor-free interval

Long term (10-20 Year) Outcome of NMIBC "Superficial" Bladder Cancer

Tumor Stage & Grade	% Recurrence (mean/range)	% Progression (mean/range)	% Death (mean/range)
Ta Low grade	64% (40-90%)	7% (2.4-18%)	3.6% (0-14%)
Ta High grade	75% (60-95%)	23% (10-39%)	14% (6-26%)
T1* (90% high grade)	84% (74-90%)	40% (30-52%)	35% (30-38%)

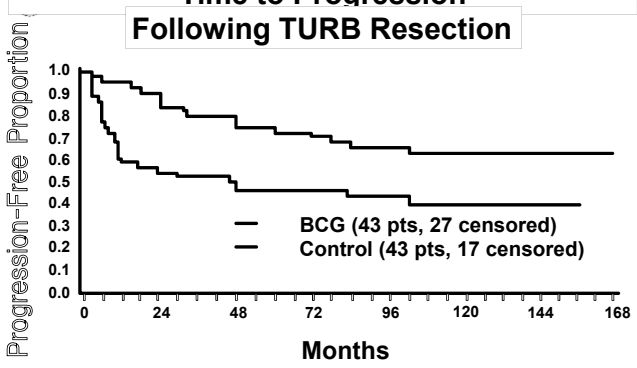
Data compiled from Haukaas S, Daehlin L, Maartmann-Moe H, and Ulvik NM. BJU 1999; 83: 957-963. Holmang S, Hedelin H, Anderstrom C, et al J Urol; 153:1823-1927,1995. Holmang S, Hedelin H, Johansson SL, et al J Urol;162:702-707, 1999. Herr HW. J Urol 2000; 163:60-62. Lebret T, Herve' JM, Botto H et al Eur Urol; 33:170-174, 1998. Leblanc B, Duclos AF, Benard R et al J Urol 1999; 162:1946.

CIS

- In association with papillary or nodular tumors
  - Majority (90%)
  - Muscle invasion develops in 42 to 83%
- Isolated finding
  - Minority (10%)
  - Microinvasive carcinoma (20-34%)
  - Focal or diffuse
  - Risk of invasion focal - 8%
    diffuse - 78%

Hudson, MA, Herr HW J Urol 153:564,1995

Time to Progression Following TURB Resection



muscle invasion and/or metastatic progression

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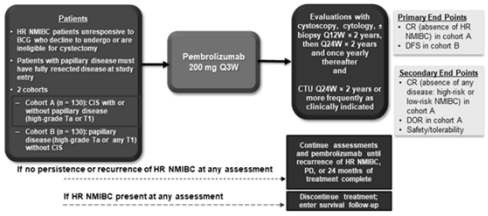
Balar KN057 ASCO-GU 2019

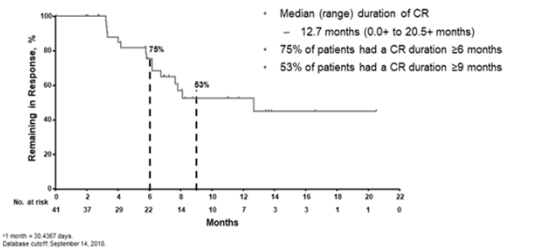
KEYNOTE-057: Single-Arm, Open-Label Phase 2 Study (NCT02625961)



Memorial Sloan Kettering Cancer Center

Balar KN057 ASCO-GU 2019

Duration of Response for Patients Who Achieved CR at Month 3[a]



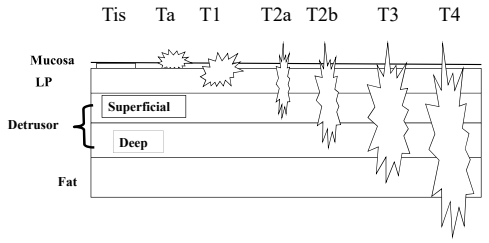
[a]1 month = 30.4367 days.
Database cutoff: September 14, 2018.

Take-home Points on NMIBC Tumors

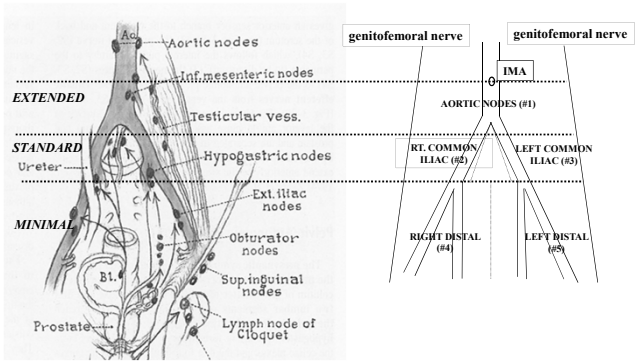
1. Grade plays a major role, high grade does much worse
2. Presence of cis is a poor prognostic variable
3. Tumor multiplicity and size (>3 cm) have a worse prognosis
4. Vascular invasion negatively impacts disease-free survival

5. Intravesical therapy not standard of care for papillary (low-grade) tumors
6. Intravesical chemotherapy reduces short term tumor recurrence but no effect on tumor progression to higher stage or metastases
7. BCG is the standard of care for high-grade NMIBC and is superior to chemotherapy for cis
8. HG NMIBC -standard of care is weekly BCG x 6; maintenance BCG also standard but controversial due to poor tolerance
9. Pembrolizumab is a standard of care for BCG-unresponsive NMIBC (no response or response duration < 12 months)

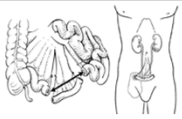
TNM Staging System
Treatment of MIBC



Standard of Care:
Cystectomy and Bilateral Pelvic Lymph Node Dissection

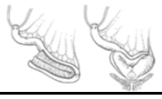


Ileal Conduit Diversion



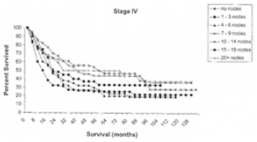
Continent Stomal Diversion

Orthotopic Neobladder Diversion

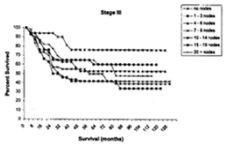


Pelvic Lymph Node Dissection (SEER)

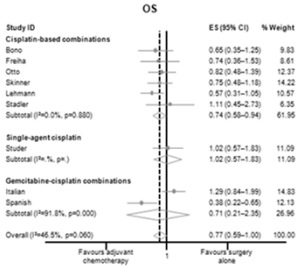
Node positive



Node negative



Should Standard of Care be Surgery followed by Adjuvant Therapy for High Risk Pts (≥ pT3, No)?



OS
HR=0.77 (95% CI 0.59–0.99)
p=0.049

OS benefit for cisplatin-based adjuvant chemotherapy

1. Leow et al. Eur Urol 2014; 945 patients from 9 randomized controlled trials

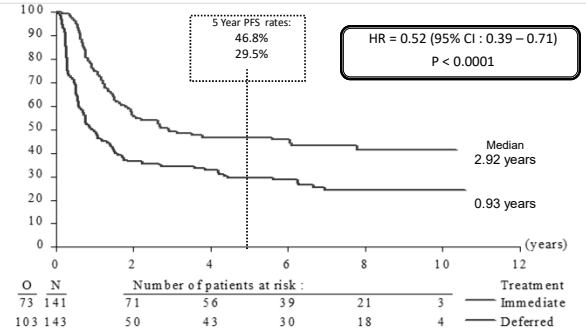
Adjuvant Chemotherapy Trials for High Risk Pts (≥ pT3, No)

Trial	Number of patients	Regimen	Survival benefit	Completed accrual
US Intergroup[1]	114	MVAC	No	No
Italian multicentre[2]	194	Gemcitabine/cisplatin	No	No
SOGUG[3]	142	Paclitaxel/gemcitabine/ cisplatin (PGC)	Yes PGC: median OS not reported; 5-year OS: 60% Observation: median OS: 26 months; 5-year OS: 31% p<0.0004	No
EORTC 30994[4]	284	Gemcitabine/cisplatin MVAC DD-MVAC	No	No

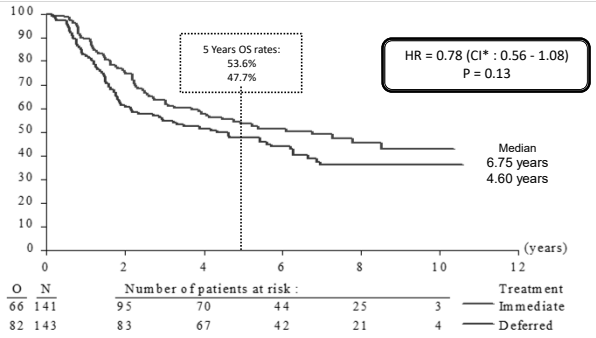
All four trials failed to meet their original accrual goals (40–60% of target) and closed early

1. Stadler et al. J Clin Oncol 2011; 2. Cognetti et al. Ann Oncol 2012; 3. Paz-Ares et al. ASCO 2010; 4. Sternberg et al. Lancet Oncol 2015

A Significant Improvement in PFS (ITT)

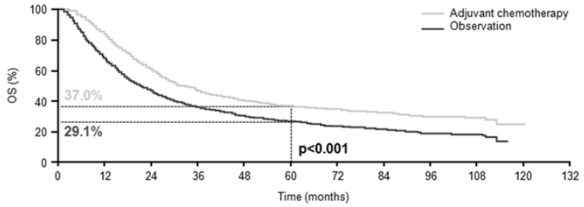


Overall Survival (ITT)
A non-significant reduction of 22% in the risk of death



*95.09%, adjusted for interim analysis

Population-based data analysis –Benefit observed
5,653 patients from the National Cancer Data Base



Stratified analyses adjusted for propensity score demonstrated an improvement in OS with adjuvant chemotherapy (HR=0.70; 95% CI 0.64–0.76)

Galsky et al. J Clin Oncol 2016

ICR The Institute of Cancer Research

POUT

CANCER RESEARCH UK

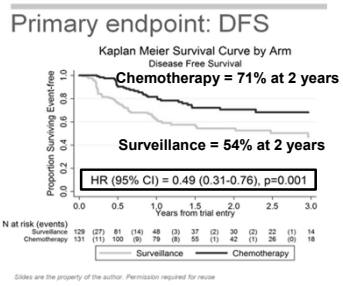
Results of POUT - A phase III randomised trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer (UTUC)

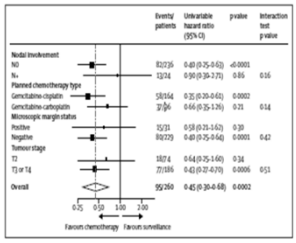
Alison Jane Birtle*, John David Chester, Robert Jones, Mark Johnson, Michaela Hill, Richard T Bryan, James Catto, Jenny Donovan, Ann French, Chris Harris, Francis Keeley, Roger Kockelbergh, Thomas Powles, Rachel Todd, Lucy Tregellas, Caroline Wilson, Andrew Winterbottom, Rebecca Lewis, Emma Hall, on behalf of the POUT Investigators
*Chief Investigator

PRESENTED AT: **2018 Genitourinary Cancers Symposium**

Memorial Sloan Kettering Cancer Center

Primary endpoint: DFS





ASCO GU Symposium 2018

Birtle et al. Lancet 2020

Cisplatin-based adjuvant chemotherapy is 'recommended' in clinical practice guidelines

VOLUME 34 · NUMBER 18 · JUNE 1, 2016
JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

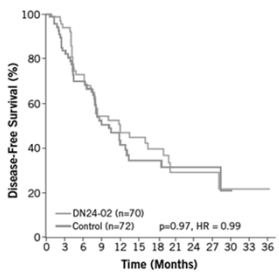
Guideline on Muscle-Invasive and Metastatic Bladder Cancer (European Association of Urology Guideline): American Society of Clinical Oncology Clinical Practice Guideline Endorsement

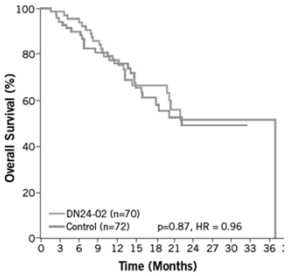
Matthew I. Milowsky, R. Bryan Rumble, Christopher M. Booth, Timothy Gilligan, Libni J. Eapen, Ralph J. Hauke, Pat Beumanoir, and Cheryl T. Lee

"Adjuvant chemotherapy may be offered to high-risk patients who have not received neoadjuvant therapy*

Prognosis of High Risk MIBC patients status post cystectomy
Phase 2 randomized trial of DN24-02 Rx vs observation

High Risk defined as ≥ pT2 post neoadjuvant ChemoRx or pT3 without prior ChemoRx





Bajorin et al. ASCO 2016

Trials for High Risk Pts s/p surgery defined as ≥ pT2 post neoadjuvant ChemoRx or pT3 without prior neoadjuvant ChemoRx

AMBASSADOR (NCT03244384)

- High risk of recurrence originating in the bladder, ureter or renal pelvis
- Surgical resection (e.g. radical cystectomy or nephroureterectomy)

Co-primary endpoints: DFS and OS; N=739

R → Pembrolizumab / Observation

CheckMate 274 (NCT02632409)

- High risk of recurrence originating in the bladder, ureter or renal pelvis
- Surgical resection (e.g. radical cystectomy or nephroureterectomy)

Co-primary endpoints: DFS in pts with ≥1% PD-L1 and all patients; N=640

R → Nivolumab / Placebo

IMvigor010 (NCT02450331)

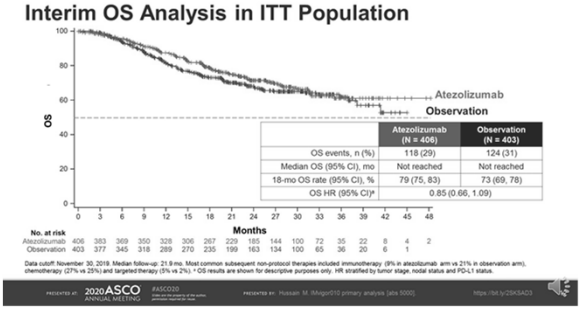
- High risk of recurrence originating in the bladder, ureter or renal pelvis
- Surgical resection (e.g. radical cystectomy or nephroureterectomy)

Primary endpoint: DFS; N=700

R → Atezolizumab / Observation

Memorial Sloan Kettering Cancer Center

Interim OS Analysis in ITT Population



	Atezolizumab (N = 406)	Observation (N = 403)
OS events, n (%)	118 (29)	124 (31)
Median OS (95% CI), mo	Not reached	Not reached
18-mo OS rate (95% CI), %	79 (75, 83)	73 (69, 78)
OS HR (95% CI)*	0.85 (0.66, 1.09)	

Data cutoff: November 30, 2019. Median follow-up: 21.9 mo. Most common subsequent non-protocol therapies included immunotherapy (9% in atezolizumab arm vs 21% in observation arm), chemotherapy (27% vs 25%) and targeted therapy (5% vs 2%). * OS results are shown for descriptive purposes only. HR stratified by tumor stage, nodal status and PD-L1 status.

2020 ASCO ANNUAL MEETING

Presented By Maha Hussain at TBD

Neoadjuvant Chemotherapy for Muscle-Invasive Disease

- Current status of Neoadjuvant Treatment
- Who benefits the most?
- The "Holy Grail" – Biomarker predictive of response
- The clinical trial landscape

ABC Meta-Analysis: Neoadjuvant Therapy (n=3005)

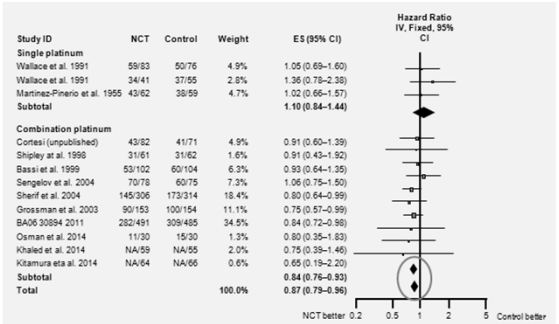
Endpoint	Chemotherapy type	Number of patients/ events	HR (95% CI)	Effect p-value	Absolute benefit at 5 years (95% CI)	p-value
Overall survival	Single-agent platinum	261/376	1.15 (0.90–1.47)	0.26	–5% (–14% to 4%)	
	Platinum-based combinations	**1430/2433**	**0.86 (0.77–0.95)**	**0.003**	**5% (2% to 9%)**	
	All trials	1691/2890	0.89 (0.81–0.98)	0.022	4% (0% to 7%)	0.029
Disease-free survival	Single-agent platinum	166/217	1.14 (0.83–1.55)	0.42	–5% (–16% to 7%)	
	Platinum-based combinations	**1681/2629**	**0.78 (0.71–0.86)**	**<0.0001**	**9% (5% to 12%)**	
	All trials	1847/2846	0.81 (0.74–0.89)	<0.0001	8% (4% to 11%)	0.024

OS benefit (HR=0.86; 95% CI: 0.77–0.95; p=0.003)
5 Yr OS Landmark benefit (OS increased from 45% to 50%)

DFS benefit (HR=0.78; 95% CI: 0.71–0.86; p<0.0001)
5 Yr Landmark benefit is 9%

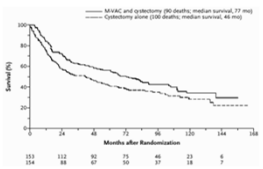
Advanced Bladder Cancer Meta-analysis Collaboration. Eur Urol 2005 (n=11 trials)

Meta-Analysis: Neoadjuvant Therapy (n=3285)



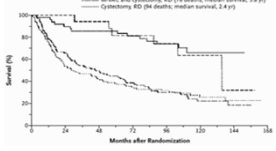
Yin et al. The Oncologist 2016 (n=15 trials)

Who benefits most from Neoadjuvant Chemotherapy?



SWOG 87-10:
MVAC plus surgery vs Surgery alone

ARM	Median Survival	Alive at 5 yrs	p-value (2-sided)
Surgery	46 mos	43%	.06
MVAC	77 mos	57%	
HR risk of death was 1.33 surgery alone			
HR risk of bladder cancer death 1.66 for surgery alone			



- pCR rates: 38% after MVAC vs 15% Cyst alone
- 5yr OS in patients with pT0N0: 85% (vs 50%)

Complete pathologic response serves as predictive marker for long term survival

Grossman et al. NEJM

[Grossman et al. NEJM 2003]

Is Gem/Cis an alternative to MVAC (N=154) ?

Cycles Delivered	No. Patients (%)
0.5	2 (1.3%)
1	2 (1.3%)
1.5	3 (1.9%)
2	6 (3.9%)
2.5	5 (3.2%)
3	9 (5.8%)
3.5	10 (6.5%)
4	117 (76%)

Chemotherapy logistics:
a) q21 days x 4 cycles (84 days)
b) Goal gem dose: 8000 mg/m2
c) Goal cisplatin dose: 280 mg/m2
d) split vs standard dose

88% received at least 3 cycles

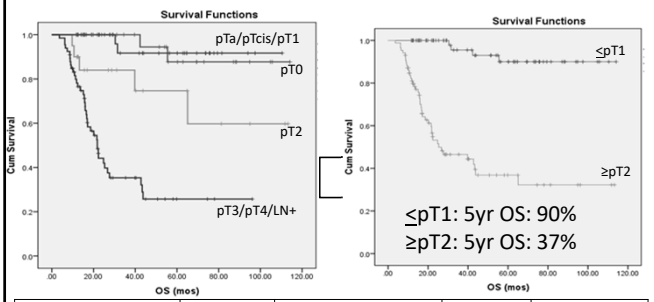
Chemo agent	Dose Intensity
Gemcitabine	89%
Cisplatin	90%

Median number of cycles: 4 (0.5-4)
Median start chemo to end: 86 (21-121)

What are the pathologic outcomes?

Pathologic Stage	No pts.	%	SWOG 8710	Dash et al.	Yeshchina et al.
pToNo	30	20%	38%	26%	25%
pTisNo	24	16%			
pTaNo	2	1%			
pT1No	12	8%			
pT2No	21	14%			
pT3No/pT4No/N+	65	42%			
< pT2No	68	44%	44%	36%	50%
≥ pT2	86	56%	56%		50%

Is pTo the appropriate endpoint?

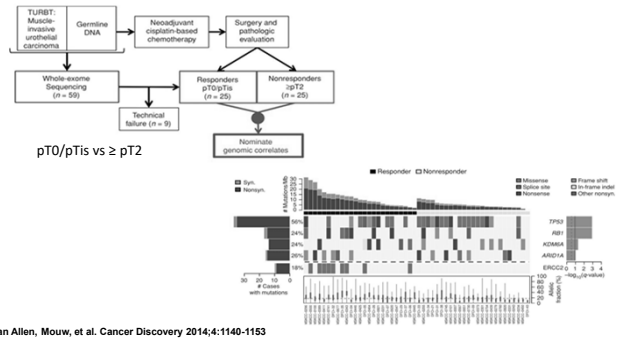


	pTo	pTa/pTcis/pT1	pT2	pT3/pT4/LN+
Median OS (mo)	N/R	N/R	N/R	22 (18-26)
5 yr OS (%)	88%	92%	75%	26%

Dose Dense Chemotherapy in MIBC

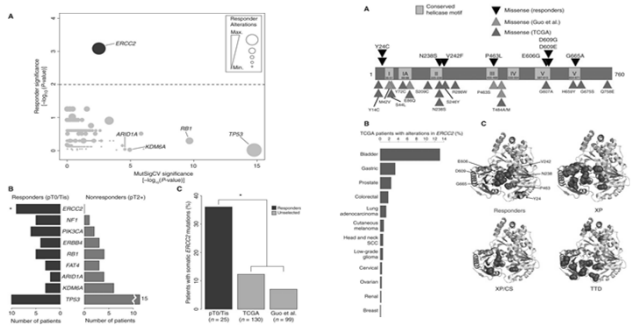
Study	Regimen cycles	Cisplatin Dose Density (mg/m²/week)	N (evaluable)	pTo	≤ pT1
Blick et al. 2011 GU ASCO	DD MVAC 3-4 cycles	35	80	43%	
*Siefker-Radtke GU ASCO 2012**	DD MVAC + Bevacizumab 4 cycles	35	44	39%	54%
Plimack et al. ASCO 2014	DD GC 3 cycles	35	31	32%	45%
Plimack et al. JCO 32:1895-1901; 2014	DD MVAC 3 cycles	35	40	38%	53%
Choueiri et al J CO 32:1889-1894. 2014	DD MVAC 4 cycles	35	39	26%	49%

Using the extreme responder approach with Whole Exome Sequencing approach



Van Allen, Mouw, et al. Cancer Discovery 2014;4:1140-1153

ERCC2 mutations are significantly enriched in responders, and mutations are found in/near conserved sites



Van Allen, Mouw, et al. Cancer Discovery 2014;4:1140-1153

Using Next Generation DNA Sequencing Approach Defects in DNA Repair Genes Predict Response to Neoadjuvant Cisplatin-based Chemotherapy

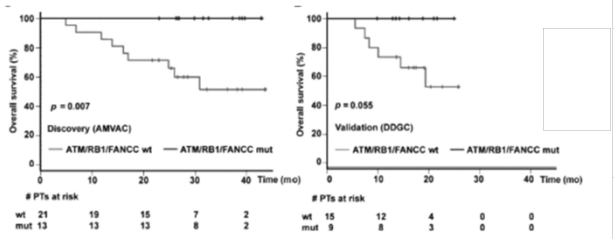


Fig. 2 Progression-free survival (PFS) and overall survival (OS) by ATM/RB1/FANCC mutation status for the AMVAC discovery and DDGC validation sets. Alteration in any one of ATM/RB1/FANCC predicts better PFS ($p = 0.00855$) and OS ($p = 0.007$) in the AMVAC discovery set, with a trend towards significance for OS ($p = 0.0545$) in the DDGC validation set. wt = wild type; mut = mutation; PTs = patients.

Plimack et al, European Urology 2015

Dose Dense GC: A multicenter phase II study

Six 14-day cycles of GC

MSKCC
NYU
UNC

≥ T2N0 disease
Cystoscopy
TURBT
Imaging

Cystectomy to assess pathologic response (chemo-sensitivity)

Correlate markers with pathologic response

Tissue for biomarker analysis

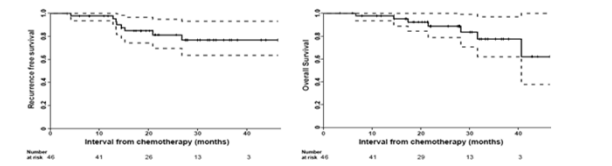
Pathologic response (<pT2) rate > 55% at cystectomy

Primary endpoint was met with 57% downstaged to <pT2N0.
For those with RC (41), 63% were down-staged to <pT2N0.

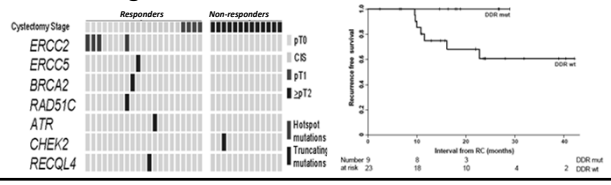
19 patients (41%) required toxicity-related dose modifications.
Seventy percent of patients completed all 6 planned cycles.

<pT2N0 (26)	T0	7
	Ta	1
	CIS	13
	T1	5
≥pT2N0 (13)	T2	7
	T3	6
Node +	T2bN1	2

Dose Dense GC: A multicenter phase II study

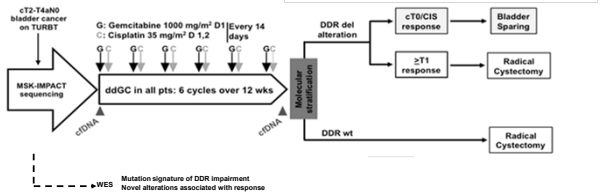


NGS using MSK IMPACT: deleterious DDR alterations



Study Design: A031701

Primary Endpoint: 3-year recurrence-free survival in bladder sparing group



Modified DDR gene panel

ERCC2
ERCC3
BRCA1
BRCA2
RAD51C
ATR
RECQL4
ATM
FANCC

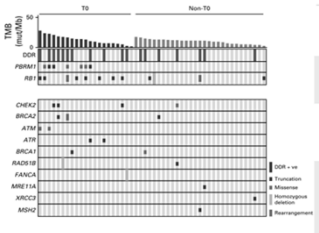
Deleterious alterations in one or more of these genes will allow patients to be potentially eligible for the bladder-sparing arm of the study

271 patients

Take-home Points for Patients with MIBC who are Eligible for Cisplatin-based Chemotherapy

1. Patients getting cisplatin-based combination neoadjuvant chemotherapy have the best survival. No benefit for chemoRX without cisplatin!!
2. Cystectomy and PLND after neoadjuvant chemotherapy is an absolute requirement for maximal survival.
3. No definitive data from phase 3 trials that adjuvant chemotherapy improves survival.
4. Trials using next generation sequencing to select those whose tumors harbor DNA Damage Repair gene defects are ongoing
5. Cisplatin-ineligible best served by surgery alone or investigational trials.

PURE Trial: Pembrolizumab as Neoadjuvant Therapy prior to Cystectomy. Necchi et al JCO 2018



Characteristic	No. (%)
Time frame of accrual	Feb 2017 to Mar 2018
Median age, years (IQR)	66 (60-72)
Gender	
Male	41 (82)
Female	9 (18)
Smoking status	
Nonsmoker	19 (38)
Former smoker	22 (44)
Current smoker	9 (18)
Clinical T stage	
T2N0	21 (42)
T3N0	27 (54)
T2-3N1	2 (4)
Hydronephrosis	9 (18)

Response	All Treated Patients (N = 50)	PD-L1 CPS ≥ 10% (n = 35)	PD-L1 CPS < 10% (n = 15)
Primary end point			
Pathologic complete response, No. (%)	21 (42)	19 (54.3)	2 (13.3)
95% CI	28.2 to 56.8		
Secondary end point			
Pathologic downstaging to pT<2, No. (%)	27 (54)	23 (65.7)	4 (26.7)
95% CI*	39.3 to 68.2		
Treatment failure, No. (%)			
pT2N0	2 (3.8)		
pT3-4N0	6 (12)		
pTanyN+	10 (20)		
Additional MVAC chemotherapy†	5 (10)		
RECIST v1.1 PD	0		

Advanced Disease: Role of Chemotherapy

MVAC: methotrexate, vinblastine, doxorubicin, cisplatin

HD MVAC: High dose MVAC (q2 rather than q4 weeks

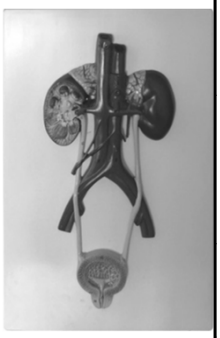
GC: gemcitabine plus cisplatin

GCP: GC + paclitaxel

GC-bev: GC + bevacizumab

G-C: Gemcitabine +carboplatin

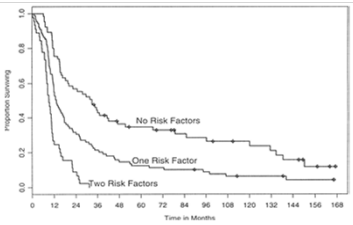
M-CAVI: methotrexate, vinblastine, carboplatin



M-VAC: The First Curable Regimen (Sternberg et al. 1989)
Prognostic Factors for Survival (1999)

MSKCC Prognostic Score
*KPS ≤ 80%
*Visceral Disease

0 = none
1 = one factor
2 = both factors



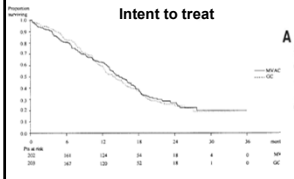
Risk #	KPS	Visceral Mets	Median	Alive at 5 years
0	≥ 80	No	33.0	33%
1	≥ 80	Yes	13.4	11%
	< 80	No		
2	< 80	Yes	9.2	0%

Bajorin JCO 1999

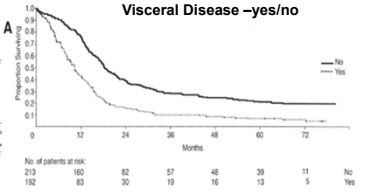
Phase III GC vs MVAC (von der Maase, 2000 and 2005)

End Point	GC (months)	MVAC (months)	Treatment Effect HR†	95% CI	P	Treatment Effect When Adjusted for Prognostic Factors* HR†	95% CI
Median overall survival	13.8	14.8	1.04	0.82-1.32	.75	0.95	0.74-1.22
Median TTPD	7.4	7.4	1.05	0.85-1.30	.66	0.99	0.79-1.24
Median TTTF	5.8	4.6	0.89	0.72-1.10	.27	0.84	0.67-1.04
Response rate,‡ %	49.4	45.7	0.97	0.62-1.52	.51	0.99	0.63-1.56

Intent to treat



Visceral Disease –yes/no



High Dose M-VAC vs standard dose M-VAC

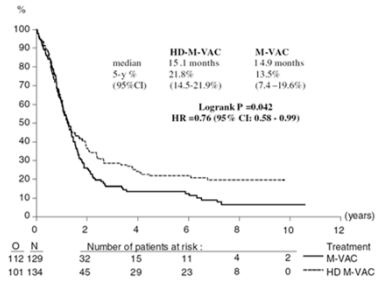
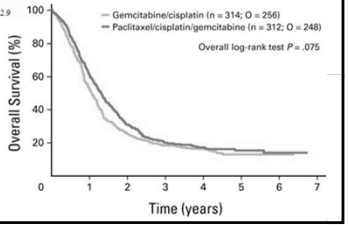


Fig. 3 – Overall survival.

Sternberg CN et al. Eur J Cancer, 2006

GC +/- paclitaxel phase 3 trial (n=626) Bellmunt et al, J Clin Oncol, 2012

Best Overall Response to Treatment	Paclitaxel/Cisplatin/Gemcitabine (n = 312)		Gemcitabine/Cisplatin (n = 314)	
	No. of Patients	%	No. of Patients	%
Complete response	42	13.5	35	11.1
Partial response	131	42.0	102	32.5
Stable disease	69	22.1	97	30.9
Progression of disease	21	6.7	47	15.0
Early death	8	2.6	7	2.2
Not assessable	31	9.9	17	5.4
Treatment never started	10	3.2	9	2.9



GC plus bevacizumab (n=43)

Hahn et al. J Clin Oncol 2012

Clinical Activity: CR 19%, PR 53%, ORR 72%

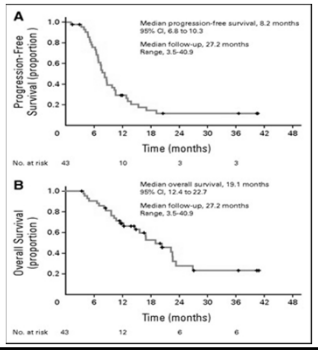
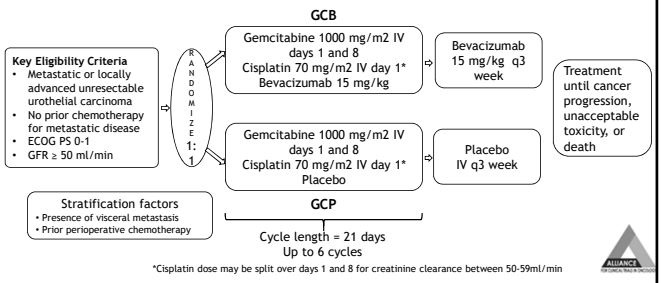


Table 1. Baseline Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	No. of Patients	%
Age, years		
Median	66	
Range	41-78	
Body mass index, kg/m²		
Median	27.7	
Range	19.1-44.0	
Creatinine, mg/dL		
Median	1.1	
Range	0.6-1.4	
WBC count, /μL		
Median	7,600	
Range	4,100-22,000	
Hemoglobin, g/dL		
Median	13.0	
Range	9.1-15.6	
Platelet count, /μL		
Median	291,000	
Range	139,000-770,000	
No. of metastatic sites		
Median	2	
Range	0-6	
Sex		
Male	33	76.7
Female	10	23.3
Prior cystectomy	17	39.5
ECOG PS		
0	26	60.5
1	17	39.5
Metastatic sites		
Any lymph node	39	90.7
Pelvic/abdominal lymph node	27	62.8
Any visceral metastases	30	69.8
Lung	18	41.9
Bone	11	25.6
Modified Bajorin risk group		
Good risk	8	18.6
Intermediate risk	23	53.5
Poor risk	12	27.9

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

CALGB 90601 Study Design



Jonathan E. Rosenberg, MD

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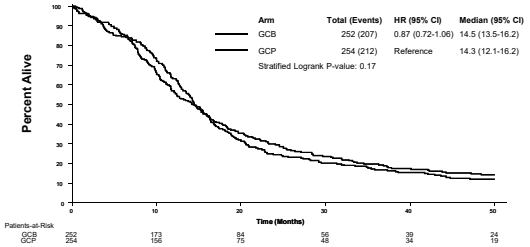
Bevacizumab did not improve overall survival in combination with gemcitabine and cisplatin



Jonathan E. Rosenberg, MD

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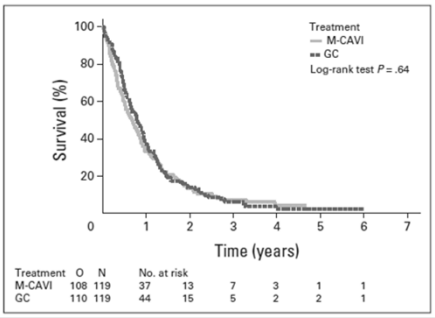
EORTC 30986 Phase II/III Trial Gemcitabine + Carboplatin vs Methotrexate + Carboplatin + Vinblastine (M-CAVI) in Pts Unfit for Cisplatin-Based Chemotherapy

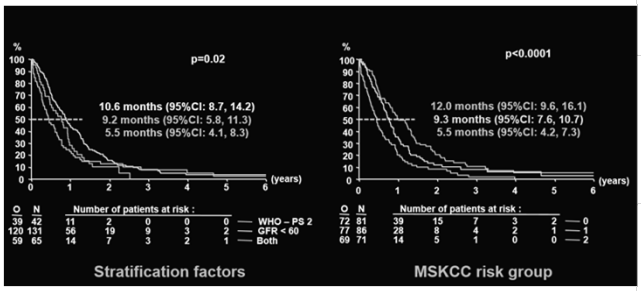
DeSantis et al. J Clin Oncol 2011

Primary end point: median OS of 9.3 months in the GC arm and 8.1 months in the M-CAVI arm. ORR in patients receiving GC was 41.2% and 30.3 % in those receiving M-CAVI.



EORTC 30986 Phase II/III Trial Gemcitabine + Carboplatin vs Methotrexate + Carboplatin + Vinblastine (M-CAVI) in Pts Unfit for Cisplatin-Based Chemotherapy

Prognostic Factor Analysis

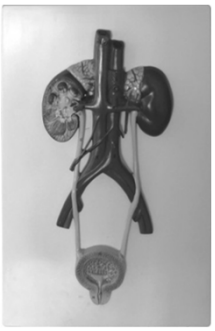


MSKCC Risk Factors: Visceral disease and Poor performance status

Take-home Points for Urothelial Cancer Patients Treated with Chemotherapy

1. M-VAC, High dose M-VAC and GC are all standards of care for cisplatin-eligible patients but only median survivals approximate 14-16 months.
2. Long-term survival is approximately 10%, better in patients with lymph node only disease in contrast to those with metastatic visceral disease.
3. Adding a 3rd chemotherapy drug (paclitaxel) to the GC doublet does not improve survival.
4. Adding an antibody targeting VEGF (bevacizumab) to GC does not impact survival.
5. Gemcitabine plus carboplatin is the standard of care for cisplatin-ineligible patients but median survival is 9 months and rare cures.
6. No major progress in survival with combinatorial chemotherapy since 1989.

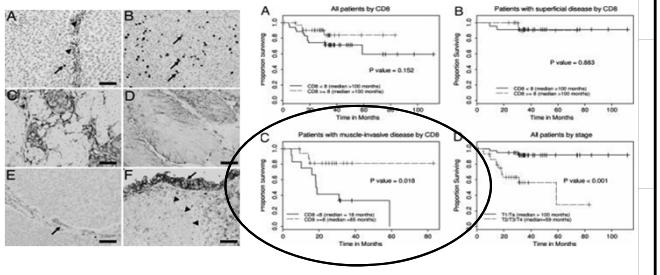
Advanced Disease: Role of Immunotherapy Single Agent Therapy



Prior to 2016: Second-line Agents for Bladder Cancer

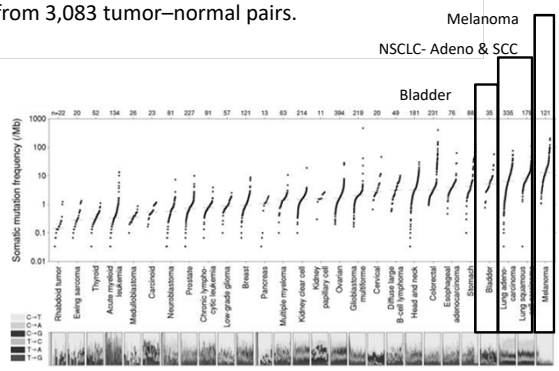
Reference	Agent	Pt #	CR (%)	PR (%)	ORR (%)	MS (months)	
Witte	Ifosfamide	56	9	11	20	NR	
Witte	Topotecan	44	0	9	9	6.3	
Roth	Piritrexim	35	0	7	7	7	
Moore	Oxaliplatin	18	0	6	6	NR	
Paz-Ares	Pemetrexed	31	0	29	29	9.5	NCCN
Sweeney	Pemetrexed	47	6	21	28	9.6	NCCN
Galsky	Pemetrexed	13	0	8	8	NR	NCCN
McCaffrey	Docetaxel	30	0	13	13	9	
Vaughn	Paclitaxel	31	0	10	10	7.2	
Culine	Vinflunine	51	0	18	18	6.6	EMA
Petrylak	Vinflunine	114	0	14.9	14.9	8.3	EMA
Wulfing	Lapatinib	59	0	3	3	4.5	
Gomez-Abuin	Bortezomib	20	0	0	0	NR	

Muscle-Invasive Bladder Cancer: CD8 tumor-infiltrating lymphocytes in primary tumor predictive of survival



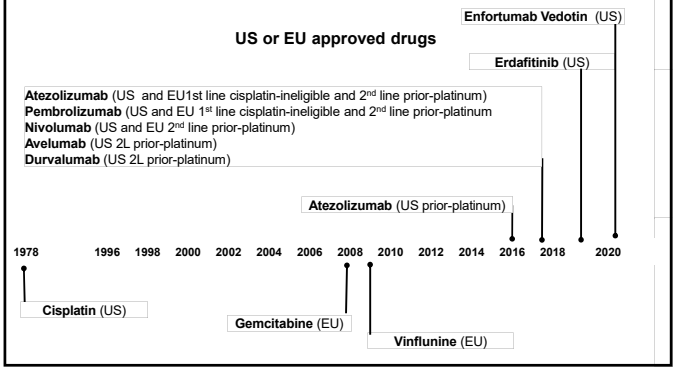
Sharma et al, PNAS, 2007

Somatic mutation frequencies observed in exomes from 3,083 tumor–normal pairs.



MS Lawrence *et al. Nature* 2013 Jul 11;499(7457):214-8

Timeline of Approved Urothelial Cancer Treatments



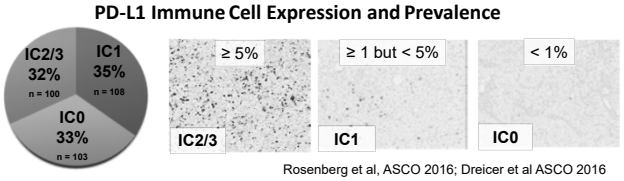
Phase 2: Atezolizumab for Previously Treated Metastatic Urothelial Cancer (N=310)

Efficacy

Responses to Atezolizumab by PD-L1 IC Subgroup

	IC2/3 n = 100	IC1/2/3 n = 207	All[a] N = 310	IC1 n = 107	IC0 n = 103
ORR: confirmed IRF RECIST v1.1 (95% CI)	28% (19, 38)	19% (14, 25)	16% (12, 20)	11% (6, 19)	9% (4, 16)
CR rate: confirmed IRF RECIST v1.1 (95% CI)	**15% (9, 24)**	**9% (6, 14)**	**7% (4, 10)**	**4% (1, 9)**	**2% (0, 7)**

PD-L1 Immune Cell Expression and Prevalence

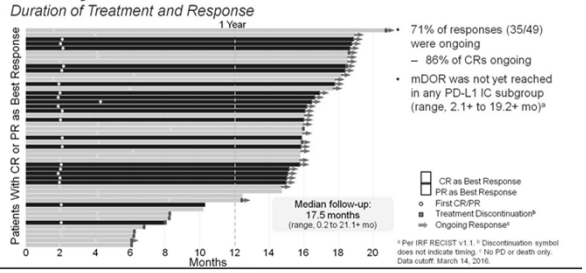


Rosenberg et al, ASCO 2016; Dreicer et al ASCO 2016

Atezolizumab for Previously Treated Metastatic Urothelial Cancer Phase II

Efficacy

Duration of Treatment and Response



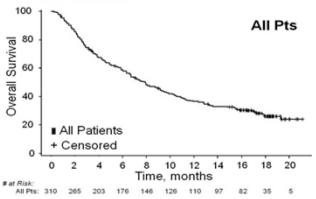
Dreicer et al, ASCO 2016

Atezolizumab for Previously Treated Metastatic Urothelial Cancer Phase II

PD-L1 subsets

Efficacy

Overall Survival



Subgroup	Median OS (95% CI) IC2/3	IC0/1	All
All pts (N = 310)	11.9 mo (9.0, 17.9)	6.7 mo (5.4, 8.0)	7.9 mo (6.7, 9.3)
2L only (n = 120)	NE (10.9, NE)	7.1 mo (5.0, 9.2)	9.0 mo (7.2, 11.3)

Subgroup	12-mo OS (95% CI) IC2/3	IC0/1	All
All pts (N = 310)	50% (40, 60)	31% (24, 37)	37% (31, 42)
2L only (n = 120)	61% (44, 77)	29% (19, 39)	38% (29, 47)

- Longer OS observed in patients with higher PD-L1 IC status
- 12-mo OS compares favorably with historic estimates of ≈ 20%[1]

Median follow-up (range):
All pts: 17.5 mo (0.2 to 21.1+ mo)
2L only: 17.3 mo (0.5 to 21.1+ mo)

Dreicer et al, ASCO 2016

Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial

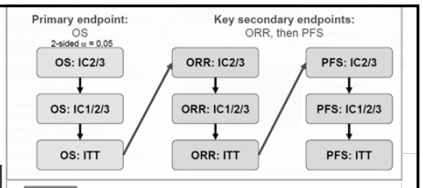
Thomas Powles, Ignacio Durán, Michiel S van der Heijden, Yohann Loriot, Nicholas J Vogelzang, Ugo De Giorgi, Stéphane Oudard, Margitta M Retz, Daniel Castellano, Aristotelis Bamias, Aude Fléchon, Gwenaëlle Gravis, Syed Hussain, Toshimi Takano, Ning Leng, Edward E Kadel III, Romain Banchereau, Priti S Hegde, Sanjeev Mariathasan, Na Cui, Xiaodong Shen, Christina L Derleth, Marjorie C Green, Alain Ravaud

Treatment: atezolizumab 1200 mg or chemotherapy (physician's choice: vinflunine 320 mg/m², paclitaxel 175 mg/m², or 75 mg/m² docetaxel) intravenously every 3 weeks.

Randomization: stratified by PD-L1 expression (expression on <1% [IC0] or 1% to <5% [IC1] of tumor-infiltrating immune cells vs ≥5% of tumor-infiltrating immune cells [IC2/3]), chemotherapy type (vinflunine vs taxanes), liver metastases (yes vs no), and number of prognostic factors (none vs one, two, or three).

Primary endpoint: overall survival was tested hierarchically in prespecified populations: IC2/3, followed by IC1/2/3, followed by the intention-to-treat population.

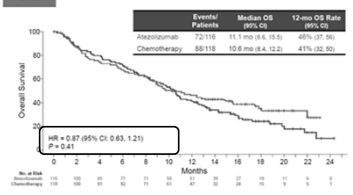
IMvigor 211 Study Design and Clinical outcomes



	IC2/3 n = 100	IC1 n = 107	IC0 n = 103
ORR	28% (19, 38)	11% (6, 19)	9% (4, 16)
CR	**15%** (9, 24)	**4%** (1, 9)	**2%** (0, 7)

EACR AACR SIC

OS Analysis: IC2/3 Population



Powles T et al. 2017, EAS

KEYNOTE-045 Study Design (NCT02256436)

Key Eligibility Criteria
- Urothelial carcinoma of the renal pelvis, ureter, bladder, or urethra
- Transitional cell predominant
- PD after 1-2 lines of platinum-based chemo or recurrence within 12 mo of perioperative platinum-based therapy
- ECOG PS 0-2
- Provision of tumor sample for biomarker assessment

R (1:1) N = 542

N = 270 → Pembrolizumab 200 mg IV Q3W for 2 years

N = 272 → Paclitaxel 175 mg/m² Q3W OR Docetaxel 75 mg/m² Q3W OR Vinflunine 320 mg/m² Q3W

Stratification Factors
- ECOG PS (0/1 vs 2)
- Hemoglobin level (<10 vs ≥10 g/dL)
- Liver metastases (yes vs no)
- Time from last chemotherapy dose (<3 vs ≥3 mo)

Key End Points
Primary: OS and PFS in total and PD-L1 CPS ≥10% populations
Secondary: ORR and DOR in total and PD-L1 CPS ≥10% populations; safety in total population

CPS = combined positive score.

Baseline Characteristics

n (%)	Pembro (N = 270)	Chemo (N = 272)
Age, median (range), y	67.0 (29-88)	65.0 (26-84)
Men	200 (74.1)	202 (74.3)
Race		
White	188 (69.6)	201 (73.9)
Asian	64 (23.7)	58 (21.3)
Other or not specified	18 (6.7)	13 (4.8)
Current or former smoker	165 (61.1)	186 (68.4)
Upper tract disease (renal pelvis/ureter)	38 (14.3)	36 (14.1)
PD-L1 CPS ≥1%	107 (40.2)	108 (42.4)
PD-L1 CPS ≥10%	74 (27.4)	90 (33.1)

n (%)	Pembro (N = 270)	Chemo (N = 272)
Hemoglobin ≥10 g/dL	219 (81.1)	223 (82.0)
ECOG PS[a]		
0	119 (44.1)	106 (39.0)
1	143 (53.0)	158 (58.1)
2	2 (0.7)	4 (1.5)
Visceral disease	240 (88.9)	233 (85.7)
Liver metastases	91 (33.7)	95 (34.9)
Time since completion of most recent prior therapy		
≥3 months	166 (61.5)	167 (61.4)
<3 months	103 (38.1)	104 (38.2)

[a]ECOG PS was missing for 6 patients in the pembro arm and 4 patients in the chemo arm.
Arrows indicate stratification factors.
Data cutoff date: Sep 7, 2016.

Baseline Characteristics cont.

n (%)	Pembro (N = 270)	Chemo (N = 272)
Setting of most recent prior therapy[a]		
Neoadjuvant	19 (7.0)	22 (8.1)
Adjuvant	12 (4.4)	31 (11.4)
First line	183 (67.8)	157 (57.7)
Second line	55 (20.4)	60 (22.1)
Third line	0	1 (0.4)
Type of prior platinum		
Cisplatin	198 (73.3)	213 (78.3)
Carboplatin	70 (25.9)	56 (20.6)
Oxaliplatin or nedaplatin	1 (0.4)	2 (0.7)

n (%)	Pembro (N = 270)	Chemo (N = 272)
Prior cystectomy or nephroureterectomy	209 (77.4)	221 (81.3)
Prior BCG	32 (11.9)	22 (8.1)
No. of risk factors[b]		
0	54 (20.0)	44 (16.2)
1	96 (35.6)	97 (35.7)
2	66 (24.4)	80 (29.4)
3-4	45 (16.7)	45 (16.5)

[a]Setting, time from completion, and prior platinum were all missing for 1 patient in each arm.
[b]Includes Bellmunt risk factors of ECOG PS >0, hemoglobin level <10 g/dL, and liver metastases (*J Clin Oncol* 2010;27:1850-1855) + time from prior chemotherapy <3 mo (*Eur Urol* 2013;63:717-723).
Data cutoff date: Sep 7, 2016.

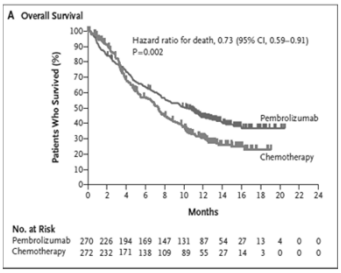
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 16, 2017 VOL. 376 NO. 11

Pembrolizumab as Second-Line Therapy for Advanced Urothelial Carcinoma

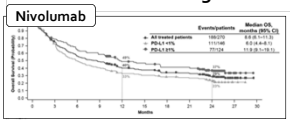
J. Bellmunt, R. de Wit, D.J. Vaughn, Y. Fradet, J.-L. Lee, L. Fong, N.J. Vogelzang, M.A. Climent, D.P. Petrylak, T.K. Choueiri, A. Necchi, W. Gerritsen, H. Gurney, D.I. Quinn, S. Culine, C.N. Sternberg, Y. Mai, C.H. Poehlein, R.F. Perini, and D.F. Bajorin, for the KEYNOTE-045 Investigators*

	Pembro	Chemo
ORR	21%	11%
CR	7.8%	2.9%
DOR	NR	4.4 mos



Phase II studies leading to accelerated approval

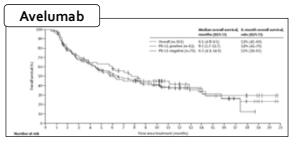
Nivolumab



	Events/patients	Median OS, months (95% CI)
All treated patients	188/270	8.6 (6.1–11.3)
PD-L1 <1%	111/146	6.0 (4.4–8.1)
PD-L1 ≥1%	77/124	11.9 (9.1–19.1)

Sharma. AACR. 2018

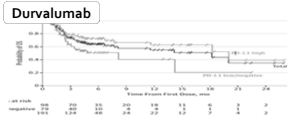
Avelumab



	Median overall survival, months (95% CI)	6-month overall survival, rate (95% CI)
Overall (n=161)	6·5 (4·8–9·5)	53% (45–60)
PD-L1-positive (n=63)	8·2 (5·7–13·7)	59% (45–70)
PD-L1-negative (n=76)	6·2 (4·3–14·0)	51% (39–62)

Patel. Lancet Onc. 2018

Durvalumab

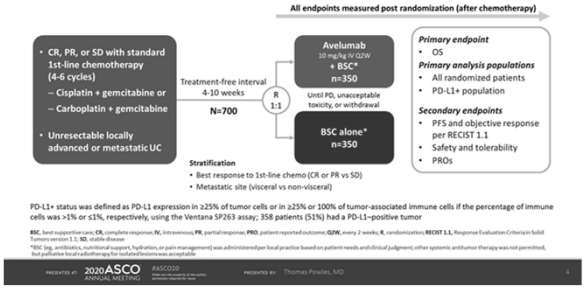


	PD-L1 High	PD-L1 Low/ Negative	Total
No. of patients (No. of events)	98 (30)	79 (35)	191 (68)
Median (95% CI), mo	20.0 (11.6, NE)	8.1 (3.1, NE)	18.2 (8.1, NE)
OS rate, % (95% CI)			
6 mo	72 (62-80)	51 (38-63)	64 (56-71)
9 mo	66 (53-77)	41 (21-60)	57 (47-66)
12 mo	63 (49-74)	41 (21-60)	55 (44-65)

Powels. JAMA Onc. 2017

Memorial Sloan Kettering Cancer Center

JAVELIN Bladder 100 study design (NCT02603432)



PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; CR, complete response; IV, intravenous; PR, partial response; PRO, patient reported outcome; Q2W, every 2 weeks; R, randomization; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

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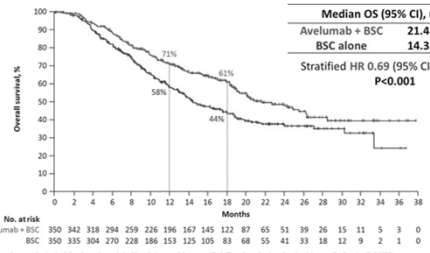
Presented By Thomas Powles

Memorial Sloan Kettering Cancer Center

OS in the overall population



Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified HR 0.69 (95% CI, 0.56, 0.86)
P<0.001

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P=0.005 3)

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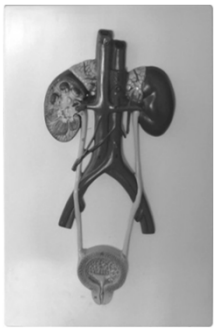
Presented By Thomas Powles

Programmed death 1 (PD-1) pathway blockade in Urothelial Cancer

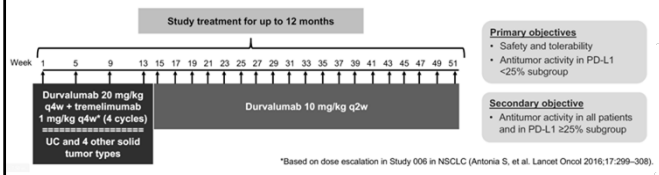
	Atezolizumab	Pembrolizumab	Avelumab	Durvalumab	Nivolumab
Mechanism	Anti-PD-L1	Anti-PD-1	Anti-PD-L1	Anti-PD-L1	Anti-PD-1
PD-L1 staining required	No	No	No	No	No
Approved 2nd Line	Yes, Accelerated Approval	Yes, Full approval	Yes, Accelerated Approval	Yes, Accelerated Approval	Yes, Accelerated Approval
Response Rate	13.2%	21.1	18.2	17.8**	19.6
Reference	Powles et al IMvigor 211 Lancet 2018	Bellmunt et al. NEJM 2017	Apolo et al. JCO 2017	Powles et al JAMA Oncol 2017	Sharma et al. Lancet Oncol 2017

*enriched for PD-L1

Advanced Disease: Immunotherapy Combinations And Novel Targeted Therapy



Durvalumab + Tremelimumab in Post Platinum Metastatic UC

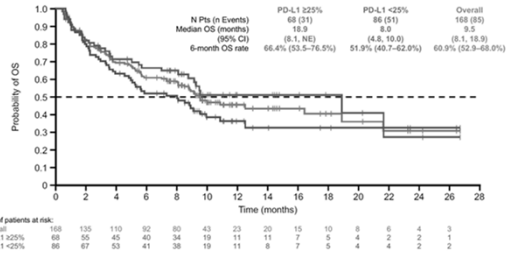


Response and survival	PD-L1 ≥25% (n=68)	PD-L1 <25% (n=86)	Total* (N=168)
Confirmed ORR (CR+PR) (95% CI), %	29.4 (19.0–41.7)	15.1 (8.3–24.5)	20.8 (15.0–27.8)
Disease control rate (CR+PR+SD≥24 weeks) (95% CI), %	32.4 (21.5–44.8)	24.4 (15.8–34.9)	29.2 (22.4–36.7)

Balar et al. AACR. 2018

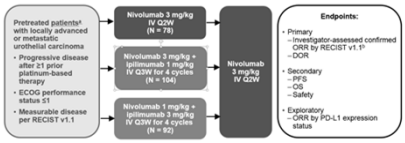
Durvalumab + Tremelimumab in Post Platinum Metastatic UC

Overall survival



Balar et al. AACR. 2018

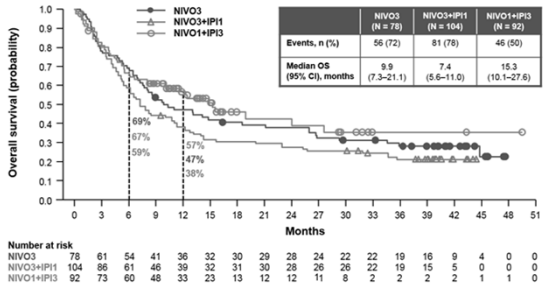
Ipilimumab + Nivolumab in Post Platinum Metastatic UC



Characteristic	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Confirmed ORR, %	25.6	26.9	38.0
95% CI	16.4–36.8	18.7–36.5	28.1–48.8
Best overall response, %			
Complete response	10.3	7.7	6.5
Partial response	15.4	19.2	31.5
Stable disease	26.9	23.1	25.0
Progressive disease	38.5	42.3	21.7
Unable to determine	9.0	7.7	13.0
Not reported	0	0	2.2

Rosenberg et al. ESMO. 2018

Ipilimumab + Nivolumab in Post Platinum Metastatic UC



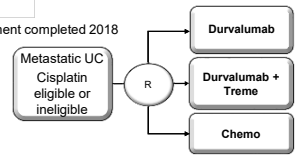
	NIVO3 (N = 78)	NIVO3+IPI1 (N = 104)	NIVO1+IPI3 (N = 92)
Events, n (%)	56 (72)	81 (78)	46 (50)
Median OS (95% CI), months	9.9 (7.3–21.1)	7.4 (5.6–11.0)	15.3 (10.1–27.6)

Rosenberg et al. ESMO. 2018

IO Doublet versus Chemo as 1st Line Treatment for Metastatic UC

DANUBE

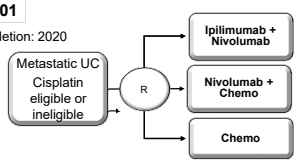
N=1340, Enrollment completed 2018



Primary endpoints: PFS and OS of durvalumab + tremelimumab combo vs standard of care

CheckMate 901

N=690, Est. completion: 2020



Primary endpoints: PFS and OS in cisplatin-ineligible pts

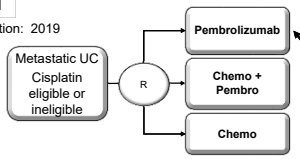
Secondary: PFS and OS in all pts; EORTC QLQ-C30

March 6, 2020: Astra Zeneca announced the Danube trial did not meet its 1º endpoint

Chemotherapy Plus ICB as First-line Treatment for Metastatic UC

KEYNOTE-361

N=990, Est. completion: 2019

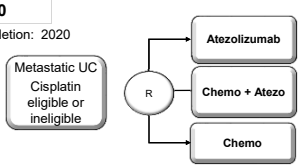


Primary endpoints: PFS (central review) and OS
Secondary: ORR and safety

U.S. FOOD & DRUG ADMINISTRATION

IMVIGOR-130

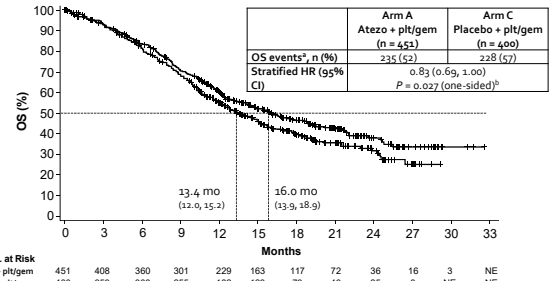
N=1200, Est. completion: 2020



Primary endpoints: PFS (investigator) and OS, and safety

June 10, 2020: Merck announced that Keynote-361 did not meet the 1º endpoint

ImVigor 130 Interim OS: ITT (Arm A vs Arm C)



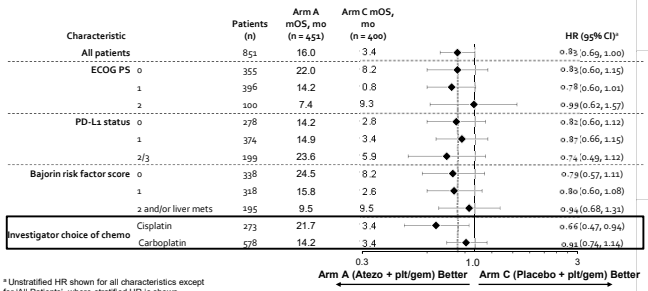
	Arm A Atezo + plt/gem (n = 451)	Arm C Placebo + plt/gem (n = 400)
OS events[a], n (%)	235 (52)	228 (57)
Stratified HR (95% CI)	0.83 (0.69, 1.00) *P* = 0.027 (one-sided)[b]	

No. at Risk												
Atezo + plt/gem	451	408	360	301	229	163	117	72	36	16	3	NE
Placebo + plt/gem	400	359	308	255	182	123	79	49	25	8	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] 5% of patients from Arm A and 20% of patients from Arm C received non-protocol immunotherapy. [b] Did not cross the interim efficacy boundary of 0.007 per the O'Brien-Fleming alpha spending function.

Adapted from Grande E, et al. ESMO 2019. LBA14_PR.

Interim OS subgroups: ITT (Arm A vs Arm C)



Characteristic		Patients (n)	Arm A mOS, mo (n = 451)	Arm C mOS, mo (n = 400)	HR (95% CI)[a]
All patients		851	16.0	3.4	0.83 (0.69, 1.00)
ECOG PS	0	355	22.0	8.2	0.83 (0.60, 1.15)
	1	396	14.2	0.8	0.78 (0.60, 1.01)
	2	100	7.4	9.3	0.99 (0.62, 1.57)
PD-L1 status	0	278	14.2	2.8	0.82 (0.60, 1.12)
	1	374	14.9	3.4	0.87 (0.66, 1.15)
	2/3	199	23.6	5.9	0.74 (0.49, 1.12)
Bajorin risk factor score	0	338	24.5	8.2	0.79 (0.57, 1.11)
	1	318	15.8	2.6	0.80 (0.60, 1.08)
	2 and/or liver mets	195	9.5	9.5	0.94 (0.68, 1.31)
Investigator choice of chemo	Cisplatin	273	21.7	3.4	0.66 (0.47, 0.94)
	Carboplatin	578	14.2	3.4	0.91 (0.74, 1.14)

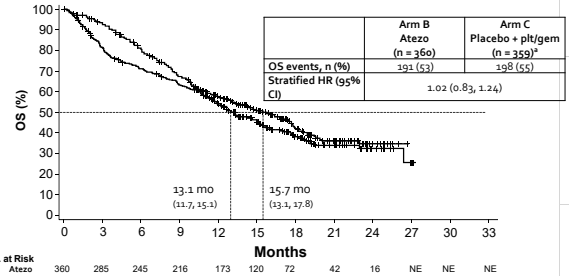
0.3 1.0 3

Arm A (Atezo + plt/gem) Better | Arm C (Placebo + plt/gem) Better

[a] Unstratified HR shown for all characteristics except for 'All Patients', where stratified HR is shown.

Adapted from Grande E, et al. ESMO 2019. LBA14_PR.

Interim OS for Monotherapy: ITT (Arm B vs Arm C)



	Arm B Atezo (n = 360)	Arm C Placebo + plt/gem (n = 359)[a]
OS events, n (%)	191 (53)	198 (55)
Stratified HR (95% CI)	1.02 (0.83, 1.24)	

No. at Risk												
Atezo	360	285	245	216	173	120	72	42	16	NE	NE	NE
Placebo + plt/gem	359	322	274	224	158	103	62	35	15	3	NE	NE

Data cutoff 31 May 2019; median survival follow-up 11.8 months (all patients). [a] Comparison only includes patients concurrently enrolled with Arm B.

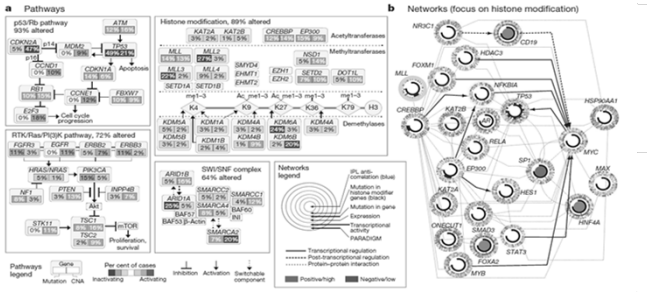
Adapted from Grande E, et al. ESMO 2019. LBA14_PR.

ARTICLE

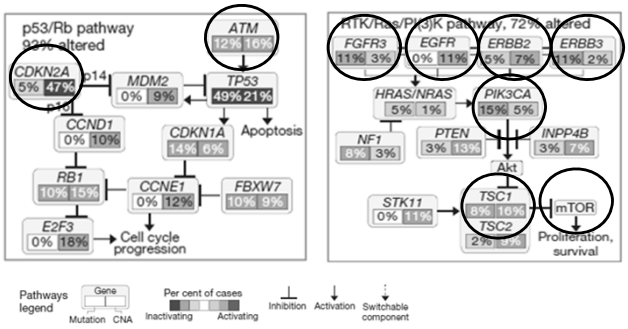
OPEN
doi:10.1038/nature12965

Comprehensive molecular characterization of urothelial bladder carcinoma

The Cancer Genome Atlas Research Network*



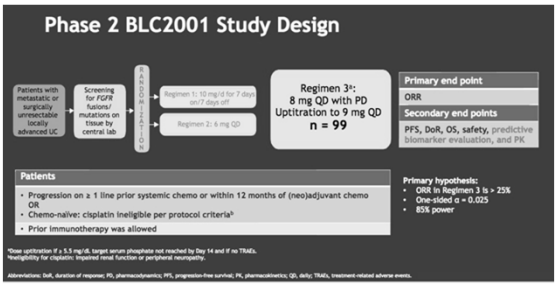
Potentially Actionable Mutations in Urothelial Cancer



TCGA-Bladder Cancer; Nature, 2014

Phase II Erdafitinib: oral pan-FGFR (1-4) inhibitor

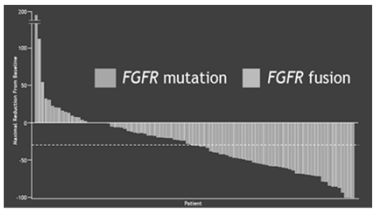
- FGFR mutation or fusion required for enrollment (prevalence in met UC: 15-20%)
- At least 1 prior systemic therapy. Prior checkpoint allowed.

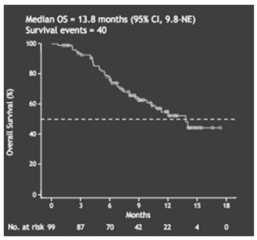


Siefker Radtke ASCO 2018

Phase II Erdafitinib: oral pan-FGFR (1-4) inhibitor

- ORR 40%, mOS 13.8 months

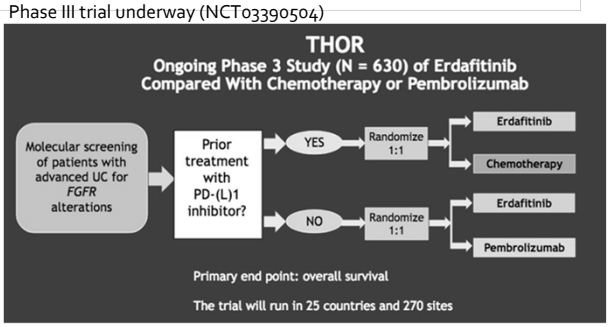




Siefker Radtke ASCO 2018

Phase 3 Erdafitinib: oral pan-FGFR (1-4) inhibitor

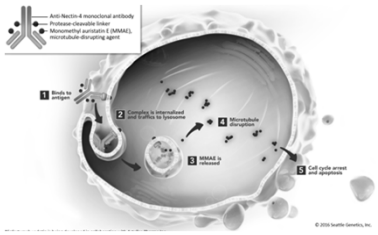
- Phase III trial underway (NCT03390504)



Siefker Radtke ASCO 2018

Enfortumab Vedotin is an Antibody-Drug Conjugate Targeting Nectin-4

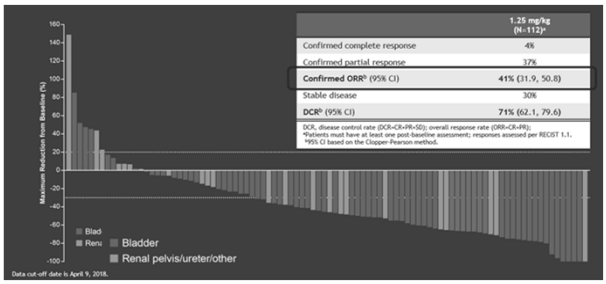
- Enfortumab vedotin (EV) is a fully humanized monoclonal antibody against Nectin-4 conjugated with the microtubule-disrupting agent monomethyl auristatin E by a protease-cleavable linker
- Nectin-4, a transmembrane cell adhesion molecule[1], was found to be highly expressed in 97% of mUC patient samples[3]



[1]Samanta D and Almo SC. *Cell Mol Life Sci.* 2015;72:645–658; [2]Challita-Eid PM et al. *Cancer Res.* 2016;76:3003–3013; [3]Petrylak DP et al. *J Clin Oncol.* 2017;35:106–106.

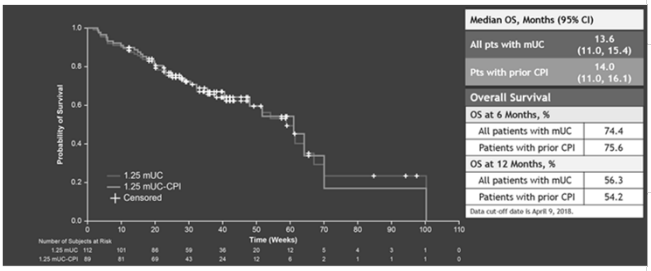
Rosenberg ASCO 2018

Phase II Enfortumab Vedotin: Response Rate



Rosenberg ASCO 2018

Phase II Enfortumab Vedotin: OS



Phase III trial vs chemotherapy enrolling (NCT03474107)

Rosenberg ASCO 2018

59

Testicular Cancer and Mediastinal Germ Cell Tumors

Darren Feldman, MD

August 19, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

59 – Testicular Cancer and Mediastinal Germ Cell Tumors

Darren R. Feldman, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

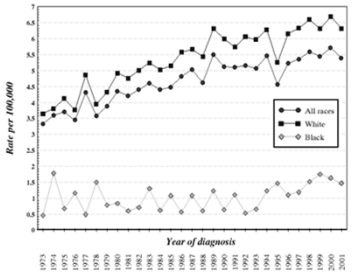
- **Research funding (Trial PI): Novartis**
- **Research funding (Institutional PI): Astellas, Seattle Genetics**
- **Research funding: Decibel Therapeutics**
- **Royalties for authorship of topic review: UpToDate**

Off-label drug use

- **None**

Germ Cell Tumors (GCT) Epidemiology

- Most common tumor in men age 15 – 40
- 9,610 new diagnoses and 440 deaths in US in 2020
- Incidence in US = 5 per 100,000 per year
- Lifetime risk 0.4% (1/263 men)
- Incidence increasing last 40 years for unknown reasons
- Caucasians > Hispanics >> African Americans
- No screening per USPTF[1]



[1]Erickson *Ann Int Med* 2010

GCT Epidemiology (continued)

- Derived from the primordial germ cells (the cells destined to become sperm in men, ova in women)
- 90 – 95% arise in gonads (testis in men, ovary in women)
- 5 – 10% extragonadal (usually midline)
  - Mediastinum (≈ 5%)
  - Retroperitoneum (≈ 1%) – probably of testis origin
  - Pineal Gland (≈ 2%, <50 y/o) – most common pineal tumor
- Risk Factors:
  - Cryptorchidism
  - Family History (brothers > fathers)
  - Infertility
  - Klinefelter syndrome – mediastinal

Feldman Cancer 2013

Symptoms and Signs of Testis Tumor

Symptoms (90%)	Signs (90%)
Pain Swelling } >50% Nodule	Painless enlargement Tenderness Painless nodule

1. Painless nodule: Pathognomonic -- but only ~10%.
2. Signs of Epididymitis/Orchitis -- COMMON
3. OK to treat as infection 1st
4. If not better in 10-14 days → Ultrasound/Urology

GCT: Initial Evaluation

- Ultrasound (2% bilateral)
- AFP, HCG, LDH
- CT of Abdomen/Pelvis
- CXR adequate for Stage I SEM
- CT Chest needed for all NSGCT or ≥ Stage II SEM
- Brain CT/MRI – if symptoms or very high HCG

NO ROUTINE VALUE IN STAGING: PET Scan, Bone Scan, MRI A/P or MRI Testis

Initial Diagnosis

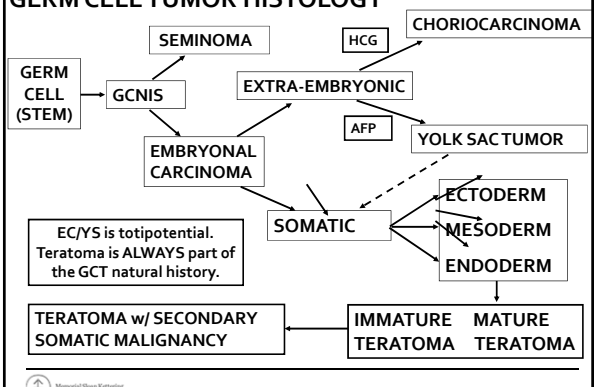
The only correct diagnostic operation is a **radical (inguinal) orchiectomy**.

A scrotal orchiectomy predisposes to pelvic/inguinal nodal metastasis, leaves the inguinal spermatic cord in place, and may seed the scrotum.

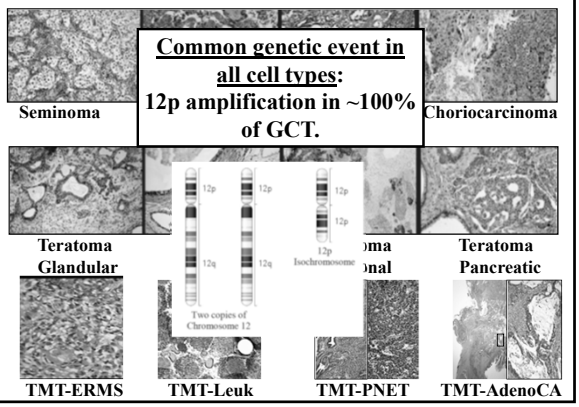
Potential complications: hematoma, infection, soreness, pain.

Histology and Biology of GCT

GERM CELL TUMOR HISTOLOGY



In Vivo Differentiation of Male GCT



Secondary Somatic Malignancy

Definition:

- Components of teratoma that are histologically transformed to somatic malignancy (e.g., PNET, enteric adenocarcinoma, RMS)

1. ~~Negative Markers (if no GCT element present).~~
2. More common in late relapse & primary mediastinal NSGCT.
3. Natural history parallels the somatic cancer
4. Treat the somatic malignancy: Surgery usually central to management (except leukemia, of course).
5. MDS/AML nearly always from Mediastinal NSGCT.

Clinical Distinction by Histology

	Non-seminoma	Seminoma
Median Age	Late 20s	Late 30s
Doubling Time	Rapid	Less Rapid
Stage Distribution	61% Stage I	86% Stage I
Radiation-sensitivity	Variable but less than Sem	High
Marker production	AFP, HCG, LDH	HCG and LDH **NEVER AFP**
Significance of Markers in Advanced Disease	Prognostic	Not prognostic
FDG-PET	Variable uptake (teratoma)	Strong uptake (no teratoma)
Post-chemo surgery	Almost always	Infrequent, complex
10-year Survival	91%	98%

Biggs *SEER Monograph* 2007

Serum Tumor Markers in GCT

Histology	AFP	HCG
Seminoma (+/- STGC)	-	+ (~15%)
Embryonal Carcinoma	++/-	++/-
Yolk Sac Tumor	++	-
Choriocarcinoma	-	++
Teratoma	-	-

STGC = syncytiotrophoblastic giant cells

1. **Increased AFP nearly always = NSGCT (but not always – see Wymer Ann Oncol 2017)**
2. **Increased HCG in both SEM and NSGCT.**
3. **Marker Half-Lives: AFP = 5 to 7 days; HCG = 1 to 3 days**

AJCC Staging System

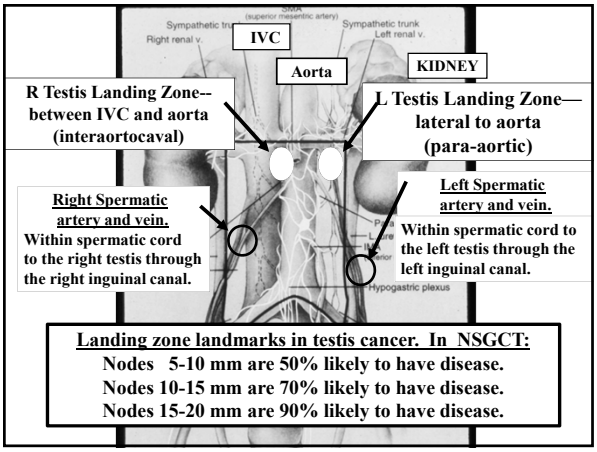
- Stage I – limited to the testis (A, B, or S)
- Stage II – spread to retroperitoneal nodes (A, B, or C)
- Stage III – spread to any other site (LN or organ; A, B, or C)

- NO STAGE IV – b/c curable at any stage (Remember Lance!)
- High markers post-orchiectomy can upstage disease

Staging: TNMS

- T Stage: T1 (**-ve vascular invasion** and -ve tunica vaginalis**)**
  T2 (**+ve vascular invasion** or +ve tunica vaginalis)
  T3 (spermatic cord)
  T4 (extends to scrotum or beyond)
- N Stage: (clinical) N1: ≤ 2cm
  N2: >2cm but ≤ 5cm
  N3: > 5cm
- M Stage: M1a: distant lymph node or lung metastasis
  M1b: Non-pulmonary visceral metastasis
- **S Stage**: S1: HCG < 5K, AFP < 1K, LDH < 1.5x ULN
  S2: HCG 5 - 50K, AFP 1 - 10K, LDH 1.5 - 10x ULN
  S3: HCG > 50K, AFP > 10K, LDH > 10x ULN

AJCC 7th edition, 2010



Stage I and II-A Nonseminoma

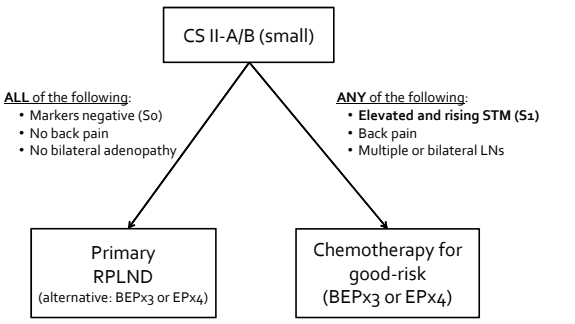
Clinical Stage I NSGCT

Clinical Stage	Features	Relapse % with S/V	Preferred Treatment Options
I-A (pT1 No Mo So)	No LVI, normal STMs	15-20%[1-7]	Surveillance preferred over RPLND or BEPx1
I-B (pT2-4 No Mo So)	+LVI, normal STMs	45-50%[1, 3-4, 6-7]	RPLND, BEPx1, or surveillance (controversial)[8]
I-S (pT1-4 No Mo S1)	Elevated and rising STMs	N/A	Treat as good-risk advanced disease (EPx4 or BEPx3)

Abbreviations: LVI, lymphovascular invasion; STMs, serum tumor markers; RPLND, retroperitoneal lymph node dissection

1. Gels ME et al. J Clin Oncol 1995 May;13(5):1188-94.
2. Sogani PC et al. J Urol 1998 Mar;159(3):855-8.
3. Colls BM et al. BJU Int 1999 Jan;83(1):76-82.
4. Sturgeon JF et al. Eur Urol 2011;59(4):556-62.
5. Rustin GJ et al. J Clin Oncol 2007 Apr;25(11):1310-5
6. Daugaard G et al. J Clin Oncol 2014 Dec;32(34):3827-33.
7. Kollmannsberger C et al. J Clin Oncol 2015 Jan;33(1):51-7.
8. Feldman J Clin Oncol 2014

Clinical Stage (CS) II-A/B NSGCT (LN ≤ 2-3cm)



Management After 1º RPLND for NSGCT

Path Stage	Criteria	Relapse rate w/o any Rx	Correct treatment	Relapse rate w/ active Rx
I (No)	Necrosis only (no TER or viable GCT)	3 – 7%	Observe	N/A
II-A (N1)	≤2cm **AND** ≤5 positive nodes **AND** no extranodal extension (ENE)	11%	Observe	<1%
II-B (N2)	Any > 2cm, or > 6 +ve nodes, or ENE BUT no LN >5cm	30-50%	EPx2 (or BEPx2) OR Surveillance	1%
II-C (N3)	Any LN >5cm (VERY RARE)	≈ 100%	BEPx3 or EPx4	<10%

McHugh *JCO* 2020

Early Stage Seminoma

Seminoma Staging Distribution

	TNM	Prop. of Cases	10-year Survival
Stage I	T1-4N0M0	86%	>99%
Stage II	T1-4N1-3M0	7%	95%
Stage III	T1-4N1-3M0	5%	75%

Stage I Sem is the single most common stage/histology combination

Biggs *SEER Monograph* 2007

Stage I Seminoma Treatment Principles

- 3 options: surveillance (favored), RT and carboplatin.
- Survival ≈100% with all 3 approaches
- Differences are in relapse rates and late toxicity
- Adjuvant "for all" strategy over-treats majority of patients & associated with acute and chronic toxicities
- Surveillance least toxic to the entire population but still requires frequent f/u, frequent CTs, pt compliance, and ability to cope with not being aggressive
- 21% patients are lost to follow-up < 5-years[1]

[1]Alomary, Urol Oncol, 2006

Management of Stage I Seminoma

	Surveillance	Radiation	Carboplatin
Relapse rate	15-20%	≈ 4%	≈ 5-6%
Dose	N/A	20-25.5 Gy; Dog-leg = PA-only	1-2 cycles AUC=7
Median time to relapse	12 – 15 months	≈12 months	≈20 months
% Relapses <2 years	70-75%	≈80%	80-90%
% Relapses > 5 years	5-7%	≈5%	Unknown
% of Relapses in RP	85%	9%	80-90%
5-year Survival	≈100%	≈100%	≈100%
Late toxicity	N/A	Secondary malignancies*	Unknown
Conclusion	**Preferred option by most**	**Rarely used d/t risk of secondary CAs**	**Awaiting long-term tox data**

* ≈ 2-fold increase in secondary malignancies with 20-30 year latency; especially gastric (RR 4.0), pancreatic (RR 3.6), bladder (RR 2.7), kidney (RR 2.4), and colorectal (RR 1.8-2.0)

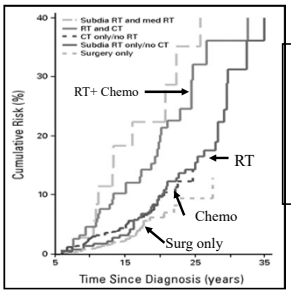
Warde JCO 2002; Kollmannsberger JCO 2015; Oliver JCO 2011; Aparicio Ann Oncol 2014; Tandstad Ann Oncol 2014; Jones JCO 2005; Fossa JCO 1999; Powles Ann Oncol 2008

Clinical Stage II-A/B Seminoma

- **Stage IIA (LN ≤ 2cm)**
  - RT or Chemo (good-risk)
  - If RT → 30 – 35Gy, **Dog-leg port**, boost to gross disease
  - Recurrence rate: RT ≈ 3 – 13% vs. Chemo ≈ 0 – 5%
- **Stage IIB (LN > 2cm but ≤ 5cm)**
  - LNs > 3cm should receive chemotherapy (adv dz)
  - LNs 2 – 3cm: Chemo (favored) or RT
  - Recurrence rate: RT ≈ 10 – 20% vs. Chemo ≈ 0 – 13%
  - Secondary CA ≈ 4% with RT, 2% with Chemo

Giannatempo *Ann Oncol* 2015

Second Malignant Neoplasms (SMN) and CVD are competing risks after GCT Treatment



Risk after RT + Chemo greater than after either Chemo or RT alone

CVD risk at 10-15 yrs
SMN risk at 20-25 yrs

van den Belt-Dusebout, JCO; 25:4370, 2007

Advanced GCT Principles

DEFINITION: Any tumor requiring primary treatment with full course systemic chemotherapy (3-4 cycles of BEP, EP, VIP, etc.)

- SEM: includes most stage II-B and higher
- NSGCT: Stage I-S, marker-pos II-A, and II-B or higher
- Initial chemotherapy determined by IGCCCG risk
- Markers should be obtained before and after orchiectomy BUT the **post-orchiectomy markers determine stage and IGCCCG risk**

IGCCCG Risk Groups for Seminoma[1]

Risk Group	Features	5-yr PFS 1997[1] → 2020[2]	5-yr OS 1997[1] → 2020[2]
Good 90%	No organ metastases other than lung (- NPVM)	82% → 89%	86% → 95%
Intermediate 10%	+ NPVM	67% → 79%	72% → 88%

NOTE: Marker levels and primary site DON'T affect outcome (? LDH)

[1]IGCCCG, JCO, 1997
[2]Gillisen, GUCS 2020

IGCCCG Risk Categories for Non-seminoma[1]

Risk Group	Features	5-yr PFS 1997[1] → 2019[2]	5-yr OS 1997[1] → 2019[2]
Good 60%	Meet all of the following: Gonadal/RP primary site, no NPVM, S0 or S1 markers	89% → 90%	92% → 96%
Intermediate 25%	Meet good-risk criteria except S2 markers	75% → 77%	80% → 88%
Poor 15%	Any of the following: 1° mediastinal site, +NPVMs, S3 markers	**41% → 54%**	**48% → 67%**

NPVM = non-pulmonary visceral metastasis, RP = retroperitoneal
S1: HCG < 5,000; AFP < 1,000; LDH < 1.5 x upper limit of normal (ULN)
S2: HCG 5,000 – 50,000; AFP 1,000 – 10,000; LDH 1.5 – 10 x ULN
S3: HCG > 50,000; AFP > 10,000; LDH > 10 x ULN

Older age and lung mets **may be additional adverse prognostic factors per IGCCCG-2 (presented, not published)

[1]IGCCCG, JCO, 1997
[2]Gillisen, ESMO, 2019

Chemotherapy for Good-Risk

- Goal: Minimize toxicity, maintain high cure rate
- Two regimens are accepted as standard of care
- 4 cycles of EP or 3 cycles of BEP
- **EP** = **E**toposide 100mg/m²/d + cis**P**latin 20mg/m²/d x 5d
- **BEP** = **B**leomycin (30u weekly) + **EP**
- Favorable response (FR) = CR or PR with normal tumor markers (PR-negative markers)

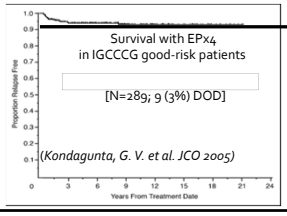
Treatment of "Good Risk" Metastatic GCT

Regimen	Author	Risk	%FR	%Rel
$BE_{500}Px3$	Indiana	IU: Min+Mod	98	~6
$E_{500}Px4$	Memorial	IGC: Good	98	~6

Table 2. Standard Treatment of Nonseminomatous Germ Cell Tumors

Good risk	BEP × 3 or EP × 4	> 90

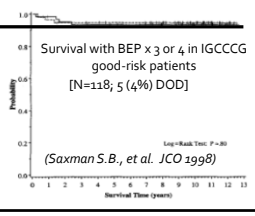
Hanna, Einhorn. JCO, 2014; 32: 3085



Survival with EPx4 in IGCCCG good-risk patients

[N=289; 9 (3%) DOD]

(Kondagunta, G. V. et al. JCO 2005)



Survival with BEP x 3 or 4 in IGCCCG good-risk patients

[N=118; 5 (4%) DOD]

(Saxman S.B., et al. JCO 1998)

Toxicity BEPx3 vs. EPx4

	Cycles		P	Patients		P
	$3BE_{500}P$ (n = 398)	$4E_{500}P$ (n = 520)		$3BE_{500}P$ (n = 132)	$4E_{500}P$ (n = 130)	
Hematology grades 3–4						
Neutropenia	179 (47%)	277 (62%)	<0.0001	95 (72%)	110 (90%)	0.0002
Febrile neutropenia	10 (2.5%)	6 (1.2%)	0.12	9 (7%)	6 (5%)	0.44
Anemia	4 (1.1%)	6 (1.1%)	0.72	3 (2%)	6 (5%)	0.25
Thrombocytopenia	10 (2.6%)	11 (2.5%)	0.92	8 (6%)	9 (8%)	0.65
Growth factors	124 (24%)	74 (19%)	0.053	47 (36%)	38 (29%)	0.20
Non-hematology						
Vomiting (grade 2+)	97 (24%)	110 (21%)	0.27	61 (46%)	58 (45%)	0.80
Mucositis (grade 2+)	8 (1.6%)	8 (2.5%)	0.30	8 (6%)	8 (6%)	0.96
Neurologic (grade 1+)	28 (7%)	10 (2%)	<0.0001	21 (16%)	7 (5%)	0.006
Dermatologic (grade 1+)	63 (16%)	16 (3%)	<0.0001	38 (29%)	11 (8%)	<0.0001
Renal (grade 1+)	5 (1.3%)	2 (1.4%)	0.13	4 (3%)	2 (1.5%)	0.42
Pulmonary (grade 1+)	15 (4%)	8 (2%)	0.034	12 (9%)	8 (6%)	0.38

- As expected, derm and pulm toxicity worse with BEP but neuropathy was also worse with BEP despite less platinum
- Neutropenia worse with EP but no difference in neutropenic fever rates and G-CSF used more commonly in BEP arm

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Culine et al., Ann Onc, 2007

Efficacy (BEPx3 vs. EPx4) in Good-risk NSGCT

Outcome	BEPx3	EPx4	P value
Favorable Responses*	**95%**	**97%**	**NR**
4-year Event-Free Survival	**91%**	**86%**	**0.14**
4-year Overall Survival	**96%**	**92%**	**0.10**
Drug Delivery			
>90% cisplatin dose intensity	**86%**	**77%**	**NR**
>90% etoposide dose intensity	**83%**	**79%**	**NR**
>2 week delay	**4%**	**8%**	**NR**

*Primary endpoint, NR = not reported

Conclusion: Both BEPx3 and EPx4 are both standard first-line options.

- Relative contraindications to Bleo: age >50, active/heavy x-smoker, poor GFR, prior thoracic RT

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Culine et al., Ann Onc, 2007

Other Important Info on Good-risk Chemo

- Don't use Carboplatin instead of Cisplatin (Cisplatin superior)[1,2]
- Don't reduce doses
  - Cisplatin (<100mg/m² a/w worse outcome)[3]
  - VP-16 (500mg/m²/cycle better than 360mg/m²/cycle)[4]
- How to handle clinical situations on the boards
  - **Don't delay treatment**
  - ANC 0.9 on C2D1 – proceed with EP/BEP at same doses
    - Indiana – proceed w/ any ANC, WBC <2.5 on D_4, no VP-16 on D_5
    - MSKCC – proceed with ANC >= 0.5, otherwise delay 1 week
  - Cr increase 1.0 → 1.5 on C2D1 – proceed at same doses w/ ↑fluids

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[1]Bajorin JCO 1993; [2]Horwich JCO 1997; [3]Samson Cancer 1984; [4]Grimison JNCI 2010

Intermediate- and Poor-risk GCT

- Seminomas are NEVER poor-risk!
- Standard of Care = BEPx4
- 40-75% cure rates
- VIPx4 is an alternative for pts who can not receive bleomycin (severe lung disease, professional cyclists, age >50, etc.)

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Randomized Trials vs. BEPx4 in Int- and Poor-Risk GCT

Author (Year)	IGCCCG Risk	Experimental	N	CR, % (BEP vs. Exp)	PFS, % (BEP vs. Exp)
Nichols 1991	Poor	$BEP_{200}x4$	153	73 vs 68	61 vs 63
De Wit 1995[1]	Poor	PveB/BEPx4	371	72 vs 76	NR
De Wit 1998[1,2]	Int	VIPx4	84	82 vs 80	79 vs 85
Nichols 1998	Poor	VIPx4	286	60 vs 63	60 vs 64
Motzer 2007	Int- and poor	BEPx2 + HDCTx2	219	55 vs 56	48 vs 52
Droz 2007	Poor	BEPx2 + HDCTx2	114	67 vs 75	47 vs 54
Daugaard 2011	Poor	VIPx1 + HD-VIPx3	131	33 vs 45	45 vs 58
de Wit 2012	Int	T-BEPx4	337	50 vs 60	71 vs 79
Fizazi 2014	Poor	Δ to dose-dense chemo if unfav STM decline	203	30 vs 40	48 vs 59
Feldman 2018[2,3]	Int- and Poor	TIPx4	91	45 vs 45	72 vs 73

No alternative to BEPx4 with clear increase in efficacy: all with ↑↑ toxicity;
Use VIPx4 when contraindication to bleomycin
Alternative to VIP is TIPx4, especially if etoposide shortage

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[1]Exclusively nonseminoma
[2]Randomized Phase II study
[3]Unpublished, presented ASCO 2018

Differential Diagnosis: Anterior Mediastinal Neoplasms

- Thymoma/Thymic Carcinoma
- Lymphoma (Hodgkin's and NHL)
- Endocrine (Thyroid and Parathyroid)
- Germ Cell Neoplasms

Mediastinal Germ Cell Tumors

- Most common extragonadal site
- Male > Female (equal for teratoma)
- i(12p) present in most
- Seminoma (favorable) vs. Nonseminoma (unfavorable)

	N	5-yr PFS	5-yr OS
Mediastinal Seminoma	51	88%	89%
Mediastinal NSGCT	287	44%	49%

- HCG and/or AFP usually elevated in nonseminoma (PM-NSGCT)
- Associated Syndromes with PM-NSGCT:
  - Hematologic disorders in 17% (e.g., AML, histiocytic sarcoma, MDS)
  - Secondary somatic malignancies (particularly sarcomas)
  - Klinefelter's (younger onset)

Hartmann JNCI 2000

Salvage Chemotherapy

- **STILL CURABLE** (up to 50%)
- Options:
  - **Conventional-dose chemotherapy (CDCT)**
    - Generally consists of cisplatin + ifos + 3rd drug patient has not previously received
    - TIP (paclitaxel + IP) and VeIP (vinblastine + IP) are most common regimens
  - **High-dose chemo with sequential (2-3) autologous stem cell transplant (HDCT/ASCT)**
    - Backbone is **2-3** cycles of high-dose Carboplatin + Etoposide
  - **Desperation surgery**

Initial salvage CDCT

- CR rate ~50%, durable CR rate ~25% with initial salvage VeIP / VIP[1-4]
  - Evaluated in pts with stable disease or better to 1st line
- **Prognostic factors[5-6]**

Factor	Favorable	Unfavorable
Primary tumor site	Gonadal / RP	Mediastinal (NSGCT)
Response to 1st line	CR or PR-negative	Stable or Incomplete
Disease-Free Interval	> 6 months	< 3 months
HCG / AFP	Normal or low elevation	> 1,000
Liver, bone, or brain mets	Absent	Present

[1]Pizocarro 1992; [2]Farhat 1996, [3]McCafffrey 1997, [4]Loehrer 1998, [5]Motzer 1991; [6]Lorch 2013

Initial Salvage TIP in Favorable Pts

- N=46
- Median f/u 69 months
- Eligibility required:
  - Gonadal primary tumor
  - CR or PR-negative markers > 6 months after initial chemo
  - Only 1 prior chemo regimen

TIP may be better than other salvage CDCT regimens but limited by selection bias and no randomized data

Outcome	N	%
CR	**32**	**70**
Chemotherapy	**29**	**63**
Chemotherapy + surgery	**3**	**7**
IR (PR- marker negative)	**14 (2)**	**30 (4)**
Relapse From CR	**3**	**7**
Continuously NED	**29**	**63**
Two-Year Overall Survival	**36**	**78**

Kondagunta et al., *JCO*, 2005

High-Dose Chemotherapy and Autologous Stem cell Transplant (HDCT/ASCT)

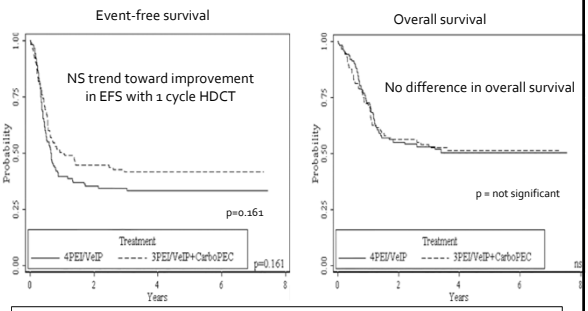
	MSKCC (n=107)[1]	Indiana (n=364)[2]
Regimen	TI x 2 → HD CE x 3	VeIP x 1-2 → HD CE x 2 → oral VP-16 x 3 cycles
Population	Unfavorable only	Mixed
PM-NSGCT	21 (20%)	20 (5%)
Late relapses	7 (7%)	0
PFS / OS	5-year: 47% / 52%	2-year: 60% / 66%
PFS, platinum-refractory	5-year: ≈43%	2-year: 37%

TI, paclitaxel + ifosfamide; HD CE, high-dose carboplatin + etoposide; VeIP, vinblastine + ifosfamide + cisplatin

- If balance prognostic factors between the two groups, outcomes are quite similar
- Both regimens use sequential HDCT (2 or 3 cycles)
- Adverse prognostic factors: Mediastinal primary, HDCT as 3rd-line or later

[1]Feldman, *JCO*, 2010
[2]Adra, JCO 2017

CDCT vs. HDCT as Initial Salvage – IT94



Conclusion: No benefit to 1 cycle of HDCT as initial salvage

Pico, Ann Oncol 2005

Difficulties in Interpreting IT-94

- Only one high-dose cycle in HDCT arm
  - Doesn't r/o benefit of sequential HDCT
- Patients with incomplete responses to 1st line chemotherapy were excluded
  - This group might benefit most from HDCT
- High toxic death rate in HDCT arm (7%) vs. CDCT arm (3%)
  - Small numbers of patients enrolled at many centers
- > 25% of pts assigned to HDCT didn't receive it

International Prognostic Factors Study Group (IPFSG) Classification at Initial Salvage Therapy

	Number of Points			
	0	1	2	3
Primary site	Gonadal	Extragonadal	--	Mediastinal
Prior response	CR/PRm-	PRm+/SD	PD	--
PFI, months	>3	≤3	--	--
AFP at salvage	Normal	≤1000	>1000	--
HCG at salvage	≤1000	>1000	--	--
LBB metastases	No	Yes	--	--

Initial Score	0	1	2	3	4	≥ 5
Reclassified Score	0	1		2		3
Histology Consideration	Subtract 1 point for Seminoma					
Final Grouping (Score)	Very Low (-1)	Low (0)	Intermediate (1)	High (2)	Very High (3)	

Adapted from Lorch et al., JCO, 2010

IPFSG Classification System for Initial Salvage Therapy in GCT

Final Category	Score	N	2-Yr PFS	3-Yr OS
Very low	-1	76	75	77
Low	0	132	51	66
Intermed.	1	219	40	58
High	2	122	26	27
Very high	3	36	5.6	6.1

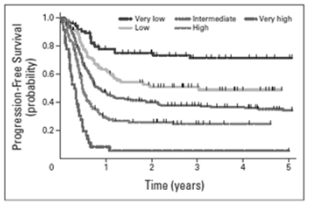


Fig 1. Progression-free survival according to prognostic category (validation set plus patients with seminoma).

Lorch, *JCO*, 2010

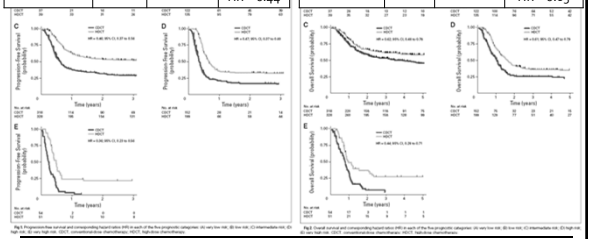
CDCT vs. HDCT as Initial Salvage in IPFSG Database

PFS

All pts (n=1594)	N	2-yr PFS	P value & HR
HDCT	821	50%	p<.001
CDCT	773	28%	HR = 0.44

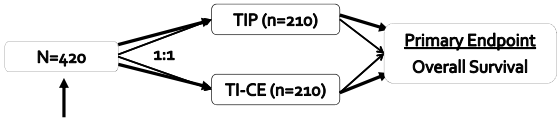
OS

All pts (n=1594)	N	5-yr OS	P value & HR
HDCT	821	53%	p<.001
CDCT	773	41%	HR = 0.65



Lorch, *JCO*, 2011

Alliance 031102 / EORTC 1407 (TIGER)



Stratification:
- IPFSG risk class
- Continent

81% power to distinguish a 29% relative improvement in OS (HR of 0.71)

Secondary Endpoints
- PFS
- Favorable RR (CR / PR-m)
- Toxicity & treatment-related deaths
- Validation of IPFSG model
- QOL (EORTC QLQ-TC26 & C30)
- Biological correlates

Eligibility
- POD to 1st-line cisplatin-based CT
- Age ≥ 14

PR-m = PR with normal tumor markers

IPFSG = International Prognostic Factors Study Group

Post-HDCT Options: Single Agents and Combinations

Drug(s)	No. Trials	N	ORR, %	CR, %
Oxaliplatin[1]	1	32	6-19*	0
Gemcitabine[2-3]	2	51	15-19	0-5
Paclitaxel[4-8]	5	98	11-30	0-10
Oral Etoposide[9-10]	2	42	29-33	0-10
Gem / Oxali[11-14]	4	92	17 – 46	5 – 18**
Gem / Paclitaxel[15]	1	32	31	19**
Gem / Oxali / Paclitaxel[16-17]	2	71	31 – 51	7-15**

* 2 dose levels studied; ** not all CRs durable

- Other agents with activity include: Vinblastine, Actinomycin-D, Epirubicin

GCT essentially not curable after HDCT failure – the one exception is desperation surgery (solitary RP or lung mass)

[1]Kollmannsberger, 2002 [2]Einhorn, 1999 [3]Bokemeyer, 1999 [4]Bokemeyer, 1994 [5]Motzer, 1994 [6]Nazario, 1995 [7]Bokemeyer, 1996 [8]Sandler, 1998 [9]Miller, 1990 [10]Porcu, 2000 [11]Kollmannsberger, 2004 [12]Pectasaides, 2004 [13]De Giorgi, 2006 [14]Uchida, 2014 [15]Einhorn 2007 [16]Oeschle, 2011 [17]Sadeghi, 2013

Salvage Chemotherapy Boards Summary

KNOW:

- Up to 50% of patients still curable
- Prognostic factors for salvage chemo: response to prior treatment, time to relapse, primary tumor site, HCG, AFP, and liver/bone/brain mets
- If salvage CDCT fails, HDCT is the only curative systemic option
- HDCT backbone is carboplatin and VP-16
- Progression after HDCT is usually not curable
  - Occasionally, desperation surgery can achieve cure

WILL NOT BE ASKED:

- To choose b/t CDCT and HDCT (controversial)
- To choose b/t 2 standard salvage regimens (TIP vs. VeIP)

Post-chemotherapy evaluation of residual disease

- **NSGCT: surgery usually needed (≥ 1cm); teratoma is always a possibility**
- **SEM: surgery usually not needed**

Post-chemo management: NSGCT (with normal markers)

	After 1st line chemo	After salvage chemo
Viable GCT (vGCT)	≈ 15%	30-50%
Teratoma (Ter)	≈ 40%	≈ 35%
Total (Ter + vGCT)	≈ 55%	65-85%
Adj. Chemo if viable GCT	YES	NO
Ter, teratoma; vGCT, viable GCT		

- **All residual LNs > 1cm should be removed after 1st line chemo**
  - <1cm controversial - many surgeries to save a few relapses but some fatal (SSM)
- Histology at 1 site does NOT reliably predict histology at others → resect all (RP LNs, lung, liver) > 1cm even if path at 1st site is necrosis
- Resect all residual disease after salvage chemo (higher rates of vGCT)

Toner JCO 1991; Fox JCO 1993; Hendry Cancer 2002; Rick JCO 2004; Spiess Cancer 2006; Eggener Cancer 2007;

Post-chemo management: Seminoma

- Surgery more difficult
- Don't have to worry about teratoma
- < 3cm: Observe (<10% chance viable Sem)
- ≥ 3cm: Obtain PET
  - PET –ve (5% viable Sem) → observe
  - PET +ve (>75% viable Sem) → options include biopsy + salvage chemo if +ve vs. surgery
- If surgery shows viable seminoma → adjuvant chemo with 2 cycles of EP can be given

Puc, J Clin Oncol 1993
Bachner, Ann Oncol 2012

Late Relapse

(Definition: Relapse ≥2 years after Rx)

TOTAL PATIENTS	83
2-5 years	23 (28%)
>5 years	60 (72%)
AFP	43 (52%)
No Markers	27 (32%)
RP/Retrocrural/pelvis	47%/14%/14%
Became NED	47 (56%)

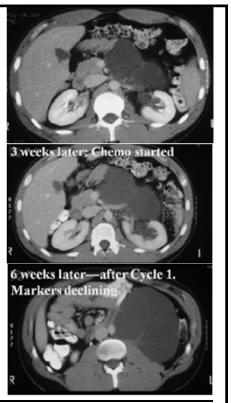
- Usually a failure to control the abdomen
- Less responsive to chemo → treat with surgery when feasible (e.g., solitary resectable mass)

(data from George et al, JCO 2003; see also Ronnen et al, JCO 2005)

Growing Teratoma

%Shrink	%Nec	%Ter	%Mal
> 90%	72	16	8
80-90%	75	17	8
50-80%	46	31	23
0-50%	23	62	15
Growth	0	90	10

- Definition: declining tumor markers but enlarging mass(es) on imaging often prompted by symptoms
- Typically in patient with teratoma in primary tumor
- Often cystic appearance to metastases
- Often find teratoma + TMT, sometimes viable GCT
- Requires interruption of chemo for surgery, can resume chemotherapy afterwards



Toner , JCO, 1990

Acute Toxicity in GCT Treatment

Toxicity	BEPx1	EPx4	BEPx3	BEPx4
Anemia (Hgb<8)		<5%	<5%	5%-10%
Platelets (<50K)		6%	8% →	20%
Febrile Neutropenia		5%	7% →	20%
Pulm Tox (≥"Mild")		2%	4% →	16%
Pulm Treatment Death		Rare	Rare →	1-2%
All Treatment Death		Rare	Rare →	2-4%

Stresses the Importance of the Correct Initial IGCCCG Risk Stratification

Miller, Cancer 1981; Williams, NEJM 1987. DeWit, JCO, 1997; Culine, Ann Oncol 2007; Albers, JCO 2007; Culine JCO, 2008.

Late Cardiovascular Toxicity

(Meinardi et al, JCO 2000)

- Myocardial Infarction: 6/87 (7%)
  - occurred at Age 30-42: **7:1 Risk Excess**
- Exercise-induced ST Depression: 6/55 (11%)

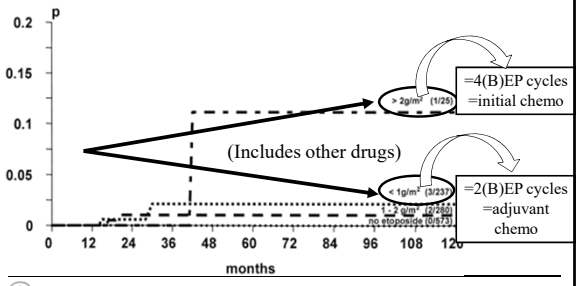
Risk Factor	Chemo	No Chemo
↑Cholesterol	79%	58%
↑BP	39%	13%
Raynaud Phenom.	24%	0%

Raynaud occurs only after bleomycin *(de Wit, JCO, 1997)*

Late GCT Chemotherapy Toxicity

Leukemia Risk after Etoposide is Dose-related

No apparent safe lower limit



Schneider *JCO* 1999

Late GCT Chemotherapy Toxicity: Paternity

Therapy	Paternity at 15 yr F/U
Surveillance	81%
RPLND	77%
Radiation Therapy	65%
Chemotherapy	62%
Salvage Chemotherapy	38%

1. 50% of men are "subfertile" at diagnosis.
2. Above results WITHOUT use of frozen sperm
3. Offer sperm banking to all pts requiring additional treatment post-orchiectomy or requiring bilateral orchiectomy

Brydoy et al, JNCI 97:1580-8, 2005

Future Directions

- **IGCCCG-2 Model (not yet used in clinical practice)**
  - NSGCT model presented at ESMO 2019[1]
    - Older age & lung mets are new adverse prognostic factors
    - LDH cutoff now 2.5 x ULN (1.5 and 10x cutoffs eliminated)
    - Individual prediction for PFS via online nomogram (vs. 3 groups)
    - Cutoff for giving BEPx4 (instead of BEPx3/EPx4) not clear
  - SEM model presented at GU Cancers Symposium 2020[2]
    - LDH > 2.5 x ULN is an adverse factor in addition to NPVMs
- **MicroRNA 371-3p**
  - More sensitive than AFP and HCG, particularly for SEM[3]
  - Many potential applications under development

[1]Gillesen ESMO 2019
[2]Beyer GUCS 2020
[3]Dieckmann *JCO* 2019

60

Ovarian Cancer

Andrea Wahner-Hendrickson, MD

August 19, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

60 – Ovarian Cancer

Andrea Wahner-Hendrickson, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Advisory Board: Clovis
- Off Label Usage – I will include discussion of investigational or off-label use of a product in my presentation.

Ovarian Cancer
Outline

- Epithelial carcinoma (90%)
  - Epidemiology and Screening
  - Initial therapy
    - Surgery
    - Adjuvant chemotherapy
    - Maintenance therapy
  - Disease recurrence
    - Platinum sensitive vs. platinum resistant
- Non-epithelial malignancies (10%)
  - Sex cord-stromal tumors (7%)
  - Germ cell neoplasms (2%)

Ovarian Cancer

Epidemiology and Screening

Gynecologic Malignancies
Incidence and Mortality

Estimated New Cases

	Males		Females	
Prostate	161,360	19%	Breast	252,710	30%
Lung & bronchus	116,990	14%	Lung & bronchus	105,510	12%
Colon & rectum	71,420	9%	Colon & rectum	64,010	8%
Urinary bladder	60,490	7%	Uterine corpus	61,380	7%
Melanoma of the skin	52,170	6%	Thyroid	42,470	5%
Kidney & renal pelvis	40,610	5%	Melanoma of the skin	34,940	4%
Non-Hodgkin lymphoma	40,080	5%	Non-Hodgkin lymphoma	32,160	4%
Leukemia	36,290	4%	Leukemia	25,840	3%
Oral cavity & pharynx	35,720	4%	Pancreas	25,700	3%
Liver & intrahepatic bile duct	29,200	3%	Kidney & renal pelvis	23,380	3%
All Sites	**836,150**	**100%**	**All Sites**	**852,630**	**100%**

Estimated Deaths

	Males		Females	
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	Breast	40,610	14%
Prostate	26,730	8%	Colon & rectum	23,110	8%
Pancreas	22,300	7%	Pancreas	20,790	7%
Liver & intrahepatic bile duct	19,010	6%	Ovary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	4%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**310,420**	**100%**	**All Sites**	**282,500**	**100%**

Siegel, R CA Cancer J Clin 2017: 67:7-30

Screening for ovarian cancer
"The Holy Grail"

- Highest mortality rate of all gynecologic malignancies
- Lifetime risk 1 in 71 women
- Overall 5 year survival rate: 46%
  - Confined to the ovary: 95%
  - Stage IV: 18%
- 75% are detected at advanced stage

CA Cancer J Clin 2009; 59(4): 225-249

Screening for ovarian cancer

No effective screening test for the general population!

Risk reducing BSO for women at highest risk for epithelial ovarian/fallopian tube cancer

Menon U, et al. Lancet Oncol, Epub ahead of print, March 10, 2009
Menon U et al: Obstet Gynecol 131:909-927, 2018

Risk of Ovarian Cancer
Protective factors and Risk factors

Protective Factors	Risk Factors
Oral Contraceptives • Relative risk of 0.7 for 2 year use • Relative risk of 0.5 for >5 year use	Advancing age • < 40 incidence 1.4/100,000 • > 50% are over age 63 • 80% occur after age 40
Pregnancy, 1st full term < age 25	Infertility/Low parity
Multiple pregnancies	Family History
Breast Feeding	Early menarche (<12), late menopause (>52)
Tubal ligation	* Endometriosis (endometrioid,clear cell carcinoma)

Hereditary Syndromes

Syndrome	Gene	Tumor
Hereditary breast and ovarian syndrome	*BRCA1/2*	Epithelial carcinoma
HNPCC (Lynch)	Mismatch repair	Epithelial carcinoma
Peutz-Jeghers	*STK11*	Sex cord tumors
Nevoid basal cell carcinoma (Gorlin)	*PTCH1*	Ovarian fibromas Fibrosarcomas (rare)
Ollier Disease (Enchondromatosis)	EXT1,2,3	Juvenile Granulosa Cell

All women with ovarian cancer should undergo genetic testing for hereditary breast and ovarian cancer syndrome

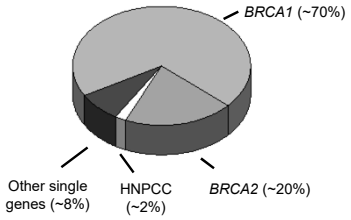
Ovarian Cancer

GERMLINE AND SOMATIC *BRCA* MUTATIONS[1-4]

	Germline	Somatic
Prevelance	18%	7%
Origin	Inherited	Acquired

1. Pennington et al. Clin Cancer Res. 2014;20(3):764-75
2. Hennessy et al. J Clin Oncol. 2010;28(22):3570-6. **3.** Petrucelli et al. In:
3. Pagon et al, eds. *GeneReviews® [Internet]*. https://www.ncbi.nlm.nih.gov/books/NBK1247/. Updated September 26, 2013.
4. Robson et al. J Clin Oncol. 2015;33(31):3660-7.

Ovarian Carcinoma
Hereditary Causes



American Society of Clinical Oncology. Hereditary Breast and Ovarian Cancer. ASCO Curriculum guidelines. Alexandria, Va. 1999.

Ovarian Carcinoma
Lifetime risks associated with specific genes

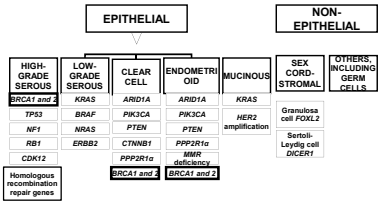
	MMR	BRCA1	BRCA2
Breast	---	35-60%	30-55%
Ovarian	6-20%	30-40%	15-25%
Endometrial	40-40%	---	---

1. Chen S, et al. *J Clin Oncol. 2007*:25(11):1329-1333.

2. Aarnio M, et al. *Int J Cancer.* 1999:81(2):214-218.

BRCA1 = breast cancer 1 gene
BRCA2 = breast cancer 2 gene
HNPCC = hereditary nonpolyposis colorectal cancer
MMR = mismatch repair

Ovarian cancer
Genetic characteristics



1. Coleman RL, Monk BJ, Sood AK, Herzog TJ. Latest research and treatment of advanced-stage epithelial ovarian cancer. *Nat Rev Clin Oncol*. 2013;10(4):211-224.
2. Banerjee S, Kaye SB. New strategies in the treatment of ovarian cancer: current clinical perspectives and future potential. *Clin Cancer Res*. 2013;19(5):961-968.
3. Lakhani SR, Manek S, Penault-Llorca F, et al. Pathology of ovarian cancers in BRCA1 and BRCA2 carriers. *Clin Cancer Res*. 2004;10:2473-2481.
4. Goodheart MJ, Rose SL, Hattermann-Zogg M, Smith BJ, De Young BR, Buller RE. BRCA2 alteration is important in clear cell carcinoma of the ovary. *Clin Genet*. 2009;76(2):161-167.

Slide courtesy of Dr. Tate Thigpen

Ovarian Cancer
Staging and Diagnosis

Ovarian Cancer
FIGO Staging

STAGE I: Tumour confined to ovaries		
IA	Tumour limited to 1 ovary, capsule intact, no tumour on surface, negative washings	
IB	Tumour involves both ovaries otherwise like IA	
IC: Tumour limited to 1 or both ovaries		
IC1	Surgical spill	
IC2	Capsule rupture before surgery or tumour on ovarian surface	
IC3	Malignant cells in the ascites or peritoneal washings	
STAGE II: Tumour involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer		
IIA	Extension and/or implant on uterus and/or fallopian tubes	
IIB	Extension to other pelvic intraperitoneal tissues	
STAGE III: Tumour involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes		
IIIA: Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis)		
IIIA1	Positive retroperitoneal lymph nodes only	
	IIIA1(i)	Metastasis ≤ 10 mm
	IIIA1 (ii)	Metastasis > 10 mm
IIIA2	Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes	
IIIB	Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen	
STAGE IV: Distant metastasis excluding peritoneal metastasis		
IVA	Pleural effusion with positive cytology	
IVB	Hepatic and/or splenic parenchymal metastasis, metastasis to extraabdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

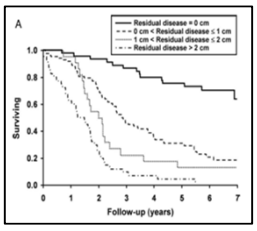
Ovarian Cancer
Classic Presentation

- Symptoms
  - Pelvic/abdominal pain
  - Abdominal bloating
  - Early satiety
  - Urinary changes
- Evaluation
  - Exam to assess for pelvic mass
  - Imaging of abdominal cavity
  - CA-125

Ovarian Cancer Treatment
Initial Diagnosis

Ovarian Cancer
Primary Surgical Cytoreduction

- Should be done by a gynecologic oncologist
- Goal: no residual disease
  - Significant survival advantage
  - Optimal: less than 1 cm residual deposits
  - Suboptimal: More than 1 cm deposits remaining at completion of surgery
- Stage IIIC



Obstet and Gynecol. 2006;107(1) 77-85

Timing of the debulking surgery
Upfront surgery vs neoadjuvant chemotherapy?

- PFS similar in both groups
- Neoadjuvant chemotherapy (NACT)
  - Candidates for NACT
    - Poor operative candidates
    - Unlikely to be optimally cytoreduced
  - Poor operative candidates
- NACT treatment plan
  - 3-4 cycles of chemotherapy
    - Carboplatin/paclitaxel +/- bevacizumab
  - Assess for surgery
  - Additional chemotherapy after completion of surgery

J Clin Oncol. 2016;34(28):34600
Lancet 2015;386(9990)249-257
Lancet 2018; 19(12)1680-1687
NEJM 2010 363(10):943-53

Initial therapy recommendations

- Quality of the surgery is critical
  - Well trained gynecologic oncologist
  - Survival advantage
- Primary debulking
  - Generally favored *unless*:
    - Optimal debulking unlikely
    - Poor surgical candidate
  - Followed by 6* cycles of adjuvant platinum/taxane
    - Maintenance therapy (bevacizumab and/or PARPi)
- Neoadjuvant chemotherapy (NACT)
  - Reassess after 3-4 cycles
  - Continue chemotherapy after the interval surgery
  - If disease progression, no surgery
  - Consider maintenance in these patients as well

Bottom line. . .

- Assuming no contraindication, every patient should have one aggressive attempt at surgical debulking
  - Goal should be no gross residual disease
  - Can be up front or interval (NACT)
  - Surgical quality is critical to outcome
    - Well trained gynecologic oncologist
    - Quality of the surgery impacts OS

Brief note on borderline and low grade ovarian tumors. . .

Borderline and low grade tumors

- Borderline tumors
  - Surgery
  - Excellent prognosis even with intra-abdominal spread (85% 5 yr OS)
  - Observation after surgery
- Low grade
  - Better prognosis than high grade
  - Adjuvant platinum based chemotherapy if advanced stage
    - Consider maintenance hormonal therapy after chemotherapy
    - Ongoing trial of chemotherapy versus hormonal therapy

J Clin Oncol 2017;35(10):1103-1111

Adjuvant Chemotherapy

Ovarian Cancer
Adjuvant chemotherapy (platinum/taxane)

- In everyone **except**:
  - Stage 1A/B grade 1
    - Tumor limited to inside the ovary
    - >95% 5 yr. relapse free survival
- Platinum/taxane
  - Usually carboplatin and paclitaxel
- Response rate: 60-80%
  - As many as 50% have a complete response
  - 75% of these patients will relapse
- Maintenance therapy
  - Bevacizumab
  - PARP inhibitors (Olaparib, niraparib)

Administration of carboplatin/paclitaxel

- Generally, regimen of choice (6-9 cycles)
  - Carboplatin AUC6/Paclitaxel 175 mg/m^2
- IP Chemotherapy
  - GOG172
    - Stage III, optimally debulked
    - More toxicity
    - Quality of life decreased in IP arm until 12 m

	IV	IP
Regimen	• Paclitaxel 135 mg/m^2/24h • Cisplatin 75mg/m^2 IV	• Paclitaxel 135 mg/m^2/24 hr D1 • Cisplatin 100mg/m^2 IP d2 • Paclitaxel 60mg/m^2 IP d8
PFS	24 m	18 m
OS	66 m	50 m

NEJM 2006;354:34-43.

Ovarian Cancer
IV or IP?

- GOG252 – (optimal debulking to 1 cm or less)

		PFS	P value HR (95% CI)
IV Carboplatin	Paclitaxel 80mg/m2/1h d1,8,15 Carboplatin AUC6 IV D1 Bevacizumab 15mg.kg/IV d1 starting cycle2	26.8 m	Reference arm
IP carboplatin	Paclitaxel 80mg/m2/1h d1,8,15 Carboplatin AUC6 IP D1 Bevacizumab 15mg.kg/IV d1 starting cycle 2	28.7m	0.416 0.947 (0.808-1.11)
IP cisplatin	Paclitaxel 135mg/m2/1h IV d1 Cisplatin 75mg/m2 IPd2 Paclitaxel 60mg/m2 IP d8 Bevacizumab 15mg/m2 d1 starting cycle 2	27.8m	0.727 1.01 (0.858-1.18)

Evidence for superior efficacy is not clear
IP chemotherapy causes more toxicity and has a greater impact on QOL
Careful patient selection, less commonly used now

NEJM 2006; 354:34-43

Trial Design
JGOG 3016- “dose dense”

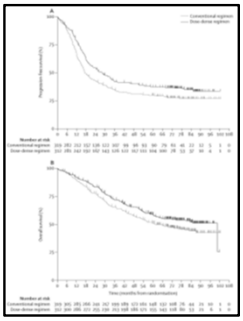
- Ovarian epithelial, primary peritoneal, or fallopian tube cancer
- FIGO Stage II-IV
- Stratified: residual disease, stage, and histology

RANDOMIZE

Standard Arm: c-TC
Paclitaxel 180 mg/m2, day 1
Carboplatin AUC 6,day 1
Q21 days for 6-9 cycles

Experimental Arm: dd-TC
Paclitaxel 80 mg/m2 days 1,8, 15
Carboplatin AUC 6 day 1
Q21 days for 6-9 cycles

JGOG 3016



- PFS: 28.2 vs. 17.5m
  - 10.7m PFS benefit (HR 0.76, p=0.0037)
- OS: 100.5 vs. 62.2m
  - 38.3m PFS benefit (HR 0.79, p=0.039)

Lancet Oncol 14(10) 1020-1026.2013.

GOG 262
Stage III/IV Disease: Large Volume Residual

RANDOMIZE

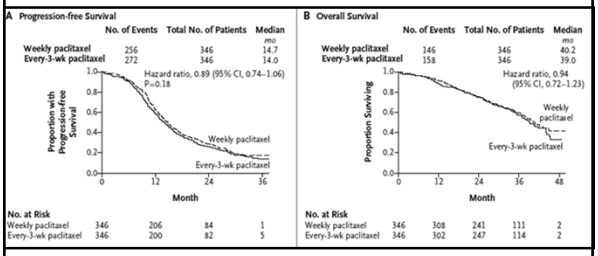
Paclitaxel 80 mg/m2 IV every week + Carboplatin AUC 6 IV every 3 weeks x 6 cycles with optional Bevacizumab 15 mg/kg IV starting with cycle 2 until disease progression

Paclitaxel 175 mg/m2 IV + Carboplatin AUC 6 IV every 3 weeks x 6 cycles with optional Bevacizumab 15 mg/kg IV starting with cycle 2 until disease progression

n = 625
Primary Endpoint = Progression free survival
Activated: Sep 27 2010
Study Chair: J Chan

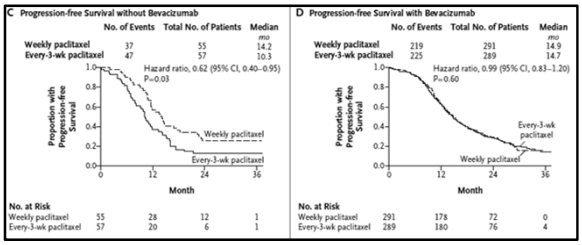
ClinicalTrials.gov Identifier: NCT01167712

GOG 262
PFS and OS



NEJM 2016;374:738-748

GOG262
Subgroup analysis



NEJM 2016;374:738-748

Trial Design
MITO-7

- FIGO IC-IV
- ECOG PS 0-2
- No prior chemotherapy
- Stratified: Center, PS, Residual disease

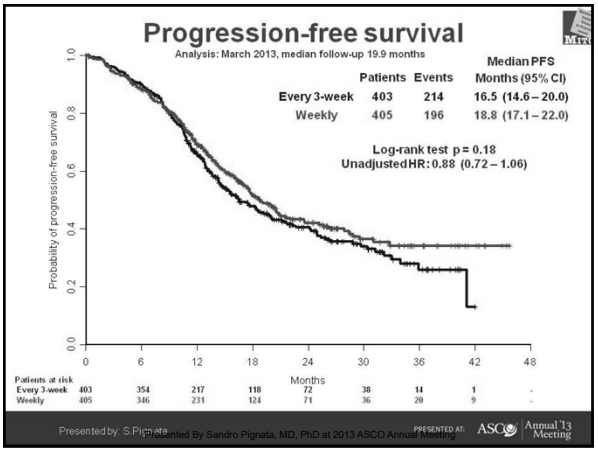
RANDOMIZE

Control arm: (403 pts.)
Carboplatin AUC 6 d1 q21
Paclitaxel 175 mg/m^2 d1 q21
6 cycles

Experimental arm: (405 pts.)
Carboplatin AUC 2 d1,8,15 q21
Paclitaxel 60 mg/m^2 d1,8,15 q21
6 cycles

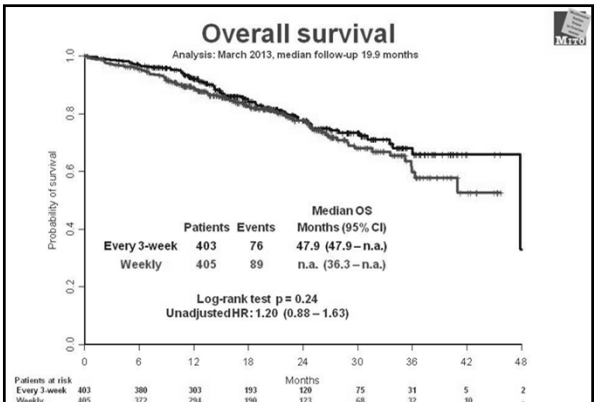
Primary endpoint: PFS , QoL
Secondary endpoints: QoL, OS, Toxicity, RR

Progression-free survival



Presented by: S.Pignata Presented By Sandro Pignata, MD, PhD at 2013 ASCO Annual Meeting PRESENTED AT: ASCO Annual '13 Meeting

Overall survival



Presented by: S.Pignata Presented By Sandro Pignata, MD, PhD at 2013 ASCO Annual Meeting PRESENTED AT: ASCO Annual '13 Meeting

Board Pearls
Initial therapy

- Combination of surgery and chemotherapy
  - Usually initial debulking unless contraindication
  - Platinum/taxane doublet unless stage IA grade 1
  - Generally at least 6 cycles
    - Can consider 3 in earlier stage
- Platinum doublet
  - Generally every three week carboplatin/paclitaxel
    - Abraxane if paclitaxel reaction
  - IP can be considered
    - Look for a contraindication
  - Weekly regimens also an option
    - Dose dense (more cytopenias)
    - MITO-7 (tends to be better tolerated in elderly)
- Consider maintenance therapy

Maintenance Therapy

Maintenance Therapy

- Two main options
  - Bevacizumab
    - Given with the chemotherapy and continued
      - Initial therapy
      - Platinum sensitive recurrence
      - Platinum resistant recurrence
  - PARP inhibitors
    - Given after completion of platinum based chemotherapy
      - After initial therapy
        - Need to respond to initial platinum doublet
      - After platinum sensitive recurrence
        - Need to respond to most recent platinum therapy

Taxane maintenance therapy

Maintenance therapy - paclitaxel

- Paclitaxel maintenance
  - GOG 178/SWOG 9701
    - 262 women
    - CR after plt/taxane
    - 175 mg/m2 paclitaxel q 28d for 3 vs. 12m
    - PFS 22 vs. 14m p=0.006
    - OS 53 vs. 48m p=0.34
    - Significant neurotoxicity, alopecia etc.

J Clin Oncol 2003;21:2460-2465; Gynecol Oncol 2009;114:195–198.

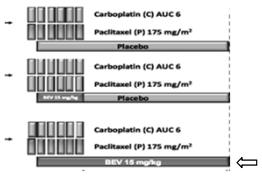
Bevacizumab in ovarian cancer

Initial therapy

Bevaciumab
Front line maintenance therapy

GOG 218

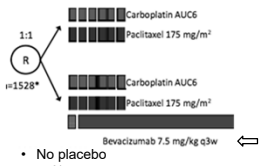
- N=1873 women
- Stage III or IV EOC



- Only 19% patients completed planned treatments (16% arm 17% arm II, 24% arm III) due to PD

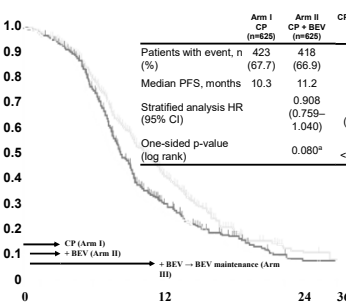
ICON7

- N=1528 women
- Stage I (high risk) –IV



- No placebo
- 90% patients completed assigned treatment; 62% completed maintenance phase
- (18 cycles total)

GOG-0218: PFS



	Arm I CP (n=625)	Arm II CP + BEV (n=625)	Arm III CP + BEV → BEV (n=623)
Patients with event, n (%)	423 (67.7)	418 (66.9)	360 (57.8)
Median PFS, months	10.3	11.2	14.1
Stratified analysis HR (95% CI)		0.908 (0.759–1.040)	0.717 (0.625–0.824)
One-sided p-value (log rank)		0.080[a]	<0.0001[a]

No OS benefit

[a]p-value boundary = 0.0116

NEJM 2011; 365:2473-2483

ICON 7 Results

Parameter	Protocol defined analysis	Post hoc analysis High risk disease
PFS	HR= 0.87; p=0.039	
CP	17.4m	
CP + Bev and Bev maintenance	19.8m	
OS	HR=0.84, p=0.099	HR=0.64; p=0.002
CP	45.5m	34.5m
CP + Bev and Bev maintenance	44.6m	45.5m

High risk: Stage IV, suboptimally debulked (>1cm) stage III, inoperable stage III

Lancet Oncol. 2015;16:928-36

Bevacizumab in front line therapy

- FDA approved June 2018
- Front line in combination with carboplatin/paclitaxel and maintenance therapy in stage III and IV debulked ovarian/fallopian/primary peritoneal cancer
- Can also use PARPi maintenance therapy (will discuss in few slides)
- Recent update:
  - FDA approval of adding olaparib to the maintenance therapy after front line treatment based on PAOLA-1 clinical data (PFS advantage, but no olaparib only arm on the trial)

NEJM 2019; 381:2416-2428

Bevacizumab

Platinum sensitive disease

Platinum sensitive recurrence

- Recurrence of 6 months or more after completion of prior platinum regimen
- Retreat with a platinum doublet
  - Carboplatin/paclitaxel
  - Carboplatin/liposomal doxorubicin
  - Carboplatin/gemcitabine
- Generally a minimum of 6 cycles

Ovarian Carcinoma
OCEANS Trial

Platinum-sensitive recurrent:

1. Epithelial ovarian
2. Primary peritoneal
3. Fallopian tube carcinoma

RANDOMIZE

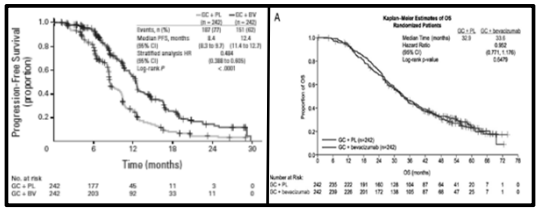
→ **Carboplatin/gemcitabine**

→ **Carboplatin/gemcitabine + bevacizumab followed by bevacizumab maintenance**

N = 484

Proc ASCO 2011: LBA 5007; J Clin Onc 2012:30(17):

OCEANS
Addition of bevacizumab



J Clin Oncol 2012 10;30(17):20392045

OCEANS
Addition of bevacizumab

Parameter	Gem/Carbo	Gem/Carbo Bev	
Patients	242	242	
Response Rate	57.4%	78.5%	P<0.0001
Median PFS	8.4 mos	12.4 mos	HR 0.484, p<0.001
Median OS	29.9 mos	35.5 mos	HR 0.751, p=0.094

J Clin Oncol 2012 10;30(17):20392045

Bev after bev?

Ovarian Carcinoma
MITO16B – MaNGO OV2B – ENGOT OV17

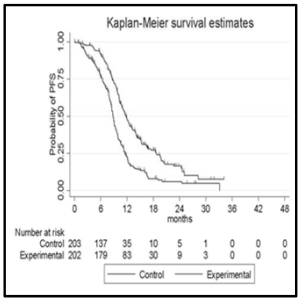
- **Stages IIIB-IV in first relapse after frontline chemo/bev**
- **PFI ≥6 mos**
- **PS 0-2**
- **RECIST progression +/- measurable disease**
- **Normal organ function**
- **Tumor samples for molecular analysis**

RANDOMIZE

- **Platinum-Based Chemotherapy**
- **Chemotherapy plus Bevacizumab Bevacizumab Maintenance**

- **Primary Endpoint: PFS**
- **Patients: 400 (265 events)**

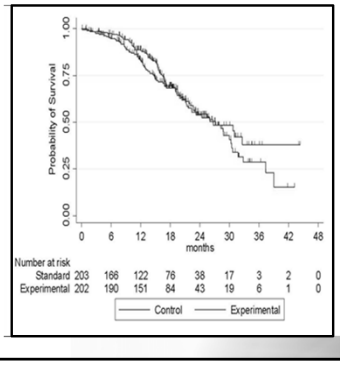
Ovarian Carcinoma (PFS)
MITO16B – MaNGO OV2B – ENGOT OV17



	Standard	Experimental	Log Rank P
# events	161	143	
Median PFS	8.8 mos	11.8 mos	<0.001
HR* (95%CI)	0.51 (0.41-0.65)		

*adjusted by: age, PS, centre size, bevacizumab at relapse, chemo backbone, residual disease at initial surgery

Ovarian Carcinoma (OS)
MITO16B – MaNGO OV2B – ENGOT OV17



	Chemo	Chemo/Bev	Log Rank P
Event	68	79	
Med OS	27.1 mo	26.6 mo	0.98
HR (95% CI)			0.97 (.70-1.35)

Bev after Bev: Response

	Chemo	Chemo/Bev	P value
Patients	143	130	
Responders	94 (65.7%)	97 (74.6%)	0.14
CR	9 (6.3%)	20 (15.4%)	
PR	85 (59.4%)	77 (59.2%)	

Summary
Bevacizumab

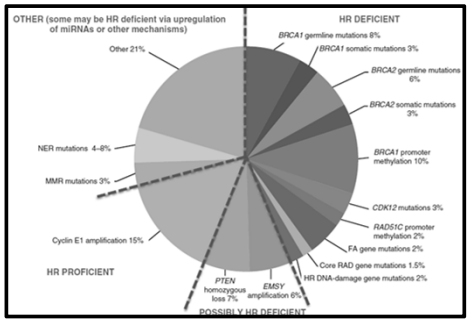
- Bevacizumab an active agent in ovarian carcinoma
- Induces responses and improves PFS
- Can be used in front line and platinum sensitive and resistant recurrences
- Can be used repeatedly

PARP inhibitors

PARP inhibitors (PARPi)
Background

- PARPi prevent repair of ssDNA breaks in tumors with HR deficiencies, leading to cell death
- 10-15% of epithelial ovarian cancer are deficient in HR due to germline BRCA1 or BRCA2 mutations
- Up to 50% of patients with high grade serous ovarian cancer could have deficient HR

PARP inhibitors
HR deficiencies in ovarian cancer



Cancer Discovery 5(11):1137, 2015

PARP inhibitors
Agents and Indications in Ovarian Cancer

Agent	Maintenance therapy*	Monotherapy
Olaparib (Lynparza)	• Front line (BRCAm) • First recurrence, platinum sensitive	Third recurrence gBRCA
Rucaparib (Rubraca)	• First recurrence, platinum sensitive	Second recurrence gBRCA or sBRCA
Niraparib (Zejula)	• Front line (all women) • First recurrence, platinum sensitive	

* Must have had a response on current therapy

PARPi in front line therapy

SOLO 1

Study design

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCAm*
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

→ Olaparib 300 mg bd (N=260) / Placebo (N=131)

2:1 randomization

Stratified by response to platinum-based chemotherapy

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

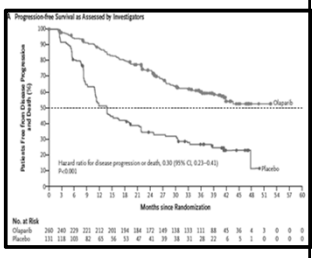
Primary endpoint
- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints
- PFS using BICR
- PFS2
- Overall survival
- Time from randomization to first subsequent therapy or death
- Time from randomization to second subsequent therapy or death
- HRQoL (FACT-O TOI score)

Moore K, NEJM 2018

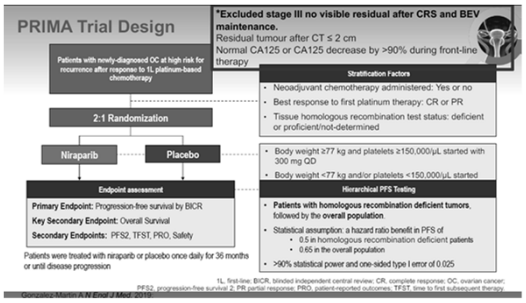
Olaparib
Front line maintenance

- FDA APPROVAL 12/2018
- Maintenance treatment of adult patients with *gBRCAm or sBRCAm* advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy
- Not given during the chemotherapy (unlike bev)



NEJM 2018; 376:26

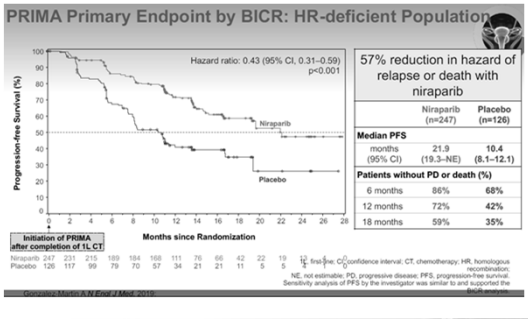
PRIMA



50% had tumors with HR deficiency

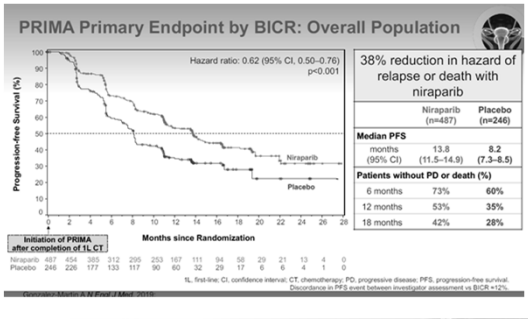
NEJM 2019 381;2391-2402

PRIMA
PARP maintenance



NEJM 2019 381;2391-2402

PRIMA
Niraparib maintenance



NEJM 2019 381;2391-2402

PRIMA subgroups: Exploratory

- *BRCA* mutation
  - 22.1m versus 10.9m (HR 0.40 CI:0.27-0.62)
- *BRCA*wt/HRD^{+}
  - 19.6m versus 8.2m (HR 0.50 CI:0.31-0.83)
- *BRCA*wt/HRD^{-}
  - 8.1m versus 5.4m (HR 0.68 CI:0.49-0.94)
- PR to platinum
  - 8.3m vs 5.3m (HR 0.60)
- CR to platinum
  - 16.4m vs 5.6m (HR 0.60)

NEJM 2019 381;2391-2402

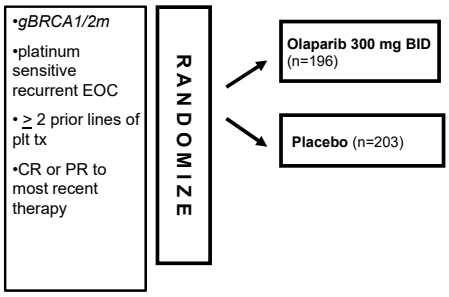
PARPi in first line therapy

- Two options
  - Olaparib
    - FDA approved for BRCAm (germline or somatic) who have responded to first line therapy
    - Twice daily dosing
  - Niraparib
    - FDA approved for all women who have responded to first line therapy
    - Once daily dosing
- Not without side effects. . .
  - Nausea, fatigue
  - AML/MDS

PARPi maintenance in first recurrence

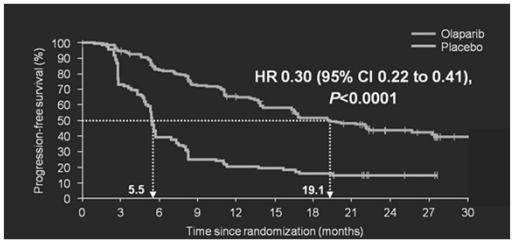
Olaparib, rucaparib, and niraparib

SOLO2



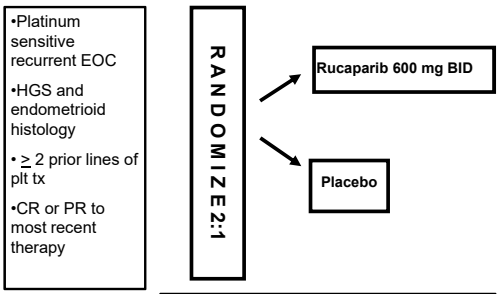
Primary Endpoint: PFS
Secondary Endpoints: OS, resection rate

SOLO2
PFS Results



SGO 2017; Lancet 18(9):1274-1284 2017

ARIEL 3
Trial Design

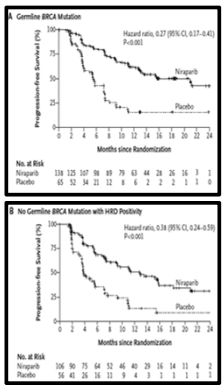


Primary Endpoint: PFS
Secondary Endpoints: OS, resection rate

PARPi Maintenance therapy
ARIEL 3 (Rucaparib)

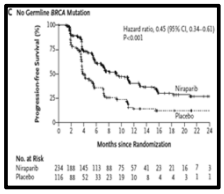
ARIEL3 Analysis Population	PFS by Investigator Review *(Primary Endpoint)*		PFS by Blinded Independent Central Review *(Key Secondary Endpoint)*	
Primary Analyses				
	Hazard Ratio	Median PFS (months) Rucaparib vs. Placebo	Hazard Ratio	Median PFS (months) Rucaparib vs. Placebo
tBRCAmut (n=196)	0.23; p<0.0001	16.6 vs. 5.4	0.20; p<0.0001	26.8 vs. 5.4
HRD-positive (n=354)	0.32; p<0.0001	13.6 vs. 5.4	0.34; p<0.0001	22.9 vs. 5.5
Intent-to-Treat (n=564)	0.36; p<0.0001	10.8 vs. 5.4	0.35; p<0.0001	13.7 vs. 5.4
Exploratory Analyses				
BRCA^{wt} / HRD-positive (n=158)	0.44; p<0.0001	9.7 vs. 5.4	0.55; p=0.0135	11.1 vs. 5.6
BRCA^{wt} / HRD-negative (n=161)	0.58; p=0.0049	6.7 vs. 5.4	0.47; p=0.0003	8.2 vs. 5.3

Lancet 390(10106)1949-1961, 2017
ESMO 2017, ESGO 2017



Niraparib Maintenance Therapy

21.0 vs 5.5 mo



9.3 vs 3.9 mo

12.9 vs 3.8 mo

HRD-negative: 6.9 mo vs 3.8 mo

Mirza MR, et al. *N Engl J Med.* 2016;375:2154-64

PARP inhibitors in recurrent platinum sensitive ovarian cancer

- Three FDA approved options:
  - Olaparib
  - Rucaparib
  - Niraparib
- Should see a response to the platinum regimen prior to the maintenance therapy
- PFS advantage seen with all three agents

PARPi as treatment

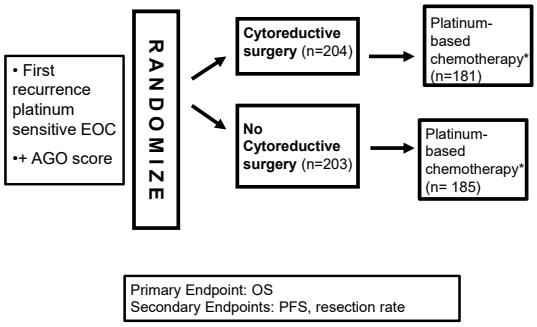
PARP inhibitors
Agents and Indications in OVARY

Agent	Maintenance therapy*	Monotherapy
Olaparib (Lynparza)	• Front line (BRCAm) • First recurrence, platinum sensitive	**Third recurrence gBRCA**
Rucaparib (Rubraca)	• First recurrence, platinum sensitive	**Second recurrence gBRCA or sBRCA**
Niraparib (Zejula)	• Front line (all women) • First recurrence, platinum sensitive	

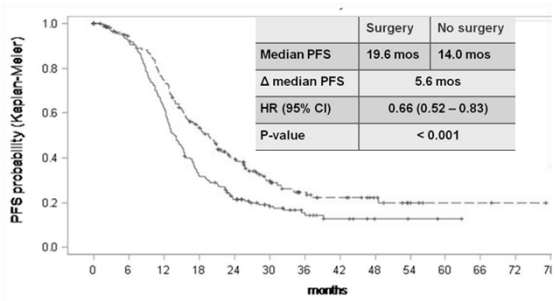
Secondary debulking

Recurrent platinum sensitive disease

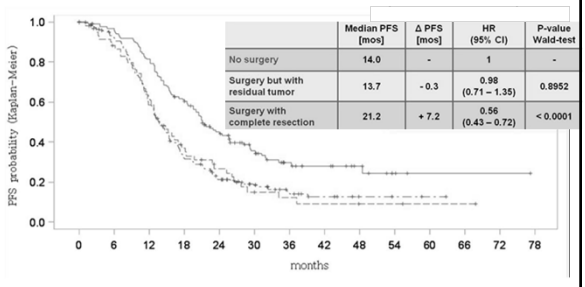
DESKTOP III
Trial Design



DESKTOP III
Results: Progression Free survival



DESKTOP III
PFS by surgical outcome



DESKTOP III
Conclusions

- Secondary cytoreductive surgery in PSROC resulted in a PFS and TTNT advantage
  - Benefit only seen in women who had complete resection
- Stresses the importance of selecting the appropriate patients and institution
- OS results presented at ASCO 2020
  - Survival advantage
  - (Not seen with GOG218)
- Consider secondary debulking in a platinum sensitive recurrence (referral to a gynecologic surgeon for evaluation)

Platinum sensitive disease recurrence

- Consider secondary debulking
- Platinum doublet
  - Taxane,gemcitabine, PLD
  - Consider bevacizumab
- Maintenance therapy
  - Bevacizumab (if started with the chemotherapy)
  - PARPi
    - Olaparib, rucaparib, niraparib
    - PARP after PARP?

Platinum resistant disease

Platinum Resistant Ovarian Cancer
Overview

- Disease recurrence within 6 months of completion of platinum therapy
- Often use single agent therapy with an average response rate of 15-20%*
  - Gemcitabine
  - Topotecan
  - Liposomal Doxorubicin (PLD)
  - Docetaxel
  - Etoposide

*Current Oncology Reports 2006;6:448-54

Trial Design
AURELIA

- Platinum-resistant OC
- ≤ 2 prior regimens
- No hx of BO, fistula, rectosigmoid involvement

RANDOMIZE

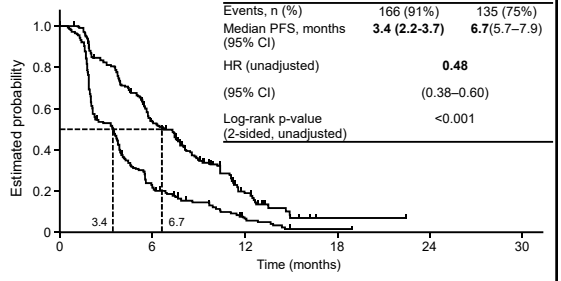
- Chemotherapy → PD/Toxicity → Optional BEV monotherapy
- Chemotherapy & BEV 15mg/kg q3wks → PD/Toxicity → Investigator's choice (without BEV)

Chemotherapy options:

- Paclitaxel 80mg/m^2 days 1,8,15,22 q4wk
- Topotecan 4mg/m^2 days 1,8,15 q4wk
- PLD 40mg/m^2 day 1 q4wk

Progression free survival
AURELIA

	CT (n=182)	BEV + CT (n=179)
Events, n (%)	166 (91%)	135 (75%)
Median PFS, months (95% CI)	**3.4 (2.2-3.7)**	**6.7**(5.7–7.9)
HR (unadjusted)	**0.48**	
(95% CI)	(0.38–0.60)	
Log-rank p-value (2-sided, unadjusted)	<0.001	



Median duration of follow-up: 13.9 months (CT arm) vs 13.0 months (BEV + CT arm)

Ovarian Cancer Recurrence
Key Take home points

- Disease recurrence
  - CA-125 usually goes up prior to disease on imaging
    - No benefit in OS or QOL to treat a rising CA-125
  - Assess the treatment free interval (initial chemotherapy)
    - Platinum sensitive (more than 6 months)
      - Consider secondary debulking
      - Platinum based chemotherapy
        - Carboplatin
        - Paclitaxel, gemcitabine, liposomal doxorubicin
        - Consider bevacizumab or PARPi
    - Platinum resistant (less than 6 months)
      - Single agent therapy
        - PLD, topotecan, etoposide, gemcitabine, docetaxel
      - Consider addition of bevacizumab
  - No current approval for immunotherapy (RR 8%-KEYNOTE100)

Malignant Germ Cell Tumors

Malignant Germ Cell Tumors

- Account for 1-2% of ovarian cancers
- Younger women (median age 16-20)
- Often diagnose early stage
  - Rapid growth with associated symptoms
- Excellent prognosis overall 5yr OS 85%
- Fertility sparing surgery appropriate in most cases
- Elevated HCG or AFP in some cases, can follow

Ovarian germ cell tumors

- Non-dysgerminomas
  - Endodermal sinus tumor
  - Immature teratomas
  - Mixed germ cell
  - Choriocarcinoma
- Management
  - Surgery
  - Systemic therapy*
    - BEP

Observation for stage 1, grade 1 immature teratoma

- Dysgerminomas (50%)
  - More likely to be bilateral
  - Usually stage 1 at diagnosis
- Management
  - Stage I, completely resected
    - Consider observation
  - Adjuvant chemotherapy
    - BEP

Management

- Consider fertility sparing procedure
- Stage I dysgerminoma, stage 1 grade 1 immature teratoma; no adjuvant chemotherapy recommended
- All others: adjuvant chemotherapy
  - BEP (3-4 cycles)
  - Adjuvant and no gross residual disease:3 cycles
  - Gross residual disease: 4 cycles

Sex Cord-Stromal Tumors

Ovarian Sex cord-stromal tumors (MSCST)

- Develop from the sex cord
  - Sertoli cell tumor
  - Granulosa cell tumor
- Develop from stromal cells
  - Fibroma
  - Thecoma
  - Leydig
- Both
  - Sertoli-leydig
- Generally, lower grade, lower stage at diagnosis
- Account for less than 8% of ovarian cancers
- Some secrete androgens or estrogens or other steroid hormones

Granulosa cell tumor

- Most common type of MSCST
  - 2-5% of all ovarian cancers
  - 90% of malignant SCSTs
  - Usually an indolent growth pattern
  - Frequently produce estrogen
    - Endometrial bx, if uterus not removed
- 2 subtypes
  - Adult type: 95% (*FOXL2*)
  - Juvenile type: 5%
- Adult type
  - Median age 52
  - 80-90% diagnosed stage I
  - 10-30% recur

Treatment

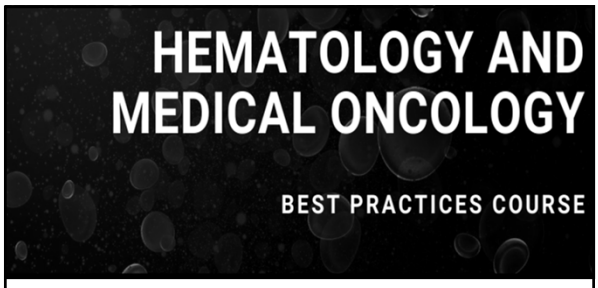
- Surgery
  - Hysterectomy and bilateral salpingo-oophorectomy
  - Early stage
    - Can consider fertility sparing procedure if confined to ovary
- Post operative management
  - Observation (can recur late)
  - Stage II-IV (category 2B)
    - BEP versus carboplatin/paclitaxel (ongoing trial)
    - Hormonal therapy
    - Radiation therapy for limited disease
  - Can follow inhibin levels

61

Endometrial Cancer

Andrea Wahner-Hendrickson, MD

August 19, 2020



61 – Endometrial Cancer

Andrea Wahner-Hendrickson, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Advisory Board: Clovis
- Off Label Usage – I will include discussion of investigational or off-label use of a product in my presentation.

Ovarian Cancer
Outline

- Epithelial endometrial cancer
  - Epidemiology
  - Type 1
    - Endometrioid
  - Type 2
    - Serous
    - Clear cell
    - Carcinosarcoma
  - Risk Factors
  - Treatment
- Uterine sarcoma

Endometrial Cancer
Epidemiology

- Third most common cancer among women in US
- Most common gynecologic cancer in US
- 80% present in early stage
- Incidence is lower in blacks but mortality rate is higher

Epithelial Endometrial Carcinoma

Endometrial Cancer
General disease facts

- 75% of women are postmenopausal
- 5 year survival rates:
  - Localized 96%
  - Regional 67%
  - Metastatic 17%
- Abnormal uterine bleeding most common presenting symptom
- Over 70% adenocarcinomas
- Poor prognosis: serous, clear cell, carcinosarcoma
- Histologic grade important (endometrioid)

Endometrial cancer

Type I	Type 2
• 85% endometrial cancer	• Clear cell
• Endometrioid histology	• Papillary serous
• Unopposed estrogen	• Carcinosarcoma (MMMT)
• Endometrial hyperplasia	• All considered high grade

Endometrial Cancer
Risk factors

Risk Factor	Relative Risk
Obesity > 30 lbs > 50lbs	 3x 10x
Late menopause	2.4x
Diabetes Mellitus	2.8x
Unopposed Estrogen	9.5x
Complex Atypical Hyperplasia	29x
Tamoxifen therapy	2x
Nulliparity	2x
PCOS (chronic anovulation)	3x
Lynch syndrome (HNPCC)	22-50% lifetime risk
Cowden syndrome	13-19% lifetime risk

Smith, CA Cancer J Clin 2001; 51:38
Seligwan, J Clin Oncol 2013; 31:2807

A word on Tamoxifen

- Increased risk 0.9 to 2 per 100
- Greatest cumulative risk after 5 years of use
- Cancers tend to be well differentiated, estrogen-receptor positive, and early stage
- Screening: immediate evaluation of vaginal bleeding

Endometrial hyperplasia

Classification	Progression to malignancy
Simple	1%
Complex	3%
Simple atypical	8%
Complex atypical	29%

- Standard of care: hysterectomy
- Alternative care: cyclic progestins

Endometrial Cancer
FIGO Stage (current)

Stage	Description
IA	Tumor confined to uterus, <50% myometrial invasion
IB	Tumor confined to uterus, ≥50% myometrial invasion
II	Cervical stromal invasion
IIIA	Tumor invasion into serosa or adnexa
IIIB	Vaginal or parametrial involvement
IIIC1	Pelvic node involvement
IIIC2	Paraaortic node involvement
IVA	Tumor invasion into bladder or bowel mucosa
IVB	Distant metastases (including abdominal metastases) or inguinal lymph node involvement

Prior FIGO Staging

Stage	Anatomic involvement
Stage I	Tumor confined to the uterine corpus
IA	No myometrial invasion
IB	<50% myometrial invasion
IC	≥50% myometrial invasion
Stage II	Cervical involvement
IIA	Endocervical glandular involvement
IIB	Cervical stromal invasion
Stage III	
IIIA	Positive peritoneal cytology and/or tumor invasion into uterine serosa and/or adnexal involvement
IIIB	Vaginal involvement
IIIC	Metastases to pelvic and/or pelvic lymph nodes
Stage IV	
IVA	Bladder and/or bowel involvement
IVB	Distant metastases, including abdominal disease and/or inguinal lymph node involvement

Staging, Classification and Prognosis

Stage	Proportion at diagnosis	5 yr survival
Stage I	80%	83%
Stage II	11%	73%
Stage III	6%	52%
Stage IV	2%	27%

- **Locoregional disease**
  - **Low-risk disease: stage IA, grades 1-2**
  - **Intermediate-risk disease: other stage I, stage II**
  - **High-risk disease: all stage III and IVA**
- **Disseminated disease: stage IVB or recurrent**

Endometrial cancer

Treatment

Early stage, low risk disease

- Stage IA, histologic grade 1,2
- Management:
  - Hysterectomy plus surgical staging
    - Bilateral salpingo-oophorectomy
    - Pelvic washings
    - Examination of abdominal cavity
    - Pelvic/para-aortic lymph nodes vs. sentinel nodes
- Surgical resection yields 5 year survival >95%
- Surgical management only

Intermediate risk

- All stage I grade 3
- Deeper invasion of grade 1,2 and other risk factors (age, LVSI)
- Stage II (involves cervical stroma)
- Approximate survival with surgery alone 85%
- How do we improve outcomes?

Intermediate risk endometrial carcinoma
GOG 99

- Stage I gr 3, stage II
- TAH-BSO, sentinel node sampling, pelvic washings
- Randomization: no further RT vs. pelvic RT

	No RT	Pelvic RT
Vaginal recurrences	13	2
Local recurrences	7.4%	1.6%
PFI at 2 yrs	88%	97% (p=0.007)
Survival at 4 yrs	86%	92% (p=0.55)

- Radiation reduces recurrence risk
- Radiation does not improve OS in intermediate risk disease

Keys et al, Gyn Oncol 92: 744-751, 2004

PORTEC 2

- Pelvic EBRT versus vaginal brachytherapy
- High intermediate risk
  - Stage IC grade 1 or 2 (more than half of myometrium)
  - Stage IB grade 2
  - Stage IIA (endocervical involvement)
  - Clear cell and serous histology excluded
- No significant difference in outcomes

	Vaginal recurrence	Pelvic recurrence	Distant
EBRT	4/214 (1.6%)	1/214 (0.5%)	13/214 (5.7%)
VBT	3/213 (1.8%)	8/213 (3.8%)	16/213 (8.3%)

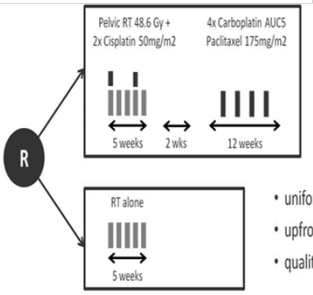
Lancet 2010;375(9717):816-823

Can we improve outcomes with chemotherapy?

PORTEC 3 (intermediate and high risk)

PORTEC-3 trial design

Intermediate Risk Endometrial Carcinoma



- uniform treatment schedule
- upfront pathology review
- quality of life analysis

Portec III: Eligibility

Eligibility Criteria

- **Stage I G3 with LVSI or deep invasion**
- **Stage II-III**
- **Stages I-III serous or clear cell (>25%)**
- **PS 0-2**
- **No macro residual**

Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
Endometrioid grade 3	32.1%	32.4%
Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

PORTEC III: Stage I-II OS/FFS

Stage	Patients	% FF 5yr	HR (P)	% Alive 5yr	HR (P)
I-II	365				
CTRT	178	81%	O.77 (0.26)	84%	0.79 (0.38)
RT	187	77%		82%	

Portec III: Stage I-II Conclusions

- No significant difference in 5-year FFS and 5-year OS
- Significantly more toxicity with CTRT in first 12 months
- PORTEC III does not support the use of concurrent chemotherapy/radiotherapy followed by chemotherapy in stage I-II endometrial carcinoma

Endometrial Carcinoma
Intermediate risk disease

- Surgical resection yields 85% 5-year survival
- Surgery followed by pelvic radiation improves local control but does not impact survival
- Recommended management: resection of all gross disease +/- vaginal radiation

High risk locoregional disease

Treatment

High risk locoregional disease

- Stage III (adnexal, serosal, vaginal, pelvic/PA node involvement)
- Stage IVA (bladder/rectal) involvement
- Surgery: relapse rate >50%
- Management:
  - Role of radiation vs. chemotherapy?

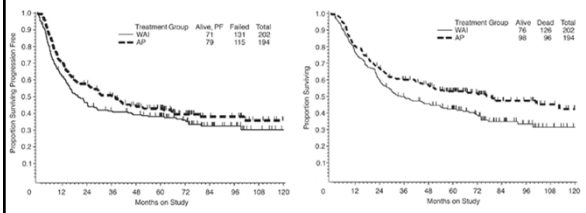
GOG 122

- Stage III-IV disease
- TAH-BSO, tumor debulking to less than 2 cm
- Tumor confined to abdomen or pelvis

Regimen 1	Regimen 2
Abdomino-pelvic RT	Doxorubicin (A) 60mg/m2 Cisplatin (P) 50 mg/m2

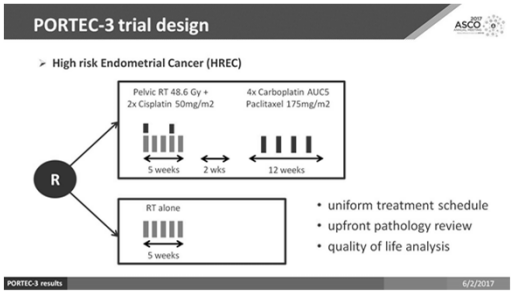
J Clin Oncol 2008 1(24):36-44.

GOG 122



-AP chemotherapy significantly improves PFS and OS compared to whole abdominal radiation
-The risk of progression or death is reduced by 30%, the risk of death by 34%.
-Increased toxicity with AP chemotherapy compared to WAI.

PORTEC III



Portec III: Eligibility

Tumour characteristics	RT alone	CTRT
Histology		
Endometrioid grade 1-2	39.7%	38.5%
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Serous/ clear cell/ other	28.2%	29.1%
LVSI		
Yes	58.2%	59.7%
No	41.8%	40.3%
Stage (%)		
I	29.4%	29.7%
II	27.3%	24.2%
III	43.3%	46.1%

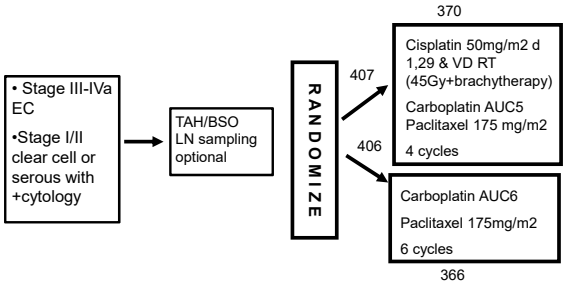
PORTEC III: Stage III OS/FFS

Stage	Patients	% FF 5yr	HR (P)	% Alive 5yr	HR (P)
I-II	365				
CTRT	178	81%	O.77 (0.26)	84%	0.79 (0.38)
RT	187	77%		82%	
III	295				
CTRT	152	69%	0.66 (0.032)	79%	0.69 (0.114)
RT	143	58%		70%	

Portec III
Conclusions

- 5-year FFS and OS for stage III vs stage I-II
  - FFS: 64% stage III vs 79% stage I-II (p<0.001)
  - OS: 74% stage III vs 83% stage I-II (p=0.003)
- 5-year FFS and OS in stage III for CTRT vs RT
  - 5-year FFS: 69% CTRT vs 58% RT (HR 0.66, CI 0.45-0.97, p=0.032)
  - 5-year OS: 79% CTRT vs 70% RT (HR 0.69, CI 0.44-1.09, p=0.114)
- What about chemotherapy without radiation?

GOG 258
Trial Design

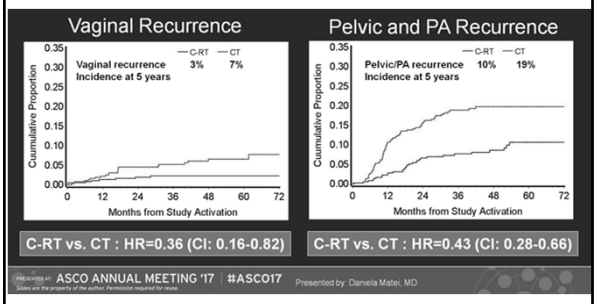


Primary Endpoint: Recurrence free survival

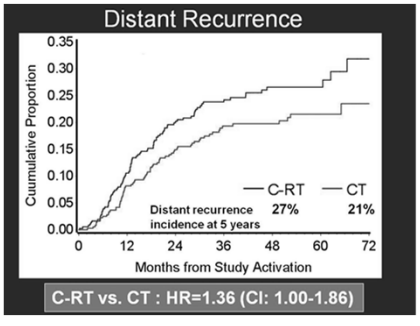
Secondary Endpoints: OS, AEs, QoL

NEJM 2019;380:2317-2326

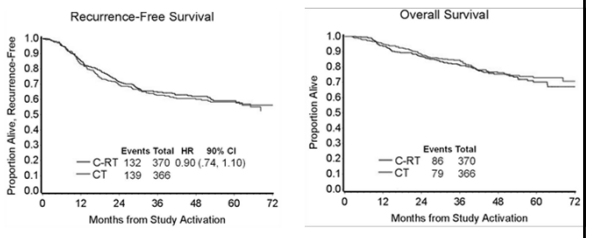
GOG 258
Local Recurrence Rates



GOG 258
Distant Recurrence Rates



GOG 258
Results



NEJM 2019;380:2317-2326

GOG 258
Conclusions

- Chemo-RT did not improve RFS compared to chemotherapy alone
- Chemo-RT reduced the incidence of vaginal, pelvic and para-aortic recurrences
- Distant recurrences were more common in the chemo-RT arm
- Survival data is not yet mature

- Management recommendations:
- Surgery followed by adjuvant therapy
  - Chemotherapy
  - Radiation can be considered to reduce local recurrence risk

Locregional disease summary

- Evidence support chemotherapy following bulk surgical reduction for stages III-IVa disease
  - Weight of evidence favors carboplatin/paclitxel when metastatic studies are taken into account
- Role of radiation remains a question in locoregionally advanced disease
  - Current studies suggest this could be option
  - May help with local control
  - Further follow-up and survival data on GOG258 are needed before final conclusion

Disseminated disease

Treatment

Disseminated Disease

- Hormone therapy (low grade)
- Chemotherapy
- Immunotherapy

Hormone therapy

- Low grade endometrioid histology
  - Grade 1, 2
  - Longer disease free intervals
  - ER/PR+
  - Asymptomatic/minimally symptomatic disease
- Progestins favored
  - Average response rate around 20%
  - Response correlate with grade and receptor status (highest in grade 1 with high ER/PR expression) RR 44%

Chemotherapy

GOG 209

- Metastatic or recurrent endometrial cancer
- Non-inferiority study, 1381 women

Standard (TAP)	Experimental (TC)
Doxorubicin 45mg/m^2 D1	Carboplatin AUC6
Cisplatin 50mg/m^2 D1	Paclitaxel 175 (135) mg/m^2
Paclitaxel 160 mg/m^2 D2	

- TC not inferior to TAP (PFS and OS)
  - PFS @13m in each arm
  - ORR @ 51% in each arm
- Toxicity profile favors TC
- TC for now is the chemotherapy of choice for patients with advanced or recurrent endometrial carcinoma

Gynecol Oncol. 2012;125S:771.

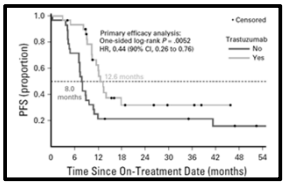
Trastuzumab in uterine serous carcinomas

- Eligibility
  - High grade serous histology
  - Stage III; IV or recurrent HER2/neu positive disease
- Regimen
  - Carboplatin/paclitaxel +/- trastuzumab
- Enrollment:
  - 61 patients
    - Majority were adjuvant therapy
    - About 15% were recurrent disease

J Clin Oncology (2018) 36(20): 2044-2051

Metastatic endometrial cancer
Recent treatment changes

- Addition of trastuzumab to carboplatin and paclitaxel in high grade serous histology



Annals of Oncology (2019) 30 (suppl_5): v403-v434
J Clin Oncology (2018) 36(20): 2044-2051

Trastuzumab in UPSC

Population	Patients	PFS PC	PFS PCT	HR (CI)	P value
All	58	8.0 mos	12.6 mos	0.44 (0.26-0.76)	0.005
Stage III-IV	41	9.3 mos	17.9 mos	0.40 (0.20-0.80)	0.013
Recurrent	17	6.0 mos	9.2 mos	0.14 (0.04-0.53)	0.003

Updated OS: 24.2m versus 29.6 m (HR 0.58 (0.34-0.99) p= 0.0462)
-benefit restricted to the stage III/IV disease; not in recurrent disease, but underpowered

J Clin Oncology (2018) 36(20): 2044-2051

Endometrial Carcinoma
Targeted Therapy

- One randomized phase II trial suggests that the addition of trastuzumab to paclitaxel/carboplatin in HER2+ patients improves PFS.
- Bevacizumab can be considered

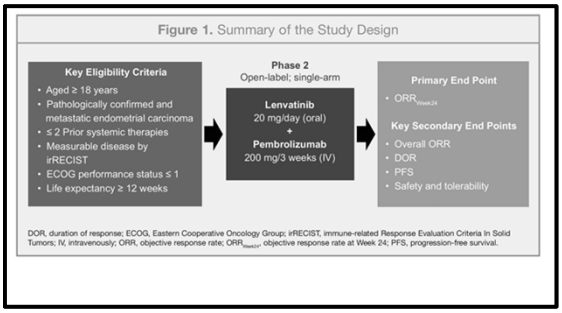
Immunotherapy

Pembrolizumab
MSI-H endometrial cancer

- FDA approval for Pembrolizumab for MSI-H tumors and MMR deficient tumors
- Pembrolizumab for MSI-high endometrial cancers
  - RR 57%
- Endometrial cancer has a pooled MSI-H/dMMR prevalence of about 26%
  - More common is endometrioid histology

Lorenzi et. al. J Oncol 2020

Study 111/KEYNOTE-146
Lenvantinib and Pembrolizumab



J of Clin Oncology 36(15) suppl 5596-5596, 2018
Lancet Oncology 20(5):711-718 2019

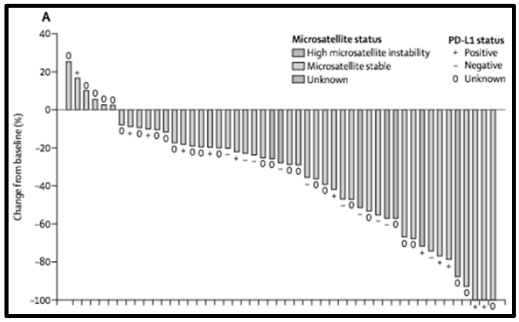
Study 111/KEYNOTE-146
Response

Objective response at week 24	21 (39·6%; 26·5–54·0)	24 (45·3%; 31·6–59·6)
Objective response at data cutoff	21 (39·6%; 26·5–54·0)	25 (47·2%; 33·3–61·4)
Best overall response		
Complete response	1 (1·9%)	3 (5·7%)
Partial response	20 (37·7%)	22 (41·5%)
Stable disease	25 (47·2%)	19 (35·8%)
Progressive disease	4 (7·5%)	5 (9·4%)
Unknown or not assessable	3 (5·7%)	4 (7·5%)
Median duration of response, months		
Median (95% CI)	NE (7·4–NE)	NE (5·8–NE)
Range*	1·2–23·4	1·2–23·4
IQR	7·4–NE	NE–NE
Proportion with responses ≥6 months	12 (83·0%; 55·9–94·2)	11 (79·3%; 48·5–92·9)
Proportion with responses ≥12 months	7 (64·5%; 32·8–84·2)	8 (79·3%; 48·5–92·9)
Median time to response, months (95% CI; IQR)	2·7 (1·3–2·8; 1·3–2·8)	2·6 (1·4–2·8; 1·4–3·7)

Data are n (%; 95% CI) or n (%), unless otherwise specified. NE=not estimable (because of an insufficient number of

J of Clin Oncology 36(15) suppl 5596-5596, 2018 ; Lancet Oncology 20(5):711-718 2019

Study 111/KEYNOTE-146
Response



J of Clin Oncology 36(15) suppl 5596-5596, 2018 ; Lancet Oncology 20(5):711-718 2019

FDA Accelerated Approval
Pembrolizumab and Lenvantinib

- September 17, 2019
- Advanced endometrial carcinoma that is not MSI-H or dMMR and who have disease progression following prior systemic therapy but are not candidates for curative surgery or radiation

Endometrial Carcinoma
Treatment by Disease Categories

- Locoregional disease
  - Low-risk disease: surgery
  - Intermediate-risk disease: surgery +/- vaginal radiation (? chemotherapy in stage II)
  - High-risk disease: surgery + chemotherapy (? radiation)
    - Consider trastuzumab in HGS histology
- Disseminated disease
  - Chemotherapy (paclitaxel/carboplatin)
  - Progestins in ER+PR+ patients no longer responsive to chemotherapy (lower grade endometrioid)
  - Pembrolizumab MSI/MMR (add lenvatinib if not)
  - Possible roles: bevacizumab, trastuzumab

Uterine sarcomas

Uterine Sarcomas

- Account for about 4% of uterine cancers
- Carcinosarcoma (Malignant Mixed Mullerian Tumor)
  - Metaplastic (dedifferentiated) carcinomas (biphasic histology)
  - Adjuvant chemotherapy even in early stage disease
    - Cisplatin/ifosfomide or ifosfomide/paclitaxel in the past
    - Carboplatin/paclitxel is not inferior to ifosfomide/paclitaxel
    - Carboplatin/paclitaxel now preferred regimen
  - Radiation often used in localized disease

J Clin Oncol. 2019;37S:ASCO #5500.

Leiomyosarcomas

- High risk cancer
  - 50-60% recurrence rate when limited to the uterus
- No adjuvant therapy in stage I or II
  - No benefit to pelvic radiation
  - No benefit to adjuvant doxorubicin
- Advanced disease after surgery
  - Adjuvant therapy debated
  - Clinical trials evaluating role of chemotherapy
- Metastatic disease
  - Gemcitabine and docetaxel
  - Doxorubicin, ifosfamide, gemcitabine

Endometrial stromal sarcoma

- Low grade tumors
- Express estrogen receptor
- Surgical management
- Hormone blockade
  - Consider post operative hormone blockade in more advanced stages
  - Hormone blockade in recurrent disease
  - Aromatase inhibitors preferred
  - Megestrol acetate/medroxyprogesterone

Uterine Sarcomas
Final Thoughts

- Carcinosarcomas are not sarcomas
  - Adjuvant therapy
    - Chemotherapy (carboplatin/paclitaxel)
    - Consider radiation therapy
- Uterine leiomyosarcomas
  - Very high recurrence risk
  - Surgical resection
  - Role of systemic therapy and radiation poorly understood
- Endometrial stromal sarcomas
  - Low grade
  - Surgery and hormonal modulation

THANK YOU

62

Cancer of Cervix, Vulva, Vagina and Gestational Trophoblastic Tumors

Daniel L. Clarke-Pearson, MD

August 19, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

62 – Cancer Of The Cervix , Vulva, Vagina
Gestational Trophoblastic Disease

Daniel L. Clarke-Pearson, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- N/A

CARCINOMA OF THE CERVIX

Cervical Cancer

HISTORICAL BACKGROUND

- With Pap smear screening, there has been a 75% reduction of cervical cancer in the US over the past 50 years
- Today, cervix cancer is 10th most common cancer in the US.
- Worldwide: 530,000 new cases of cervix cancer and 275,000 deaths annually (second most common cause of cancer death)

Cervical Cancer

EPIDEMIOLOGY

Risk Factors:

- **HPV types 16, 18, 31, 33, 45, 52, 58**
- Early coitus (<18 yrs)
- Multiple consorts (>2)
- High-risk sexual partner
- Tobacco use
- Immunosupression or HIV infection

Cervical Cancer

HUMAN PAPILLOMA VIRUS (HPV)

- Present in >99% of all SIL (squamous intraepithelial lesions; dysplasia) and cervical cancers
- > 100 subtypes have been identified by DNA sequencing
- Low Risk types: 6, 11
  LG-SIL/Condylomata
- High Risk types: 16, 18, 31, 33, 45….
  HG-SIL, Cancer
- Co Factors:
  HSV, HIV, Smoking, Immunosupression

Cervical Cancer

HUMAN PAILLOMA VIRUS (HPV)

10-20 million women have HPV
1.2 million develop SIL

12,200 new cases of cervix cancer
4,200 deaths from cervix cancer

Most women with HPV do not develop cervix cancer.

HPV Vaccines

- **GARDASIL (Merck)**
  - **HPV Types 6, 11, 16, 18**
- **CERVARIX (GSK)**
  - **HPV Types 16, 18**
- **GARDASIL 9**
  - **HPV Types 6, 11, 16, 18, 31, 33, 45, 52, 58**
- **Girls and Boys ages 9-26 years**
- **Two doses: @ 0, and 6 months**

CERVIX CANCER

Cervix Cancer

HISTOLOGY

Squamous Cell Carcinoma (70%)
- **Large Cell Keratinizing**
- **Large Cell Non-Keratinizing**
- **Small Cell with neuroendocrine elements**

Adenocarcinoma (Endocervical) (30%)

Cervix Cancer

SPREAD PATTERNS

Local
- Cervix Stroma
- Vagina
- Parametria

Lymphatic
- Pelvic ⇨ Common ⇨ Para-aortic

Hematogenous (rare)
- Liver, lung

Cervix Cancer

PRETREATMENT EVALUATION

Clinical Staging System **(FIGO)**
- Physical Exam
- CXR
- CT Scan, MRI
- PET

- Cystoscopy, Proctoscopy

Cervix Cancer

2018 FIGO STAGING CRITERIA

Stage I	Confined to Cervix
Ia_1	< 3 mm depth of invasion
Ia_2	≥3 but < 5 mm
Ib_1	≥ 5 mm depth < 2 cm lesion
Ib_2	≥ 2 mm depth ≤ 4cm lesion
Ib 3	≥ 4 cm lesion

Cervix Cancer

2018 FIGO STAGING CRITERIA

Stage II	
II A	Involves upper 2/3 of vagina without parametrial involvement
IIA 1	< 4cm lesion
IIA 2	≥ 4 cm lesion
IIB	Parametrial involvement but not to sidewall

Cervix Cancer

2018 FIGO STAGING CRITERIA

Stage III	
III A	Involves lower 1/3 of vagina without sidewall involvement
IIIB	Extension to sidewall or hydronephrosis
III C	Involvement of pelvic and/or paraaortic nodes Designate "r" (imaging) or "p" (pathology)
IIIC 1	Pelvic node metastasis only
IIIC 2	Paraaortic node metastasis

Cervix Cancer

2018 FIGO STAGING CRITERIA

Stage IV	
IV A	Spread to adjacent organs (bladder/rectum)
IV B	Spread to distant organs

Prognostic Factors

- Depth of invasion
- Lymph-vascular invasion
- Clinical Stage
- Tumor Size
- Tumor Grade
- Lymph node status

Cervix Cancer

RISK of PELVIC and AORTIC LYMPH NODE METASTASES

Clinical Stage	%Pelvic (+)	%Aortic (+)
I a_1	< 1%	0
I a_2	5%	1%
I b	15-20%	2%
II a	25-30%	10%
II b	35%	20%
III b	50%	30%

Discussion Outline

- Treatment of Primary Disease
  - Radiation with Chemosensitization
  - Surgery
- Roles for Chemotherapy
  - Neoadjuvant
  - Postoperative in High Risk Patient
  - Palliation: Advanced and Recurrent Disease
- Management of Recurrent/Metastatic Disease
  - Surgery (Pelvic Exenteration)
  - Palliative chemotherapy

Cervix Cancer

TREATMENT of PRIMARY DISEASE

Ia1 (micro invasive)	**CKC or TAH**
Ia2-IIa	**Radical Hysterectomy and Pelvic lymphadenectomy**
	OR
	Radiation therapy
Ia2-IVa	**Radiation Therapy**
	with chemo-sensitizer

Cervix Cancer

RADIATION THERAPY

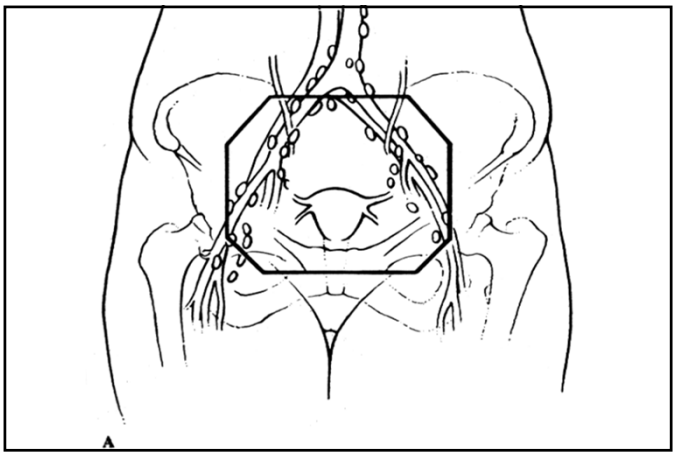
External beam radiation (Teletherapy)

Whole pelvis

Extended field=para-aortic

Daily fraction 180-200 cGy/d

to ~ 4500-5000 cGy



Cervix Cancer

RADIATION THERAPY

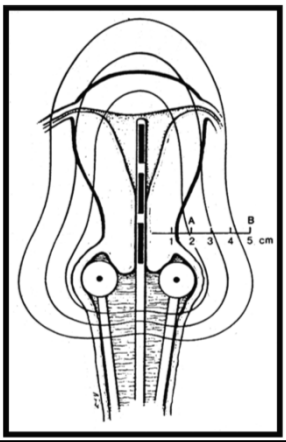
Intracavitary (Brachytherapy)

Fletcher-Suit tandem and ovoids

-Cesium-low dose rate

-High-dose rate (Irridium)

Interstitial volume implant



Radiation Therapy Quality Indicators

- Brachytherapy
- Concurrent Chemotherapy
- Radiation course completed in less that 63 days

Radiation Therapy Quality Indicators

Quality Indicators met (1508 pts 1999-2011)

- Brachytherapy -- 78%
- Concurrent Chemotherapy --79%
- Radiation course completed in less that 63 days --64%

Int J Rad Oncol Biol Phys. 2015: 92-260

Radiation Therapy Quality Indicators

- 98% met one quality indicator
- BUT only 44% met all 3 quality benchmarks!
- And, little improvement over time: 1999-2011

Int J Rad Oncol Biol Phys. 2015: 92-260

Cervix Cancer

PRIMARY SURGICAL THERAPY

Limited to early stage disease

Radical hysterectomy

Resection of Uterus
Cervix
Upper vagina (margin)
Parametria

Pelvic lymphadenectomy

Postoperative Radiation with Chemosensitization

High and Intermediate Risk Surgical Patient

- Positive Nodes
- Positive surgical margins
- Lymph-vascular invasion
- Deep cervical stromal invasion

RESULTS & COMPLICATIONS OF THERAPY

	Radical Hysterectomy	Radiation
5-Year Survival (Stage IB)	85%	85%
Severe complications	5%	5%

- Hemorrhage, infection, VTE, fistulae
- Radiation cystitis, SBO, proctitis, fistulae

TREATMENT CONSIDERATIONS FOR EARLY CERVICAL CANCER

Radical Hysterectomy

Ovarian function preservation
Improved vaginal preservation
Minimal long-term complications

Radiation Therapy

Readily applied to most patients
Minimal immediate morbidity

Cervix Cancer

CHEMOTHERAPY in the TREATMENT of CERVIX CANCER

- Neoadjuvant chemotherapy followed by surgery
- Radiation sensitizer
- Palliation of advanced/recurrent disease

Neoadjuvant Chemotherapy

- Neoadjuvant chemotherapy followed by radical hysterectomy is inferior to primary chemoradiation for locally advanced disease.

Neoadjuvant Chemotherapy

	5 year DFS	5 year OS
Neoadjuvant chemo and Radical Hysterectomy	69.3%	75.4%
Chemoradiation	76.7% *	74.7%

HR 1.38, CI 1.02–1.87 p = .038
J Clin Oncol 2018; 36: 1548

Neoadjuvant Chemotherapy

	5 year DFS	5 year OS
Neoadjuvant chemo and Radical Hysterectomy	57%	72%
Chemoradiation	76.7%*	74.7%
* HR 0.87 CI 0.65–0.15		

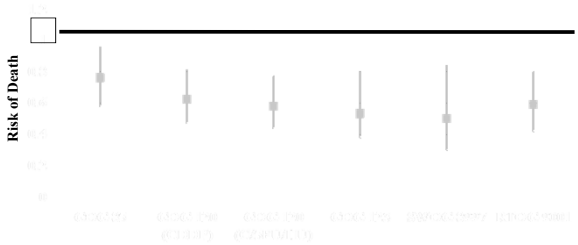
J Clin Oncol 2019: 373S, ASCO #5503

Cervix Cancer

RADIATION SENSITIZERS

Platin based regimens given concurrently with radiation improve response and survival.

Summary – Chemoradiation



NCI Clinical Announcement 1999

*

GOG #120 (*NEJM*, 1999;340:1144)

Stage IIB – IVA Cervical Cancer

Radiation plus concomitant chemotherapy

- – Hydroxyurea 3 gm/m² 2x/wk
- – 5FU 4 gm/m² over 96 h week #1, 4
  – Cisplatin 50 mg/m² week #1, 4
  – Hydroxyurea 2 gm/m² 2x/wk
- Cisplatin 40 mg/m²/wk

GOG #120

RESULTS

	Toxicity (grade 3/4 WBC)	Survival (@ 30 mo)	Relative Risk of death	CI
Hydroxy	20%	49.5%	–	–
CIS/5FU/H	46%*	67.1%	.58	(.41–.81)
Cisplatin	23%*	66.7%	.61	(.44–.85)

*p<.00001

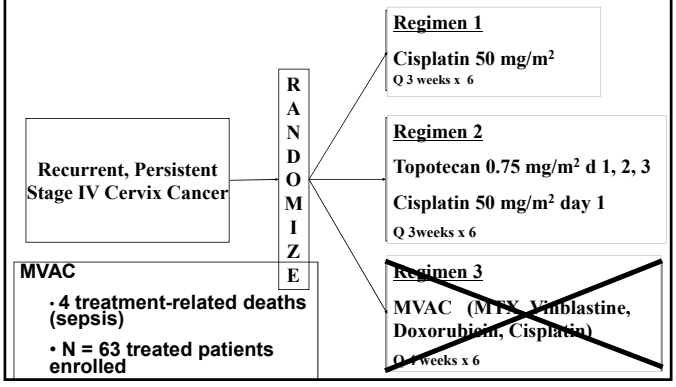
Cervix Cancer

OVERALL 5 YEAR SURVIVAL

Stage	Survival
IB	85%
IIA	70%
IIB	70%
IIIA	48%
IIIB	50%
IVA	36%
IVB	14%

CHEMOTHERAPY FOR ADVANCED AND RECURRENT DISEASE

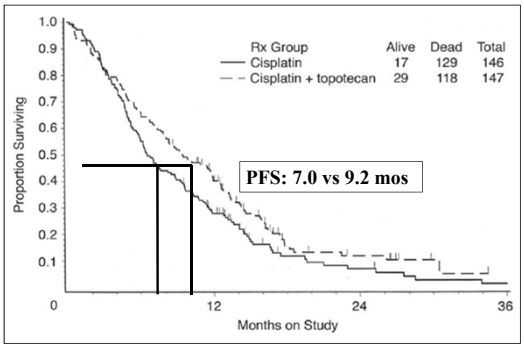
GOG-179: Design



GOG #179

- Response — Cisplatin — Cis/Topo
  - Overall Response — 13% — 26%
    - P= .004
  - Median PFS — 2.9 mo — 4.6 mo
    - P= .00048
  - Survival — 7.0 mo — 9.2 mo
    - P= .015
    - **This is the first regimen to demonstrate a survival advantage over single agent cisplatin**

GOG-179: Overall Survival



Factors Impacting Outcome

- Disease free interval before recurrence
- Prior Platin administered as a chemo-sensitizer

GOG-179: Conclusions

- **Combination Topotecan/Cisplatin was superior to single agent Cisplatin**
  - **First Phase III trial to demonstrate a survival advantage**
- **Significantly higher frequency and grade of hematologic toxicity observed with the combination**
  - **However, QoL is not reduced**
- **Lower single agent response likely due to prior cisplatin-based chemoradiation**
- **Time to recurrence is an important covariate**

Phase III: GOG-204

Primary Stage IVB or recurrent/persistent carcinoma of the cervix

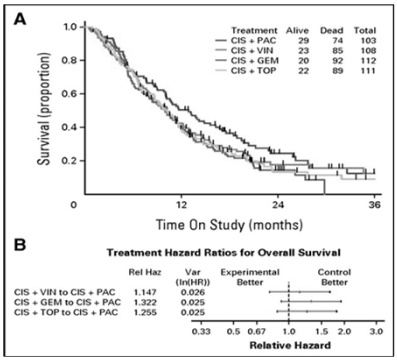
- **Measurable disease**
- **GOG PS 0-1**
- **ANC > 1500/µl**
- **Platelets > 100,000/µl**
- **Serum Cr ≤ 1.5 mg/dl**
- **No CNS disease**
- **No past invasive cancer**
- **No prior chemotherapy (unless concurrent with radiation)**

RANDOMIZE

- **Paclitaxel 135 mg/m² over 24 hours and CDDP 50 mg/m² repeated q 3 wks x 6**
- **Vinorelbine 30 mg/m² IV bolus day1 and 8 and CDDP 50 mg/m² IV day 1 repeated q 3 wks x 6**
- **Gemcitabine 1000mg/m² IV day 1 and 8 and CDDP 50 mg/m² IV day 1 repeated q 3 wks x 6**
- **Topotecan 0.75 mg/m² over 30 minutes days 1-3 CDDP 50 mg/m² IV day 1, q 3 wks x 6**

ALL REGIMENS- QoL
Baseline
Before cycle 2
Before cycle 5
9 mo. after study entry at follow-up visit

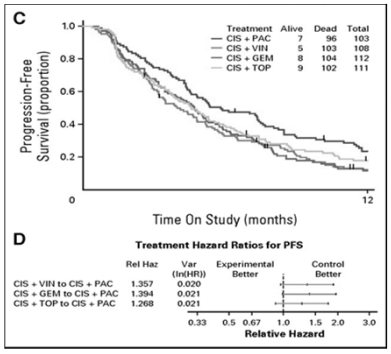
GOG #204: Survival



Monk B J et al. JCO 2009;27:4649-4655

JOURNAL OF CLINICAL ONCOLOGY

GOG #204: Progression Free Survival



Monk B J et al. JCO 2009;27:4649-4655

JOURNAL OF CLINICAL ONCOLOGY

GOG 240

Randomized Phase III Trial (4 arms)

- Cisplatin plus Paclitaxel
- Cisplatin plus Paclitaxel plus Bevacizumab
- Topotecan plus Paclitaxel
- Topotecan plus Paclitaxel plus Bevacizumab

NEJM 2014: 370; 734

GOG 240

	PFI	Median Survival
Chemo (225)	5.9 mo	13.3 mo
Chemo + Bev (227)	8.2 mo	17.0 mo
	p= 0.002	p= 0.0035

NEJM 2014: 370; 734

GOG 240
Complications

	Chemo	Chemo + Bev	P value
Neutropenia	57 (26%)	78 (35%)	0.04
VTE	3 (1%)	18 (8%)	0.001
GI/GU Fistula	1 (<1%)	13 (6%)	0.002
Hypertension	4 (2%)	54 (25%)	<0.001

NEJM 2014: 370; 734

GOG 240
Conclusions

Cisplatin/Paclitaxel = Topotecan/Paclitaxel

The addition of Bev was superior to chemo alone (Improved OS 3.7 months)

NEJM 2014: 370; 734

Carboplatin may be substituted for Cisplatin

- Carbo plus Paclitaxel was noninferior to Cis plus Paclitaxel (HR 0.994)
- May be best for patients with renal compromise
- Carbo had more thrombocytopenia and neuropathy

- J Clin Oncol 2015; 33: 2129

Summary
Chemotherapy for Metastatic Disease

- Palliative
- Response more likely
  - for mets in non-irradiated areas (e.g., lungs)
  - When there has been a longer PFI
  - When CDDP has not been previously used
- Responses are short lived
- GOG #179: Survival advantage with Cisplatin and Topotecan vs. single agent Cisplatin
- GOG #204: Survival similar with other Platin combinations
- GOG #240 Addition of Bevacizumab improves survival

Cervix Cancer

RECURRENT DISEASE

80% of recurrences are detected in 1st 2 years of follow up

Symptoms:

Vaginal discharge
Bleeding
Pelvic pain
Leg edema
Cough

Majority of patients are symptomatic

Cervix Cancer

RECURRENT DISEASE

Treatment Options

Chemotherapy – Palliative not curative
Cisplatin/Taxol/ Bev
Second-line agents

Radiation – Palliative unless disease recurs in pelvis after radical hysterectomy

Surgical – Pelvic exenteration

Second-line Chemotherapy

- Trials of second line single agent chemotherapy show no evidence of increased survival compared with best supportive care.

Second-line Chemotherapy

Drug	Response Rate
Carboplatin	15%
Vinorelbine	15%
Paclitaxel	20-25%
Ifosfamide	22%
Topotecan	19%

Second-line Chemotherapy

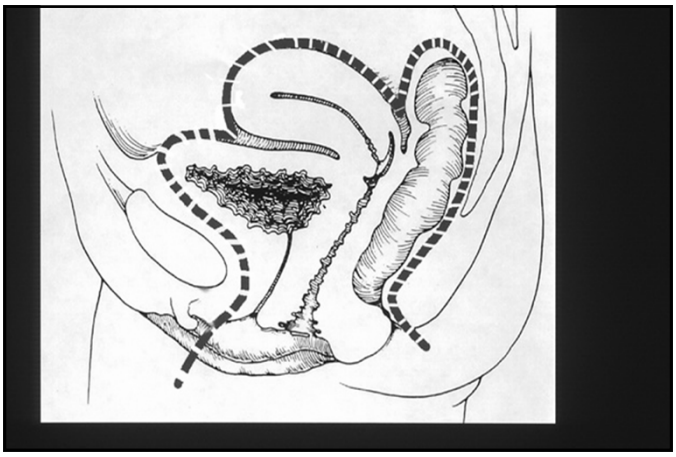
- Pembrolizmab demonstrated a 30% response rate in patients with high tumor mutational burden of PD-L1.

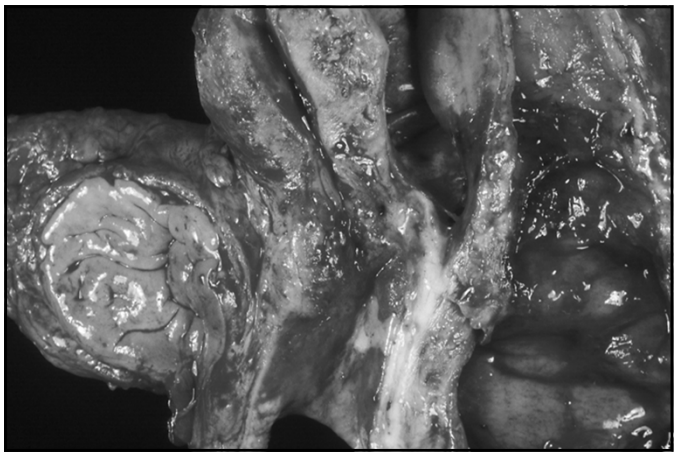
Cervix Cancer

PELVIC EXENTERATION

Curative surgery for patients with a CENTRAL pelvic
recurrence after radiation therapy

5% operative mortality rate
50–60% 5 year survival





Cervix Cancer

PELVIC EXENTERATION

Total pelvic exenteration –
resection of bladder
rectum
vagina
uterus/cervix

Reconstruction
- continent urinary conduit
- rectal anastamosis
- myocutaneous neovagina

CARCINOMA OF THE VULVA AND VAGINA

VULVAR CANCER

- 4% of gynecologic cancers
- Mean age of 65 years
- Squamous 90%
  - Melanoma
  - Adenocarcinoma
  - Basal Cell
  - Verruccous
  - Sarcoma

Vulvar Cancer

SPREAD PATTERNS

- Direct extension
  - Vagina
  - Urethra
  - Anus
- Lymphatic
  - Inguinal
  - Femoral
  - Pelvic
- Hematogenous (late)

Vulvar Cancer

PRIMARY TREATMENT

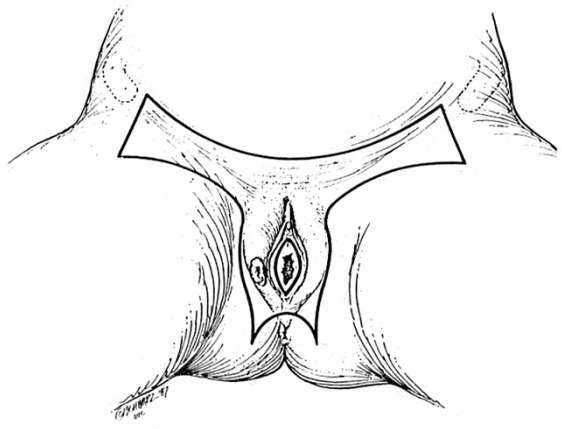
- **Radical excision with 1cm margins ("modified radical vulvectomy")**
- **Inguinal-femoral lymphadenectomy or Sentinel Node***

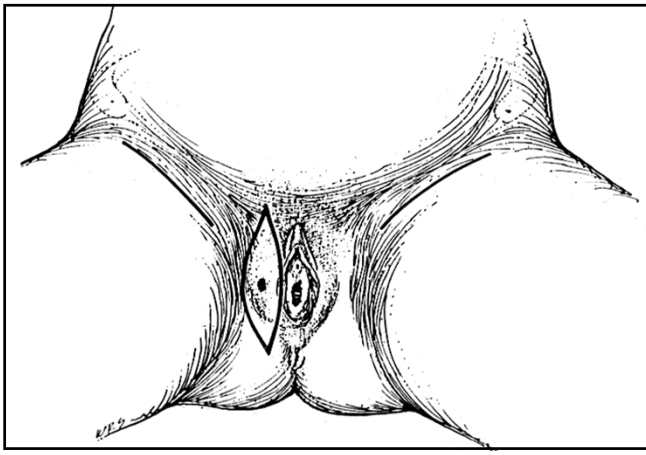
***95% Sensitivity 98% negative predictive value**

Vulvar Cancer

PROGNOSTIC FACTORS

- Size/location of lesion
- Depth of Invasion
- Inguinal lymph node metastases





Vulvar Cancer Staging

Stage	
Ia	< 2 cm lesion, <1mm invasion
Ib	> 2cm lesion, > 1 mm invasion
II	Involvement of distal urethra, vagina, anus
IIIa	1-2 positive nodes
IIIb	3 or more positive nodes
IIIc	Extranodal extension
IVa	Involvement of upper vagina, bladder, rectum
IVb	Distant metastases

Vulvar Cancer

TREATMENT OF EARLY STAGE DISEASE STAGE I

- Stage Ia, Ib: Observation
- Stage II: Postoperative Vulvar Radiation
- Stage III: Inguinal and Pelvic Chemo/RT
- Stage IVa: Vulvar, inguinal, pelvic Chemo/RT
- Stage IVb: Chemotherapy

Impact of adjuvant chemotherapy with radiation for node-positive vulvar cancer

- National Cancer Data Base (NCDB)Analysis
- Retrospective (1998-2011)
- Of 1797 pts, 26% received adjuvant Cisplatin
- Median Survival
  - **Radiation only 29.7 mos**
  - **Radiation plus Chemo 44 mos**
  - HR 0.62, 95% CI 0.48-0.79, p < 0.001

Gynecol Oncol 2015: 137; 365

Vulvar Cancer

LOCALLY ADVANCED DISEASE

- **Vulvectomy and pelvic exenteration**
- **Intracavitary/interstitial radiation and vulvectomy**
- **Teletherapy (5000 cGy) and wide local excision**
- **5FU and Cisplatin plus-RT followed by wide excision**
- **Cisplatin plus RT followed by wide excision**

Chemosensitization in Vulvar Cancer:
GOG 205 Phase II

- Locally Advanced Vulvar Cancer
- Treatment: Vulvar, Inguinal-Pelvic RT + weekly Cisplatin
- Local excision following RT
- CR : 64%

- **Gynecol Oncol 2012: 124; 529**

Treatment of Stage IVb

- No Phase III Trials
- Chemotherapy similar to cervix cancer

VAGINAL CANCER

1-2% of Gynecologic Cancers

Median Age 60 years

Squamous	85%
Adenocarcinoma	8%
Melanoma	3%
Sarcoma	3%

Most are metastatic: Cervix, vulva, uterus, choriocarcinoma, urethra, bladder, rectal, ovary

Vaginal Cancer

TREATMENT

Radiation Therapy

Teletherapy
- 5000 cGy whole pelvis
- Inguinal nodes if in lower 1/3 of vagina
- Combined with weekly Cisplatin

Brachytherapy
- Tandem and ovoids
- Vaginal cylinder
- Interstitial

Surgery
- Radical vaginectomy (hysterectomy) and pelvic lymphadenectomy Stage I lesions in upper 1/3

ADENOCARCINOMA OF THE VAGINA

- 7% of vaginal cancers
- Often from other site: endometrium, cervix, ovary, colo-rectal
- In younger patients consider DES exposure in utero (not used in the US after 1972)

CLEAR CELL ADENOCARCINOMA OF VAGINA AND CERVIX

- Association of clear cell adenocarcinoma of the vagina and DES exposure in utero
- DES used in high risk pregnancies until 1971
- Estimated risk <1:1000 exposed to DES
- Peak age at diagnosis 19 years
- Other benign changes of cervix and vagina (cock's comb, hood collar, adenosis)
- Treatment goals: Preserve ovarian and vaginal function

Herbst and Scully, *CANCER* 25:745,1970

GESTATIONAL TROPHOBLASTIC DISEASE

Hallmarks of GTD

- Rare, highly malignant disease affecting young women of reproductive age
- Reliable tumor marker (hCG)
- Exquisitely sensitive to chemotherapy
- Even with widely metastatic disease, most patients can be cured
- Fertility may be preserved in nearly all cases

Spectrum of GTD

Hydatidiform mole
- Complete or Partial

Gestational Trophoblastic Neoplasia (GTN)

Histology not specified: "malignant behavior"
- Invasive mole
- Choriocarcinoma
- Placental-site Trophoblastic Tumor (PSTT)
- Epithelioid Trophoblastic Tumor (ETT)

Hydatidiform Mole: Epidemiology

- Incidence
  - 1:1500 births: US and Europe
  - 1:125 births: Mexico and Asia
- Increased risk
  - Carotene/Vitamin A deficiency
  - Folate deficiency
  - Advanced Maternal age

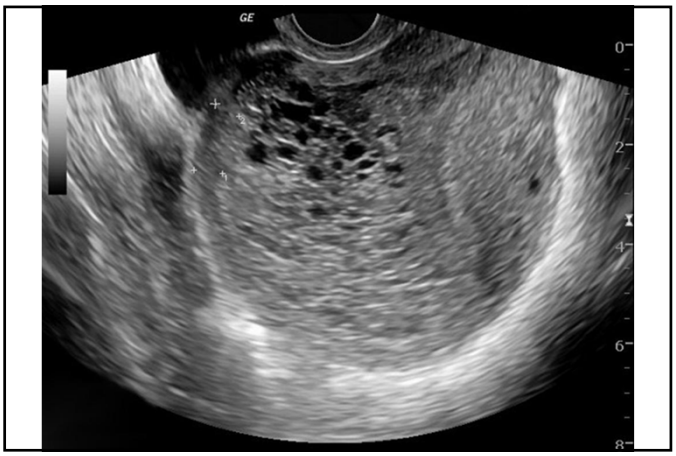
Diagnosis of Molar Pregnancy

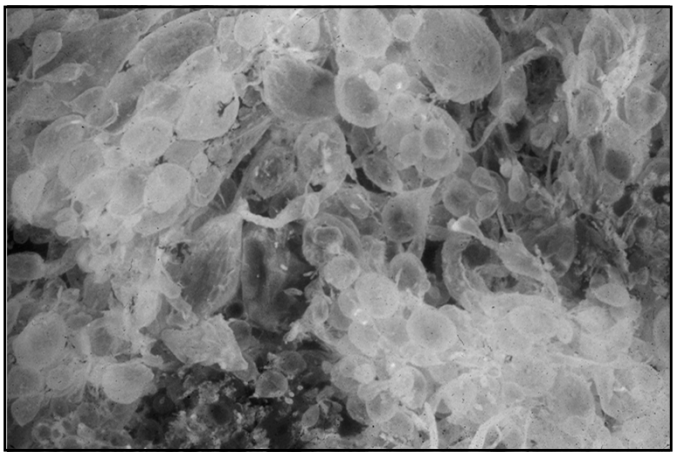
Trend toward earlier diagnosis due to increased use of ultrasound in early pregnancy.

Ultrasound findings
absent fetus, "snowstorm" or "honey-comb" appearance of placenta

Classic Symptoms (1st and 2nd trimester)
Bleeding, uterine size > than expected

Patients with uterine size > 14-16 weeks have more medical complications (25%)
Theca lutein cysts (9%), hyperemesis (6%), preeclampsia (1.3%), hyperthyroidism





Hydatidiform Mole: Management

-Preop evaluation for preeclampsia, hyperthyroidism and anemia (CBC, thyroid panel, CXR, hCG level)

- Suction D+E
  - IV Oxytocin
- Hysterectomy in Selected Cases
- Postop Respiratory failure (2%)
  - trophoblastic emboli, fluid overload
  - preeclampsia, thyroid storm

-Rh Immune Globulin if Rh negative

Hydatidiform Mole Postoperative Surveillance

Risk of subsequent GTN/malignant sequelae
Complete Mole
- 20% after evacuation
- 5% after hysterectomy
Partial mole 4% persistence

Quantitative hCG weekly until 3 consecutive negative values (Average time to remission is 9-11 weeks)

- Monthly hCG for 6 months
- Effective contraception
  OCP's, Depoprovera, barrier

Criteria for postmolar GTN

- hCG level rise > 10% on **three consecutive** weekly hCG assays (days 1, 7, 14)
- hCG plateau +/− 10% on **four consecutive** weekly hCG assays (days 1, 7, 14, 21)
- Histologic diagnosis of choriocarcinoma, PSTT, ETT
- Persistent hCG >6 months after evacuation
- Metastatic disease on exam or x-ray studies

GTN Following a Molar Pregnancy

Elevation or plateau of hCG indicates persistent GTD (? metastatic)

Risk Factors for Malignant Sequelae

- **Age > 35**
- **Preevacuation hCG > 1,000,000 mIU**
- **Uterine size > 20 weeks**
- **Theca-lutein cysts**
- **Prior mole**

Diagnosis of Malignant GTN

After Molar pregnancy (50-60%)
- **plateau or rise in hCG level**
- **can indicate invasive mole, choriocarcinoma, PSTT, ETT**

After miscarriage / ectopic / term pregnancy (40-50%)
- **continued bleeding after pregnancy termination (1 per 20-40,000 pregnancies)**

Malignant Histology
- **invasive mole, choriocarcinoma, PSTT, ETT**

High index of suspicion in young women with metastatic sites of unknown primary
- **check hCG level**

Evaluation of Malignant GTN

Initial work up

History, physical, hCG level, CBC, LFT's, CXR

Metastatic sites (Relative incidence)

Lung	**80%**
Vagina	**30%**
Abdomen/pelvis	**20%**
Liver	**10%**
Brain	**10%**

Chest CT, abdomen/pelvic CT, brain CT or MRI, pelvic ultrasound or MRI.

Classification and Staging of GTN

Optimal treatment (and outcome) determined by initial staging.

Staging Systems
- **FIGO**
- **Clinical Classification**
- **WHO Criteria**

Clinical Classification of Malignant GTN

I. Nonmetastatic GTD: No evidence of disease outside of uterus

II. Good-prognosis metastatic GTD
1. Short duration (‹4 months)
2. Low hCG level (‹40,000 mIU/ml serum ß-hCG)
3. No metastases to brain or liver
4. No antecedent term pregnancy
5. No prior chemotherapy

III. Poor-prognosis metastatic GTD: any high-risk factor
1. Long duration (›4 months since last pregnancy)
2. High pretreatment hCG level (›40,000 mIU/ml)
3. Brain or liver metastases
4. Antecedent term pregnancy
5. Prior chemotherapy

World Health Organization Prognostic Index Score

Prognostic factors	0	1	2	4
Age (yr)	≤39	>39	–	–
Antecedent Pregnancy	H mole	Abortion	Term	–
Interval (mos)	<4	4 – 6	7 – 12	>12
hCG (IU/l)	$<10^3$	$10^3 - 10^4$	$10^4 - 10^5$	$>10^5$
Largest tumor, including uterine tumor	–	3 – 4 cm	5cm	–
Site of metastases	–	Spleen, kidney	GI tract	Brain, liver
Number of metastases identified	–	1 – 4	4 – 8	>8
Prior chemotherapy	–	Single drug	Two or more	

The total score for a patient is obtained by adding the score for each prognostic factor. 0–4 = low risk, 5–7 Intermediate risk, 8–12 high risk, >13 extra high risk

GTN Risk Scoring System (FIGO)

Int J Gyn Cancer 2001; 11:73

	Score			
Risk factor	0	1	2	4
Age	<39	>39		
Prior Pregnancy	H Mole	Abortion	Term	
Time between pregnancies	< 4 mo	4–6 mo	6–12 mo	> 12 mo
Pre Rx hCG	<1,000	1,000–10,000	10,000–100,000	>100,000
Largest Tumor	<3cm	3–4 cm	> 5cm	
Mets	None	1–4	4–8	>8
Location	–	Spleen, kidney	GI	Brain, Liver
Prior Rx	–	–	Single agent	2 or more drugs

Low Risk: 0–6 High Risk: 7 or greater

Risk Stratification of GTN Directs Initial Therapy

Categorize as Low risk or High risk

LOW RISK
- Clinical Staging: non-metastatic or low risk mets
- WHO Criteria Score ≤7, FIGO <7

Treatment: Dactinomycin or MTX 1–2 cycles past remission

HIGH RISK
- Clinical staging: poor prognostic factors
- WHO criteria score ≥7, FIGO ≥ 7

Treatment: Combination chemotherapy 2–3 cycles past remission
Multimodality treatment

Treatment of Low Risk GTN

Dactinomycin
1.25 mg/m2 IV q 14 d (Bolus)
9–13 mg/kg IV x 5 d (recycle 14 days)

Methotrexate (weekly)
MTX 30–50 mg/m^2 IM weekly

Methotrexate (5 day regimen)
0.4 mg/kg/d IM x 5d (repeat 12–14 days)

Methotrexate and folinic acid (8 regimen)
MTX 1 mg/kg IM days 1, 3, 5, 7
Folinic acid (Leucovorin) 0.1 mg/kg IM days 2, 4, 6, 8
repeat if hCG elevated or plateaued for 3 weeks

89% of patients will be able to preserve fertility.

Treatment of Low Risk GTN

- GOG Randomized Trial
- Dactinomycin 1.25 mg/m2 IV every 2 weeks until hCG normal, then 1 dose Dact
- Weekly MTX 30 mg/m2 IM until hCG normal, then 1–2 additional weeks of MTX
- Primary Remission: 69% vs 53% (p=0.015)

Osborne. J Clin Oncol 2011; 29: 825

Treatment of Low Risk GTN

- If first agent fails, change to alternative: 70–90% salvage with "other" single agent; less toxicity than multiagent salvage regimens
- Consider hysterectomy to reduce amount of chemotherapy if fertility NOT an issue

Treatment of High Risk Metastatic GTN

	Remission (%)
EMA-CO	70-84%
Methotrexate/Dactinomycin/ Cyclophosphamide	63-80%
CHAMOMA (Bagshawe)	61-82%

Treat 2-3 cycles past normal hCG level

EMA-CO Chemotherapy for High-Risk Metastatic GTD

Course A

Day 1	Etoposide	100 mg/m²	IV infusion over 30 minutes
	Methotrexate	100 mg/m²	IV bolus
		200 mg/m²	IV infusion over 12 hours
Day 2	Dactinomycin	500 µg	IV bolus
	Etoposide	100 mg/m²	IV infusion over 30 minutes
	Dactinomycin	500 µg	IV bolus
	Folinic acid	15 mg	IM/PO q 6 hr x 4 doses Begin 12 hours after methotrexate infusion completed

Course B

Day 8	Vincristine	1.0 mg/m²	IV bolus
	Cyclophosphamide	600 mg/m²	IV infusion

Day 15 Recycle Course A

High Risk GTN Salvage Regimens

- EMA-EP
- VBP, BEP – recycle at 14 day intervals
- APE – French salvage regimen
- VIP – (VP-16, Ifos, Platin)
- 5FU prolonged infusion – Chinese primary chemotherapy, little activity in salvage
- Taxanes – anecdotal responses

Multimodality Therapy

Surgery

- Hysterectomy in patients who no longer desire fertility (reduces number of cycles of chemotherapy 3.8 vs 5.9 cycles)
- Resection of resistant foci in lung, bowel, kidney

Brain Mets

3000 cGy whole brain radiation therapy
Surgery for neurologic decompensation

Hepatic Mets

Surgery or hepatic embolization for hemorrhage
2000 cGy whole-liver radiation

Monitoring During Therapy

Weekly quantitative serum hCG.

Remission > 3 normal hCG levels over 14 days.

hCG levels q 2 weeks x 3 months.
Then monthly for 1 year.

Effective contraception for 1 year.

Treatment Results High Risk GTN

- 80-86% overall remission rate
- CNS mets: 75% survival primary therapy
- Liver or kidney mets: 25-50% survival
- 40-50% patients have surgery or radiation therapy in addition to chemotherapy
- 10-15% recurrence rate – maintenance chemo x 3 cycles after hCG values normalize
- Up to 2% risk of leukemia with etoposide chemo
  - Increases with >6 cycles EMA

Factors Associated with Treatment Success

- Rapid diagnosis and evaluation
- Appropriate systemic therapy
- Aggressive medical management and supportive care
- Experienced treatment team
- Careful surveillance

Recurrent GTD

- < 5% non-metastatic or low risk metastatic GTD
- 20% in high risk patients
- 80% are identified within 12 months of primary therapy
- 1.3% incidence of H. mole in subsequent pregnancy

Placental Site Trophoblastic Tumors (PSTT)

- Rare (comprised of intermediate cytotrophoblast)
- PSTT does not produce hCG in proportion to tumor volume (hCG not as reliable a marker)
- Human Placental Lactogen may be a better marker
- Tends to invade locally and spread via lymphatics
- Hysterectomy as primary therapy
- Insensitive to chemotherapy although complete remissions reported with EMA-CO and EMA-EP

63

Pancreatic Cancer

Hedy Lee Kindler, MD

August 19, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

63 – Pancreatic Cancer

Hedy Lee Kindler, MD

Disclosures

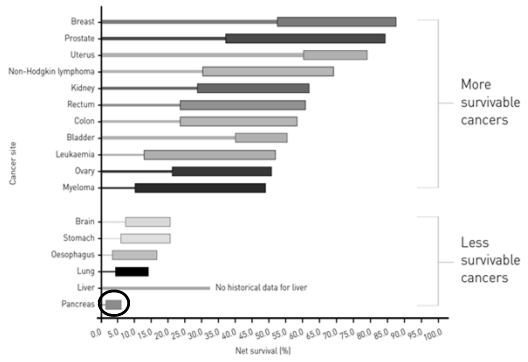
Disclosures of Financial Relationships with Relevant Commercial Interests

- N/A

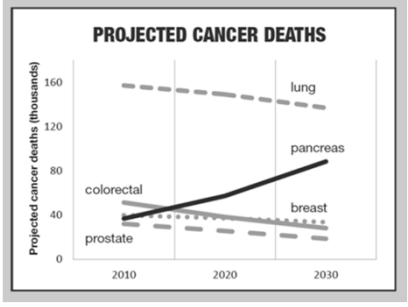
Pancreatic cancer: A dismal prognosis

- 3rd leading cause of cancer death in the US
- The worst survival of any solid tumor
- Only ~9% of all PC patients are cured
- In 2020 it is estimated that there will be:
  - 57,600 new cases
  - 47,050 deaths
- These dismal statistics reflect:
  - the early distant spread of PC
  - the inadequacy of current therapies

5-year survival of common cancers



Within this decade, pancreas cancer is projected to become the 2nd leading cause of cancer death in the US



Who gets pancreatic cancer?

Incidence by gender in 2020:

- 30,400 men
- 27,200 women

Deaths by gender in 2020:

- 24,640 men
- 22,410 women

Age:

- Most patients are between 65 and 80 at diagnosis

Race:

- African-Americans are more likely to develop PC than Caucasians

Risk Factors

Tobacco smoking

- >30% of PC cases are due to smoking

Pancreatitis (5% of PC cases)

- Familial >> Acquired

Increasing age

Weaker association

- Post-gastrectomy, post-cholecystectomy
- Diet: high fat intake, high meat intake
- Industrial carcinogens
- Diabetes

Family History (5-10%)

Evaluating Susceptibility to Pancreatic Cancer

ASCO Provisional Clinical Opinion 2019[1]

- All patients diagnosed with pancreatic cancer should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk
- Germline genetic testing for cancer susceptibility may be discussed with individuals diagnosed with PC, even if family history is unremarkable
- Consideration of germline testing should be performed early in the disease course

NCCN

- Germline testing is recommended for any patient with a confirmed pancreatic cancer

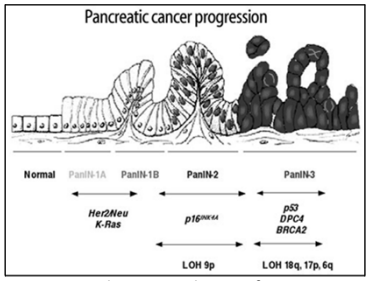
1. Stoffel, *JCO* 2019

Familial Syndrome	Genetic abnormality
Peutz-Jaegers	STK11/LKB1
Familial pancreatitis	PRSS1, SPINK1
FAMM	CDKN2A
HNPCC	hMLH1, hMSH2
Hereditary breast-ovarian syndrome	BRCA1, BRCA2, PALB2
Cystic fibrosis	CFTR
FAP	APC
Ataxia-telangiectasia	ATM
Li-Fraumeni	p53
Familial pancreatic cancer	unknown

Familial Pancreatic Cancer (FPC)

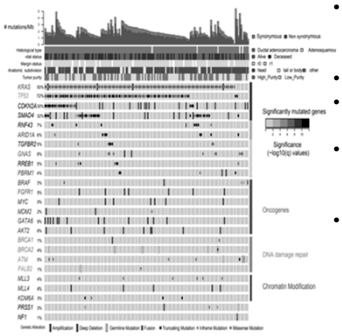
- Requires at least two 1st-degree relatives with PC who do not fulfill criteria for other syndromes
- Median age at diagnosis: 40–60 years
  - vs. sporadic (non-familial) PC: 60–80 years
- Risk of PC in 1st-degree relatives:
  - 2 affected family members: 18X
  - ≥ 3 affected family members: up to 57X
  - Younger generations
    - die ~10 years earlier than affected parent
- The resected pancreas may have multifocal dysplasia or carcinomas

Habbe, *Endocrinol Metab Clin NA* 2006; Lochan, *Br J Surg* 2007



- In PC, as in CRC, the accumulation of genetic mutations is linked to specific stages of cancer development
- PC arises from pancreatic ductal epithelial cells via a series of precursor lesions
  - Pancreatic Intraepithelial Neoplasias (PanIN 1-3)

Genetic alterations in pancreatic cancer: TCGA



- Integrated genomic, transcriptomic, and proteomic profiling
- 150 resected PC, Stage I-III
- Complex molecular landscape
- **"Top 4" mutated genes are KRAS, TP53, CDKN2A, SMAD4**
- Predicted pathogenic germline mutations in 8% of patients: BRCA2, ATM, PALB2, BRCA1, others

Cancer Cell 2017; Messersmith *ASCO* 2019

Is it worthwhile to do somatic tumor profiling in PC? Lessons from the PanCAN Know Your Tumor Program

1856 referred

1082 received report

282 (26%) actionable mutations

189 outcome measurements

46 matched therapy

143 non-matched therapy

Pishvaian, *Lancet Oncol* 2020

	#	OS
Actionable mutation, received matched therapy	46	2.58 years
Actionable mutation, no matched therapy	143	1.51 years
No actionable mutation	488	1.32 years

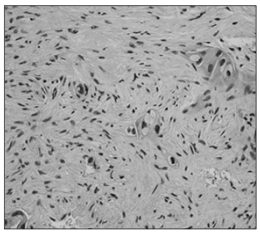
Actionable mutations with matched therapies in KYT

AKT1	ALK	ATM	BRAF
BRCA1	BRCA2	CDK4	HER2
IDH1	MSI-H	NTRK1	PALB2
RET	ROS1	STK11	

Pathology

Exocrine carcinoma
- Adenocarcinoma (>90%)
- Acinar: younger
- Cystic: less aggressive

Neuroendocrine carcinoma
- Important to distinguish
- More indolent



Invasive pancreatic ductal adenocarcinoma with a few infiltrating malignant glands and cell clusters and a prominent desmoplastic stromal reaction

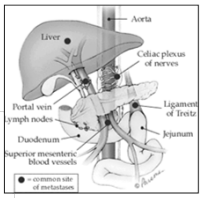
Clinical Presentation

- pain
- jaundice
- weight loss
- anorexia
- depression
- nausea/vomiting
- thrombophlebitis
- pruritus
- fatigue
- new onset diabetes

Patterns of dissemination

Local spread
- SMA
- SMV/portal vein
- Celiac branches

Lymphatic metastases
- Locoregional:
  - Peripancreatic
  - Portal
- Distant:
  - Celiac
  - SMA
  - Root of mesentery



Distant metastases
- Liver
- Lungs

Peritoneal "drop" metastases
- Sister Mary Joseph nodules
- Peritoneal carcinomatosis
- Microscopic peritoneal cytology

Up to 70% of PC patients present with biliary obstruction, which can be relieved by stent placement

Via ERCP

(Endoscopic Retrograde Cholangio-Pancreatography)
- Less subject to infection
- Highly skill-dependent

Via PTC

(Percutaneous Transhepatic Cholangiography)
- Complementary to ERCP
- Higher infection rate
- Not advantageous preoperatively

Stent complications

- Plastic stents: susceptible to overgrowth with biofilm, tumor, sludge, or infection
  - Symptomatic re-obstruction: median of 3 mo
- Metallic stents: remain patent for ≥ 6 mo
- Preferred stent:
  - Metal: if life expectancy ≥ 6 mo
  - Plastic or short metal: if surgery is anticipated
- In a pt with a biliary stent, even subtle signs of obstruction or infection, such as fever, chills, or leukocytosis, require *urgent* evaluation
  - Stent change and antibiotics may be required

Wiebe, *Oncology* 2009

CA 19-9

- Mucinous glycoprotein
- Sialylated Lewis A antigen
  - Patients who are Lewis antigen negative cannot synthesize CA 19-9
- Normal <37
- An elevated CA 19-9 is not always due to tumor progression:
  - Cholangitis, pancreatitis, biliary obstruction can all raise the CA 19-9

TNM Staging

T1 Limited to pancreas <2 cm
T2 Limited to pancreas >2 cm
T3 Beyond pancreas, not involving SMA or celiac axis
T4 Extension to SMA or celiac axis

N0 No nodal involvement
N1 Regional nodes involved

M0 No distant metastases
M1 Distant metastases present

TNM Staging for Pancreatic Cancer

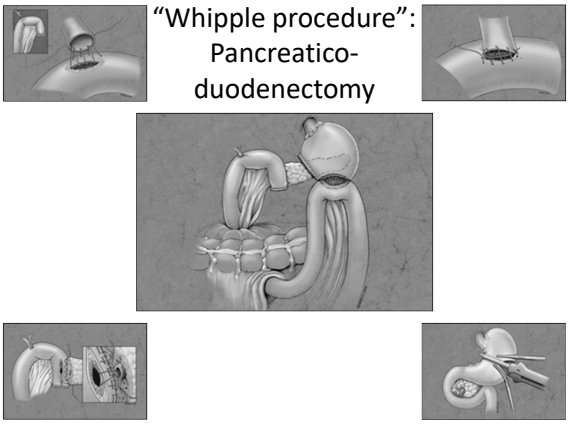
Stage I	$T_{1-2}N_0M_0$	Tumor ≤2 cm in greatest dimension, no lymph nodes, no metastasis
Stage II	$T_3N_0M_0$	Tumor extends directly to duodenum, bile duct, or peripancreatic tissues, no lymph nodes, no metastasis
Stage III	$T_{1-3}N_1M_0$	Regional lymph node involvement, no metastasis pN1a: single regional lymph node pN1b: multiple regional lymph nodes
Stage IVA	$T_4N_{Any}M_0$	Tumor extends directly to stomach, spleen, colon, or adjacent large vessels; involvement of 1 or more regional lymph nodes
Stage IVB	$T_{Any}N_{Any}M_1$	Presence of metastatic disease

Real World Staging

- Resectable
- Borderline resectable
- Locally advanced, unresectable
- Metastatic

- Location
  - Head: 80% (more likely to be resectable)
  - Other: 20%

"Whipple procedure": Pancreatico-duodenectomy



Surgery for PC

Radical pancreaticoduodenectomy (Whipple)

- Sacrifices: proximal pancreas, lower stomach, bile duct, duodenum, proximal jejunum

Other options:

- Head: Whipple with pylorus-preserving procedure
- Body/tail: distal or total pancreatectomy

<15% of patients are resectable:

- Operative mortality 1-5%, major morbidity 20%
- 5-year survival ~20%; median survival 18-24 months
- Surgery improves median survival *only* in patients with negative margins

The surgeon <u>really</u> matters

High volume institutions (>10 Whipple procedures per year) and high volume surgeons have:

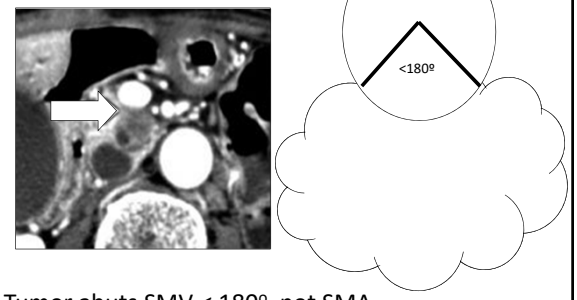
- Longer survival
- Less perioperative morbidity and mortality

Perioperative mortality	
Low volume MD, low volume hospital	~15%
High volume MD, high volume hospital	<3%

Criteria for resectability

- No non-contiguous, extra-pancreatic disease
- Patency of the superior mesenteric/splenic/portal vein confluence
  - SMV, portal vein can be resected with vein reconstruction
- No tumor extension to, or encasement of, the superior mesenteric artery

Resectable

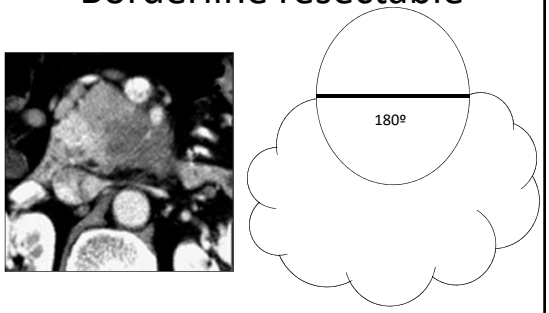


Tumor abuts SMV < 180º, not SMA

Borderline resectable PC

- Tumor-associated deformity of SMV or portal vein
- Tumor abutment of SMV or portal vein > 180^0
- Short-segment occlusion of SMV or portal vein
- GDA encasement up to hepatic artery, with either short segment encasement or direct abutment of HA w/o extension to celiac axis
- Tumor abutment of SMA ≤ 180^0

Borderline resectable

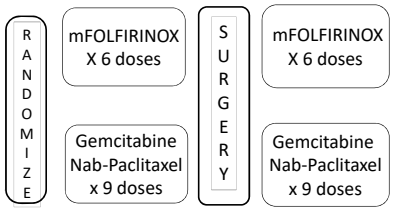


Tumor partially encases SMA

Neo-adjuvant chemotherapy for resectable and borderline resectable PC: Rationale

- Down-stage tumor
  - maximize the potential for R0 resection
- Treat micro-metastatic disease early
- Give chemotherapy when it is easier to tolerate
- Improve outcome by selecting patients with stable or responding disease
  - sparing those who will inevitably progress
- Unanswered questions include the optimal chemo regimen, optimal duration of treatment, and the role of radiation

S1505: Perioperative mFOLFIRINOX vs. Gemcitabine/nab-Paclitaxel in resectable PC



Arm	N	2-yr OS	Median OS
mFOLFIRINOX	55	43.1%	22.4 months
Gem-nab-P	47	46.9%	23.6 months

Sohal, *ASCO* 2020

PREOPANC: Phase III trial of immediate surgery vs. pre-operative gemcitabine/RT in resectable and borderline resectable PC

	Resectable N=133		**Borderline resectable N=113**	
	Preop ChemoRT (N=65)	Immediate Surgery (N=68)	Preop ChemoRT (N=54)	Immediate Surgery (N=59)
Median OS	14.6 mo	15.6 mo	17.6 mo	13.2 mo
Median DFS	9.2 mo	9.3 mo	6.3 mo	6.2 mo
Resection rate	68%	79%	52%	64%
R0 resection rate	66%	59%	**79%**	**13%**

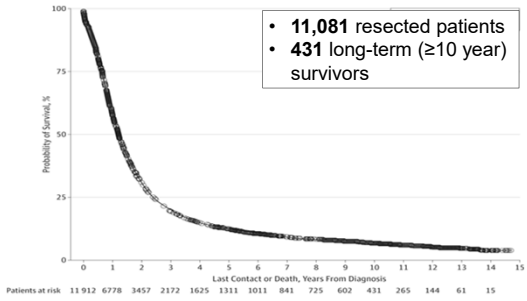
Versteijne, *JCO* 2020

ESPAC-5F: Randomized phase II trial of immediate surgery, neoadjuvant GEMCAP, FOLFIRINOX or chemoRT in borderline resectable PC

	Immediate surgery	GEMCAP	FOLFIRINOX	CRT
N	32	20	20	16
1-yr survival	42%	79%	**84%**	64%
	Immediate surgery	Neoadjuvant therapy		
Resection rate	62%	55%		
R0 resection	15%	23%		
1-yr survival	**42%**	**77%**		

Ghaneh, *ASCO* 2020

Even after "curative" resection, survival is limited



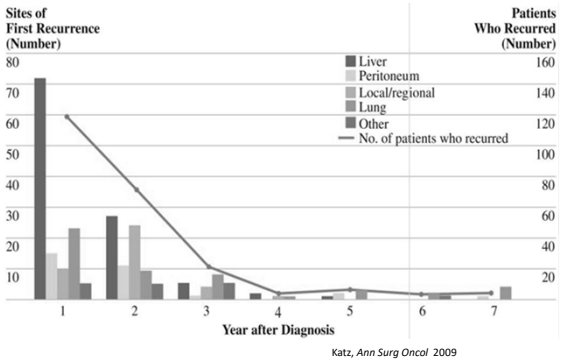
Paniccia, *JAMA Surgery* 2015

Predictors of long-term survival in PC Listed in order of importance

		OR
LN positivity ratio	0%	4.6
Adjuvant chemotherapy		2.4
Pathologic T stage	T1	3.1
Patient age	50-60	3.4
Tumor grade	Well-differentiated	2.2
Surgical margin	Negative	1.9
Pathologic M stage	M=X	5.6
Tumor size	< 2cm	1.7
Educational level	> High school grad	1.7
Insurance status	Private	2.0

Paniccia, *JAMA Surgery* 2015

Patterns of recurrence after resection



Katz, *Ann Surg Oncol* 2009

CONKO-001

Resected pancreatic cancer
N=368

Gemcitabine for 6 months

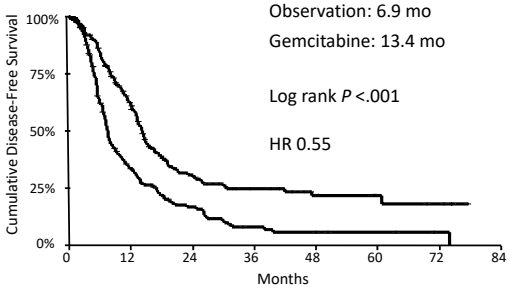
Observation for 6 months

Stratification:
Tumor stage: T1-2 vs. T3-4
Nodal status: N0 vs. N1
Resection status: R0 vs. R1

Primary endpoint: Disease-free survival

Oettle, *JAMA* 2007

CONKO-001: Disease-Free Survival



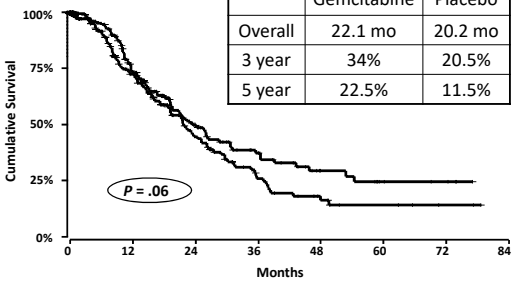
Observation: 6.9 mo
Gemcitabine: 13.4 mo

Log rank *P* <.001

HR 0.55

Oettle H et al. *JAMA.* 2007;297:311-313

CONKO-001: Overall Survival



	Gemcitabine	Placebo
Overall	22.1 mo	20.2 mo
3 year	34%	20.5%
5 year	22.5%	11.5%

Oettle H et al. *JAMA.* 2007;297:311-313

CONKO-001: 11 year follow-up

	Gemcitabine (n=179)	Observation (n=175)
Median DFS	13.4 months	6.7 months
Median OS	22.8 months	20.2 months
5-Year OS	20.7%	10.4%
10-year OS	12.2%	7.7%

Oettle, *JAMA* 2013

CONKO-001: Conclusions

- Adjuvant gemcitabine significantly improves both disease-free and overall survival compared to observation
- Adjuvant gemcitabine is associated with a doubling of 5-year survival
- The overall survival benefit from gemcitabine holds for R0 and R1 resections, node +/- disease, and all T stages
- This study supports adjuvant gemcitabine as a community standard
  - Best level 1 evidence: disease-free survival, median and 5 year survival all superior to observation

Adjuvant data from ESPAC trials

	Pts	Median survival (months)		
		Observation	5-FU/LV	Gemcitabine
ESPAC-1/ ESPAC-3	458	16.8	23.2	
ESPAC-3 (V2)	1088		23.0	23.6

These studies demonstrated that adjuvant 5-FU and gemcitabine were equivalent, but gemcitabine was less toxic

ESPAC-4

730 patients

Gemcitabine 1000 mg/m²
Days 1, 8, 15
x 6 cycles

Gemcitabine 1000 mg/m²
Days 1, 8, 15
Capecitabine 1660 mg/m²/day
Days 1-21 Q28 days
x 6 cycles

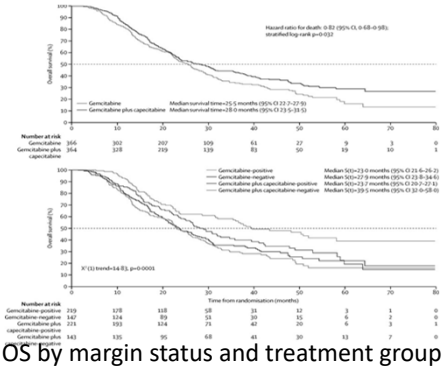
Primary endpoint: Overall survival

Neoptolemos, *Lancet* 2017

ESPAC-4: Efficacy

		G	GC	HR
Number of patients		366	364	
Median overall survival (months)	All patients	**25.5**	**28**	0.82
	R1 resection	23.0	23.7	0.90
	R0 resection	**27.9**	**39.5**	0.68
Estimated overall survival	1 year	80.5%	84.1%	
	2-year	52.1%	53.8%	
	5-year	**16.3%**	**28.8%**	
Relapse-free survival	Median (mo)	**13.1**	**13.9**	0.86
	3-year	20.9%	23.8%	
	5-year	11.9%	18.6%	

ESPAC-4: Overall survival by treatment group



OS by margin status and treatment group

Key predictors of survival on multivariate analysis in ESPAC-4

		HR
Treatment	Gem vs. GemCap	0.79
Resection margin	Positive vs. negative	1.27
Post-op CA 19-9		1.24
Tumor grade	Well vs. moderately differentiated	1.65
	Well vs. poorly differentiated	2.58
Lymph node status	Positive vs. negative	1.74
Maximum tumor size		1.12

ESPAC-4: Conclusions

- Adjuvant gemcitabine + capecitabine:
  - Significantly improves median overall survival compared to gemcitabine alone
    - 28.0 vs. 25.5 months, HR 0.82
    - OS benefit is mostly in R0 patients:
      - 39.5 vs. 27.9 mo, HR 0.68
  - Yields a near doubling of the estimated 5-year survival:
    - 28.8 vs. 16.3%
  - Does not improve recurrence-free survival:
    - 13.9 vs. 13.1 mo, HR 0.86
- Author's conclusions: ESPAC-4 supports adjuvant gemcitabine-capecitabine as a new standard of care

ESPAC-4: Questions and future prospects

- The study was performed exclusively in Europeans
  - Americans experience greater toxicity from capecitabine than Europeans
    - Likely related to folate fortification in the US diet
  - Can American patients tolerate this dose and schedule of capecitabine?
- Will these results be supplanted by more active regimens?
  - FOLFIRINOX?
    - Yes
  - Gemcitabine-nab-paclitaxel?
    - No

PRODIGE 24

-Age 18-79
-PS 0-1
-R0/R1 resection
-CA 19-9 < 180
-Able to receive chemo within 12 weeks of surgery

Stratification:
-Center
-Margin (R0 vs. R1)
-CA 19-9 (≤ 90 vs. 91-179)
-pN0 (< 12 vs. ≥ 12 examined nodes) vs. pN1

mFOLFIRINOX
-Oxaliplatin 85 mg/m^2
-LV 400 mg/m^2
-Irinotecan 180 mg/m^2*
-CIVI 5-FU 2400 mg/m^2 over 46 hours
Q2 weeks, x 12 cycles
*reduced to 150 mg/m^2 after pt 162 (b/c 20% gr ¾ diarrhea)
-No bolus 5-FU

Gemcitabine
1000 mg/m^2 Days 1, 8, 15 x 6 cycles

Primary endpoint: Disease free survival

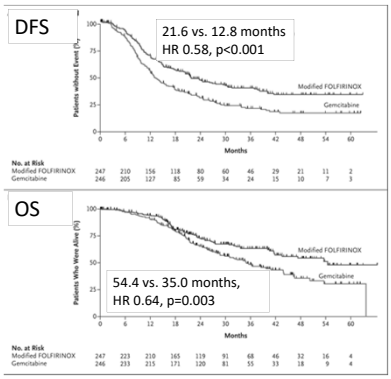
Stats: 80% power to detect an increase of 10% in 3-year DFS (17% to 27%) corresponding to a **HR=0.74**

Conroy, *NEJM* 2018

PRODIGE 24: Efficacy

	mFFX	G	HR	P
Relative dose intensity >70%	48.7%	91.4%		<0.001
Median disease-free survival	**21.6** mo	**12.8** mo	**0.58** 95% CI: 0.46-0.73	<0.0001
3-year disease-free survival	39.7%	21.4%		
Metastasis free survival	30.4 mo	17.7 mo	0.59 95% CI: 0.46-0.75	<0.0001
Overall survival	**54.4** mo	**35.0** mo	**0.64** 95% CI: 0.48-0.86	<0.003
3-year overall survival	63.4%	48.6%		

PRODIGE 24: Disease-free and overall survival



Prognostic factors for disease-free survival on multivariate analysis on PRODIGE 24

Factor	HR (95% CI)	P value
mFOLFIRINOX	0.59 (0.46-0.75)	<0.001
Moderately or poorly differentiated tumor	1.42 (1.09-1.86)	<0.001
Portal vein resection	1.43 (1.05-1.94)	<0.001

PRODIGE 24: Grade 3-4 Toxicity

	mFFX N=238	**G** N=243	P
Neutropenia	28.4%	26%	0.56
G-CSF use	**59.9%**	3.7%	<0.001
Febrile Neutropenia	2.9%	3.7%	0.65
Thrombocytopenia	1.3%	**4.5%**	0.03
Diarrhea	**18.6%**	3.7%	<0.001
Neuropathy	**9.3%**	0%	<0.001
Fatigue	**11%**	4.6%	0.003
Vomiting	**5%**	1.2%	<0.001
Mucositis	**2.5%**	0%	<0.001
Hand-foot syndrome	0.4%	0%	0.023

PRODIGE 24: Conclusions

- Compared to gemcitabine, adjuvant mFOLFIRINOX significantly improves:
  - Disease-free survival (21.6 vs. 12.8 mo, HR 0.58)
  - Metastasis-free survival (30.4 vs 17.7 mo)
  - Overall survival (54.4 vs. 35.0 mo)
  - 3-year survival (63.4 vs. 48.6%)
- Although mFOLFIRINOX is more toxic than Gem, it is a safe regimen with manageable toxicities
- Author's conclusions: mFOLFIRINOX should now be considered a new standard of care after pancreatic cancer resection in patients with good performance status

ASCO Clinical Practice Guideline 2019 Update[1]:

- mFOLFIRINOX is preferred for adjuvant treatment of PC in the absence of concerns for toxicity or tolerance

1. Khorana, *JCO* 2019

APACT: Phase III open-label trial

Eligibility:
- Age ≥ 18
- Resected PC: T1-3, N0-1, R0/1
- PS 0-1
- CA 19-9 < 100
- Able to be randomized within 12 weeks of surgery

Stratification:
- Geographic region
- Resection status (R0 vs. R1)
- LN status: LN = vs. LN-

Nab-paclitaxel 125 mg/m^2
Gemcitabine 1000 mg/m^2
Days 1, 8, 15 q 28 days
X 6 cycles

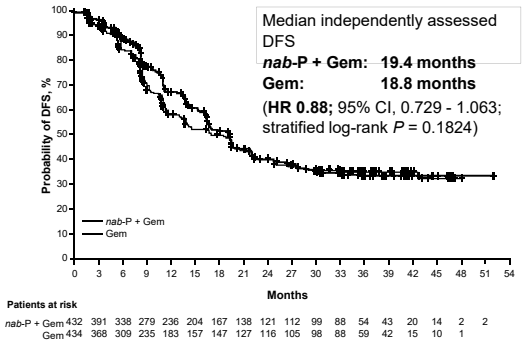
Gemcitabine 1000 mg/m^2
Days 1, 8, 15 Q 28 days
X 6 cycles

Primary endpoint:
Independently-assessed
Disease-free survival

Stats: 90% power to detect an improvement in DFS from 13.5 to 18.5 months corresponding to a HR=0.73

Tempero, *ASCO,* 2019

Primary endpoint: Independently assessed DFS (ITT population)



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APACT: Efficacy

	nab-P/G N=429	**G** N=423	HR	P
Median # cycles	6	6		
Median relative dose intensity	Nab-P: 75% Gem: 80%	Gem: 91%		
Primary endpoint: Median independently assessed DFS	19.4 mo	18.8 mo	0.88	0.1824
Median investigator-assessed DFS	16.6 mo	13.7 mo	0.82	0.0168
Median OS	40.5 mo	36.2 mo	0.82	0.045

The APACT trial: Author's conclusions

- The primary endpoint of independently assessed DFS was not met
  - Investigator-assessed DFS aligned more closely with OS results than independently assessed DFS
- Consistent with other trials, the survival with Gem monotherapy was markedly improved, suggesting better patient selection and benefit from treatment with contemporary therapies upon recurrence of disease
- The *nab*-P + Gem safety profile was consistent with what was observed in the MPACT trial
- Results of ongoing biomarker and QoL analyses will be presented at future meetings
- Final OS data will clarify the role for adjuvant *nab*-P + Gem
  - Continued investigation of the regimen is warranted

The APACT trial: My interpretation

- **This was a negative trial which did not meet its DFS primary endpoint**
  - Target HR of 0.73 was not achieved via either independent or investigator-assessed DFS
- OS data is immature, correlative studies are pending
- This trial demonstrates the importance of performing a randomized trial rather than simply extrapolating data from the metastatic to the adjuvant setting

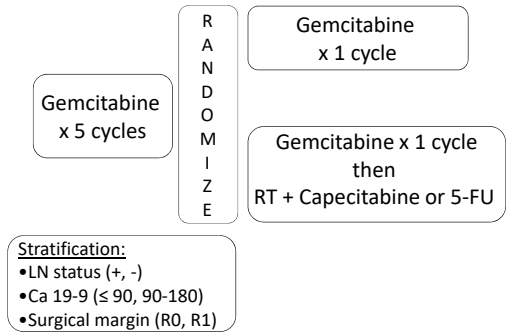
EORTC/FFCD/GERCOR

Randomized phase II trial of Gem vs. Gem→Gem-RT in resected PC

	Gemcitabine x 4 cycles (N=45)	Gem x 2 cycles, then Gem-RT (N=45)
Median DFS (months)	10.9	11.8
Median OS (months)	24.4	24.3
2-year survival (%)	50.2	50.6
Sites of first progression		
Local recurrence only	24%	11%
Local + distant recurrence	13%	20%
Distant recurrence only	40%	42%

Van Laethem, *JCO* 2010

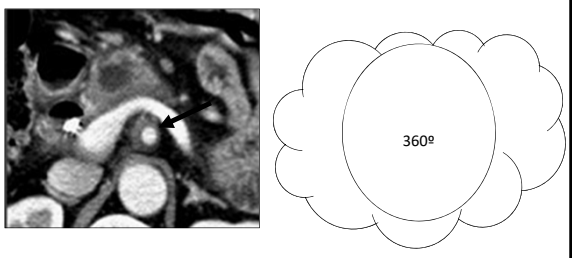
The recently completed Intergroup adjuvant trial: RTOG 0848



Summary: Adjuvant therapy for PC

- Adjuvant therapy options increasingly include systemic chemotherapy alone
  - Role of radiation is uncertain
- Gemcitabine (CONKO-001) improves DFS and OS
- 5-FU/LV (ESPAC-1, 3) is equivalent to gemcitabine but is more toxic
- Gemcitabine + capecitabine (ESPAC-4), improves OS (in pts with an R0 resection) but does not improve RFS
- mFOLFIRINOX (PRODIGE 24) improves DFS and OS and should be SOC in good PS patients
- Nab-paclitaxel/gemcitabine does not improve DFS

Locally advanced, unresectable



Tumor encases SMA

LAPC: A distinct clinical entity Treatment is poorly defined

- Locally advanced disease
  - ~1/3 of PC patients
  - Inoperable due to locoregional extent of 1^0 tumor
  - Different biology, outcomes than metastatic PC
- Role of radiation is controversial
  - Provides effective pain control
  - Requires radio-sensitization
    - 5-FU, capecitabine, or gemcitabine
  - Often poorly tolerated: N/V, fatigue
- Optimal timing of radiation uncertain

Induction chemotherapy before radiation in LAPC

- Up to ⅓ of LAPC patients develop metastatic disease within the first few months of starting chemotherapy
- Up-front chemotherapy
  - May eradicate occult micro-metastatic disease
  - Spares patients who develop early metastatic progression from toxicities of RT
  - Limits radiation to patients whose tumors are well-controlled with systemic therapy

GERCOR retrospective analysis in LAPC

Impact of CRT after disease control with chemotherapy

- 181 LAPC pts: chemotherapy for at least 3 months
  - 29% developed metastatic disease during induction chemotherapy
- Investigators choice in the remaining 128 patients
  - Chemo-RT or continue chemotherapy

	Chemo-RT (55%)	Chemo (44%)	P value
PFS	10.8 mo	7.4 mo	.005
OS	15 mo	11.7 mo	.0009

Retrospective study: No definitive conclusions
Hypothesis generating

Huguet, *JCO* 2007

LAP-07: Trial design

Does CRT ↑ OS in pts w/tumor control after induction chemo?

1st RANDOMIZATION

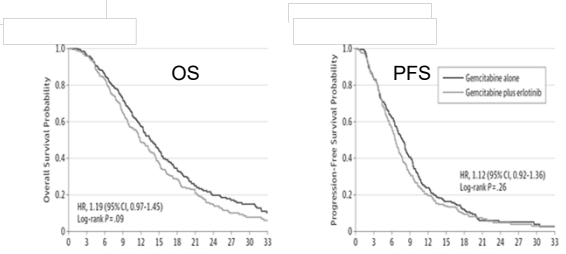
- Gemcitabine x 4 months
- Gemcitabine + Erlotinib x 4 months

2nd RANDOMIZATION

- Gemcitabine x 2 months → Stop
- 5040 cGy RT + Capecitabine → Stop
- Gemcitabine + Erlotinib x 2 months → Maintenance Erlotinib
- 5040 cGy RT + Capecitabine → Maintenance Erlotinib

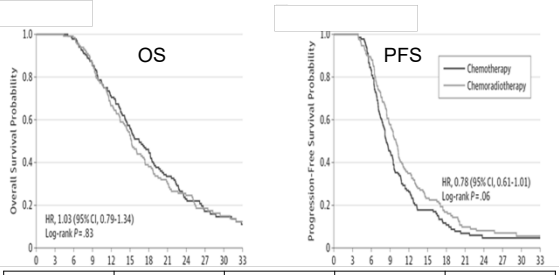
Futility boundary for 1^0 hypothesis crossed after 442 pts randomized

LAP-07: Gemcitabine vs. gemcitabine/erlotinib



	G	GE	HR	P
OS	13.6 mo	11.9 mo	1.19	.09
PFS	7.8 mo	6.5 mo	1.12	.26

LAP-07: Chemo vs. Chemo-RT



	C	CRT	HR	P
OS	16.5 mo	15.2 mo	1.03	.83
PFS	8.4 mo	9.9 mo	0.78	0.06

LAP-07: Conclusions

In LAPC patients whose tumor is controlled after 4 months of gemcitabine induction:

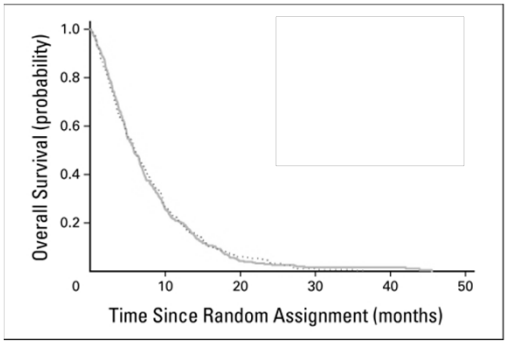
- CRT does not increase OS compared with chemotherapy
  - –15.2 vs. 16.5 months
- The increased PFS with CRT (9.9 vs. 8.4 mo) resulted in:
  - – A longer period without treatment
    - 6.1 vs. 3.7 months, p=0.02
  - – Fewer locoregional tumor progressions
    - 32% vs. 46%
- In LAPC, the addition of erlotinib to gemcitabine:
  - – Does not improve survival
  - – Increases toxicity

Chemotherapy for advanced pancreatic cancer

Long-standing, well-deserved therapeutic nihilism

- Countless trials over several decades
- Many drugs and combinations tested
- Minimal to no activity observed

This is the typical result for a phase III pancreatic cancer trial presented at ASCO



Why is it so difficult to develop active drugs for pancreatic cancer?

- Highly lethal disease
- No effective screening tests, so most diagnoses are made late
- Very resistant to most agents evaluated
- Biology of the disease not well understood
- Few readily druggable molecular targets

Key milestones in the development of new drugs for PC

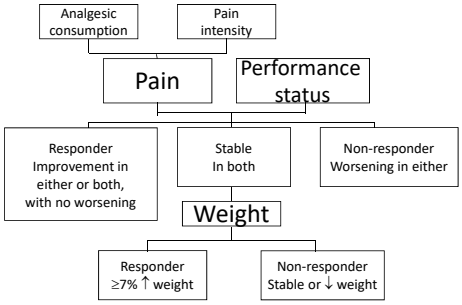
Pre-1996	The dark ages. Nothing works. Median RR 0%
1996	Gemcitabine improves survival compared with 5-FU
1996-2005	Many agents tested. No drug or drug combination is better than Gemcitabine
2005	Erlotinib/Gemcitabine modestly improves OS c/w Gem
2005-09	More drugs tested. More negative trials.
2010	FOLFIRINOX improves survival c/w Gem
2012	*nab*-Paclitaxel + Gemcitabine improves OS c/w Gem
2016	Nano-liposomal irinotecan/5-FU improves OS c/w 5-FU
2017	Pembrolizumab for MSI-H/dMMR tumors (<1% PC)
2019	Maintenance Olaparib improves PFS in *gBRCA*m PC

Gemcitabine has a genuine, but modest impact on survival and QOL

	Gemcitabine	5-FU	P value
Patients	63	63	
Tumor Response	5.4%	0%	
Survival	5.65 mo	4.4 mo	0.0025
1-year survival	18%	2%	0.0025
TTP	2.1 mo	0.9 mo	
Clinical Benefit Response	24%	5%	0.0022

Burris, *JCO* 1997

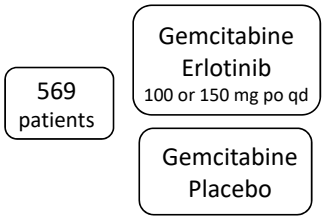
We administer gemcitabine principally because it produces "clinical benefit"



It has been remarkably difficult to improve upon the modest outcomes achieved with gemcitabine

- Most drugs don't work in pancreatic cancer
- Gemcitabine:
  - Makes sick people feel better
  - Is less toxic than most other drugs or drug combinations

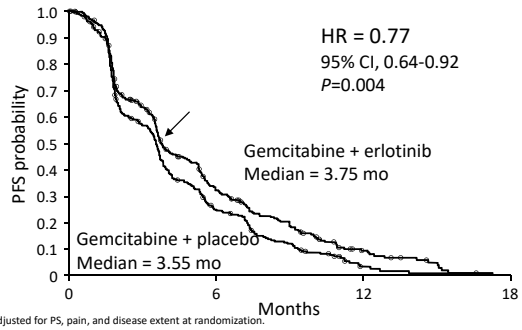
The NCIC PA3 trial demonstrated a modest improvement in survival for gemcitabine + erlotinib



Statistics: 80% power to detect a 33% ↑ survival, α=0.05

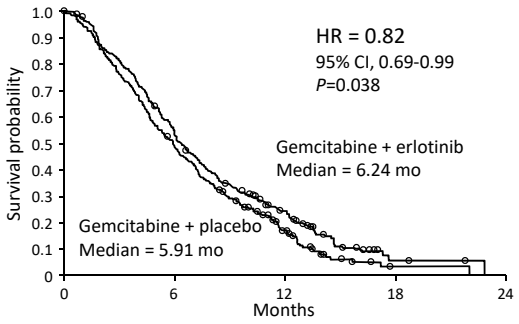
Moore, *JCO* 2007

Progression-Free Survival



*Adjusted for PS, pain, and disease extent at randomization.

Overall Survival



*Adjusted for PS, pain, and disease extent at randomization.

Gemcitabine + erlotinib: A modest improvement

	GE	G	HR	P
Patients	285	284		
Response	8.6%	8.0%		
Median survival (mo)	6.24	5.91	0.82	0.038
1-year survival	23%	17%		0.023
PFS (mo)	3.75	3.55	0.77	0.004
QOL (EORTC QLQ-C30)	Better on placebo (↑ diarrhea on GE)			
GE: Cost/YLG	$500K			
In 2005, the FDA approved erlotinib in combination with gemcitabine for advanced PC				

Can a biomarker predict the activity of erlotinib?

KRAS mutations

- Confer resistance to EGFR inhibitors
- Very common in PC (75-90%)
  - The highest incidence of any cancer

Activating EGFR mutations

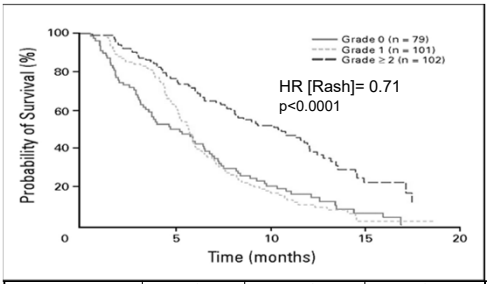
- Rare (<4%)

Molecular subset analysis of PA3 trial

- KRAS status did not predict a survival benefit for gemcitabine + erlotinib

da Cunha Santos, *Cancer* 2010

Severity of rash correlates with survival



	Grade 0 N= 79	Grade 1 N= 108	Grade ≥2 N= 103
Median survival	5.29	5.75	10.51
1-yr survival	16%	11%	43%

Dose escalation to rash: The RACHEL study

In patients with grade 0-1 rash after 4 weeks of gemcitabine + erlotinib:

•Does escalating the erlotinib dose to >100 mg improve survival?

	Standard dose erlotinib (N=75)	Dose-escalated erlotinib (N=70)	p
Rash ≥ Grade 2	9%	41%	<0.0001
OS (mo)	8.4	7.0	0.2026
PFS (mo)	4.5	3.5	0.6298

Dose-escalating erlotinib increases rash, not survival

Van Cutsem, 2012

Gemcitabine + Erlotinib in context

- PA3 is the 1st randomized trial to demonstrate that *any* drug added to Gem prolongs survival in PC

Erlotinib + gemcitabine produces:

- A statistically significant improvement in OS (HR 0.82) and PFS (HR 0.77)
- Modest toxicity
- No improvement in QOL
- Substantial cost ($500K/YLG)
- No biomarker to select those most likely to benefit

Questions:

- How clinically meaningful are these results?
- Is the modest benefit worth the expense & toxicity?

Who is the best patient for this regimen?

Over the next 5 years, several more negative phase III trials were reported

Trial	Drug	N	G + X (mo)	G (mo)	P value
GEMCAP	Capecitabine	533	7.1	6.2	0.08
GIP	Cisplatin	400	7.2	8.3	0.38
E6201	Oxaliplatin	832	5.7	4.9	0.22
	FDR Gem		6.2		0.04
CALGB 80303	Bevacizumab	602	5.8	5.9	0.95
S0205	Cetuximab	704	6.4	5.9	0.14
GemAx	Axitinib	632	8.5	8.3	0.54
AViTA	Bevacizumab (vs. GemErlotinib)	607	7.1	6.0	0.21

Then came the study that changed the way we think about chemotherapy for pancreatic cancer

In 2010: A substantial treatment advance
The PRODIGE 4 - ACCORD 11 trial

342 patients

No prior chemo
PS 0-1
< 76 yrs
Measurable metastatic disease
T. bili < 1.5 x ULN

RANDOMIZE

- FOLFIRINOX
- Gemcitabine

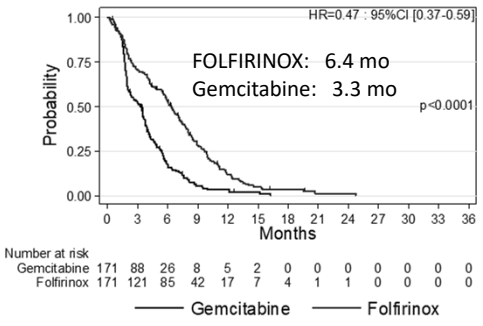
Primary endpoint: OS

Stratification:
- Center
- PS: 0 vs. 1
- 1^0 tumor location: head vs. other

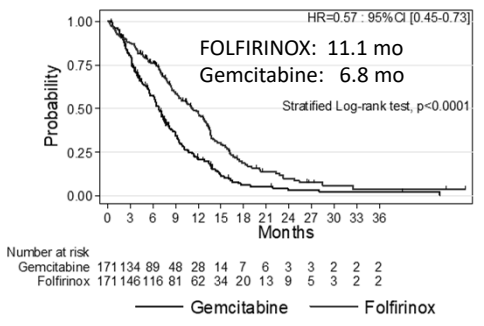
Statistics: 80% power to detect an ↑ in median OS from 7 to 10 mo (HR 0.70, α= 0.05)

Conroy, *ASCO* 2010, *NEJM* 2011

Progression-free survival



Overall survival



FOLFIRINOX vs. Gemcitabine

Efficacy

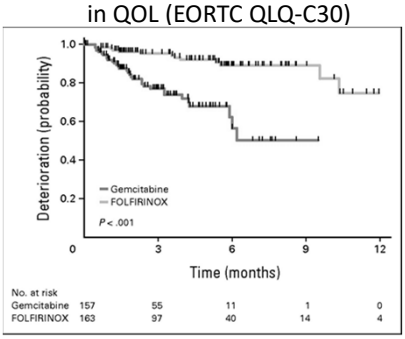
	F	G	HR	P
Patients	171	171		
Objective Response	31.6%	9.4%		0.0001
Stable disease	38.6%	41.5%		
Disease control (PR+SD)	70.2%	50.9%		0.0003
Median survival (mo)	11.1	6.8	0.57	<0.0001
1-year survival	48.4%	20.6%		
18 month survival	18.6%	6%		
PFS (mo)	6.4	3.3	0.47	<0.0001

FOLFIRINOX vs. Gemcitabine

Selected grade 3 and 4 toxicities

	F	G	P value
Neutropenia	45.7%	21%	<0.001
Febrile neutropenia	5.4%	1.2%	0.03
G-CSF usage	42.5%	5.3%	
Thrombocytopenia	9.1%	3.6%	0.04
↑ ALT	7.3%	20.8%	<0.001
Diarrhea	12.7%	1.8%	<0.001
Fatigue	23.6%	17.8%	NS
Neuropathy	9%	0%	<0.001
Vomiting	14.5%	8.3%	NS
Alopecia (grade 2)	32.5%	3%	0.0001

There is a clinically meaningful difference in time to definitive deterioration in QOL (EORTC QLQ-C30)



Gourgou-Bourgade, *JCO* 2013

FOLFIRINOX in context

- Significantly improves median OS
  - 11.1 vs. 6.8 mo, HR 0.57, p<0.0001
- Significantly improves PFS
  - 6.4 vs. 3.3 mo HR 0.47, p<0.0001
- Yields a meaningful delay in worsening of QOL
- Is cost-effective
- Is more toxic:
  - 46% gr ¾ neutropenia, 5% febrile neutropenia
  - Vigilant patient selection, education, monitoring are essential
- Impact of routine dose modifications unclear
- No biomarker identified to date

The MPACT Trial

861 patients

- Stage IV
- No prior treatment for metastatic disease
- KPS ≥ 70
- Measurable disease
- Total bilirubin ≤ ULN

nab-Paclitaxel
125 mg/m² IV qw 3/4

Gemcitabine
1000 mg/m² IV QW 3/4

1:1, stratified by KPS, region, liver metastasis

Gemcitabine
1000 mg/m² IV QW 7/8
then QW 3/4

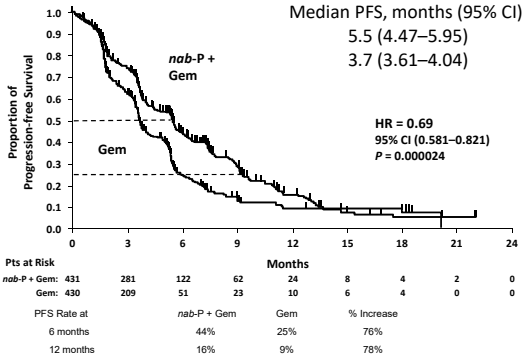
Primary endpoint:
Overall survival

151 sites
enrolled 861 patients
on 3 continents
over 3 years

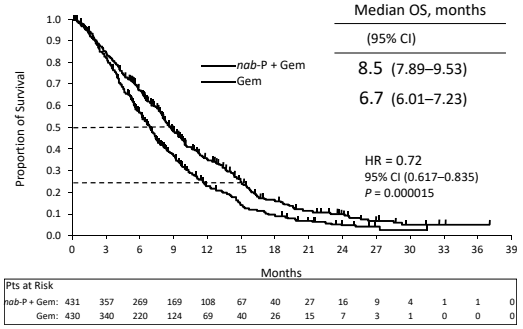
- 608 events, 90% power to detect OS; HR = 0.769 (2-sided α = 0.049)
- Treat until progression
- CT scans Q8 wks
- PET scan subset: baseline, wks 8, 16
- CA19-9: at baseline and Q8 wks

von Hoff, *ASCO* 2013, *NEJM* 2013

Progression-free survival



Overall survival



Efficacy: *nab*-Paclitaxel-Gemcitabine vs. Gemcitabine

	nab-G	G	HR
Patients	431	430	
Objective Response	23%	7%	
Stable disease	25%	26%	
Disease control (PR+SD)	48%	33%	
Median survival (mo)	8.5	6.7	0.72
1-year survival	35%	22%	
18-month survival	16%	9%	
24-month survival	9%	4%	
PFS (mo)	5.5	3.7	0.69
Median treatment duration (mo)	3.9	2.7	

Toxicity: *nab*-Paclitaxel-Gemcitabine vs. Gemcitabine

	Nab-G	G
Neutropenia	38%	27%
Febrile neutropenia	3%	1%
Thrombocytopenia	13%	9%
Anemia	13%	12%
Diarrhea	6%	1%
Fatigue	17%	7%
Neuropathy	17%	<1%
G-CSF usage	26%	15%

The MPACT trial in context

1st randomized trial to demonstrate that a cytotoxic agent added to Gem prolongs survival in PC

nab-Paclitaxel + Gemcitabine

- Significantly improves OS
  - 8.5 vs. 6.7 mo, HR 0.72, *P* = 0.000015
- Significantly improves PFS
  - 5.5 vs. 3.7 mo, HR 0.69, *P* = 0.000024
- More grade ¾ toxicity:
  - Neutropenia 38%, neuropathy 17%, fatigue 17%
- QOL:
  - Not collected prospectively, Q-TWiST favorable
- Cost effectiveness: ?
- Biomarker: SPARC data negative

We're not accustomed to having good treatment choices in PC

FOLFIRINOX or Gemcitabine-nab-paclitaxel:

How do you decide which combination is best for which patient?

- By understanding the current data
  - And its limitations
- No biomarker can predict which patient will respond to a particular treatment
- No randomized trial compares these 2 regimens
  - Cross-trial comparisons can be problematic

How do these regimens compare?

FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine

Patient characteristics

	FFX			*nab*-G		
Centers	1 country			3 continents		
Patients	342			861		
Median age	61			62		
Age ≤75	100%			90%		
% Male	62%			57%		
Performance status	ECOG	0	37%	KPS	100	16%
		1	62%		90	42%
		2	0.6%		80	35%
					70	7%
Pancreatic head tumors	39%			44%		
Biliary stent	16%			19%		
Liver metastases	88%			85%		

How do these regimens compare?
FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine

Toxicity

	FFX	*nab*-G
Neutropenia	46%	38%
Febrile neutropenia	5%	3%
Growth factor usage	43%	26%
Thrombocytopenia	9%	13%
Diarrhea	13%	6%
Fatigue	24%	17%
Neuropathy	9%	17%

How do these regimens compare?
FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine

Efficacy: Control Arms are Similar

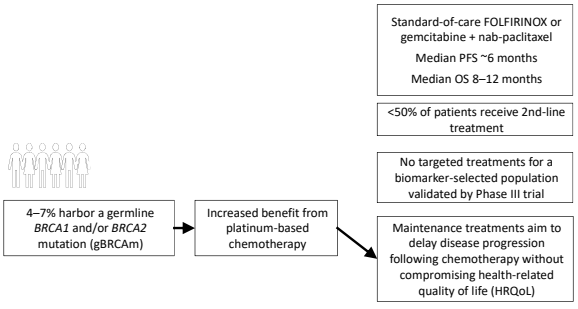
	FFX	*nab*-G
	Gemcitabine arm	
Patients	171	430
Objective Response	9%	7%
Disease control (PR+SD)	51%	33%
Median survival (mo)	6.8	6.7
1-year survival	21%	22%
18-month survival	6%	9%
PFS (mo)	3.3	3.7

How do these regimens compare?
FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine

Efficacy: Experimental arms

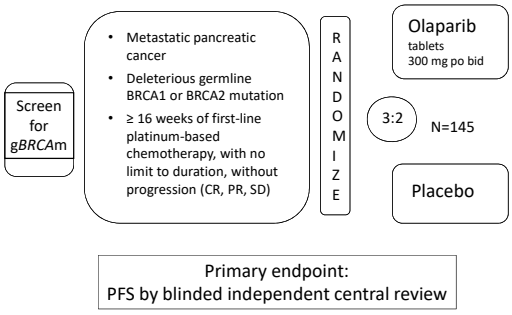
	FFX	*nab*-G
Patients	342	861
Objective Response	32%	23%
Disease control (PR+SD)	70%	48%
Median survival (mo) (HR)	11.1 (0.57)	8.5 (0.72)
1-year survival	48.4%	35%
PFS (mo) (HR)	6.4 (0.47)	5.5 (0.69)
QOL better than gem?	Yes	?
More cost-effective than gem?	Yes	?

Olaparib as maintenance treatment following first-line platinum-based chemotherapy in patients with a germline BRCA mutation and metastatic PC: POLO trial

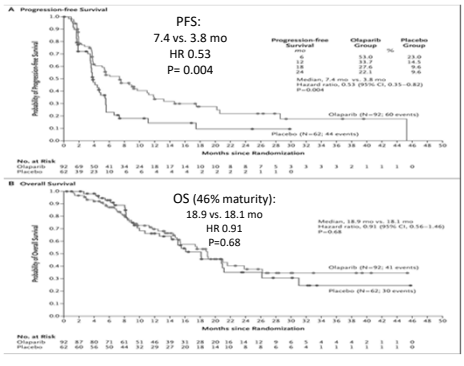


Golan, *NEJM* 2019

POLO Study design

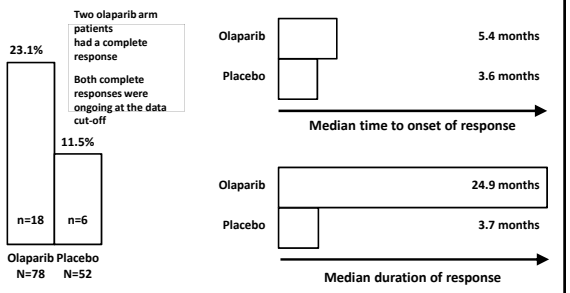


POLO: PFS and OS



Golan, *NEJM* 2019

Objective response in patients with measurable disease by blinded independent central review



POLO: Conclusions

- Maintenance olaparib provided a statistically significant and clinically meaningful improvement in PFS to patients with a g*BRCA*m and metastatic PC whose disease had not progressed during platinum-based chemotherapy
  - Interim OS data (at 46% maturity) showed no difference between arms. Final OS results will be evaluated at 69% data maturity
- Maintenance olaparib was well tolerated, with an AE profile similar to that seen in other tumor types
- HRQoL was preserved with olaparib treatment and showed no difference between arms
- These results are the first from a Phase III trial to validate a targeted treatment in a biomarker-selected population of PC patients, highlighting the importance of g*BRCA*m testing in this setting
- Maintenance olaparib was FDA-approved for g*BRCA*m PC in December 2019

Pembrolizumab in MSI tumors

- Pembrolizumab was approved for a tissue agnostic indication in mismatch repair deficient (MMR-D) solid tumors
- In PC, MMR-D is rare
  - Frequency is 0.8% (7/833)[1]
- Pivotal trial of pembrolizumab in MMR-D solid tumors[2]:
  - 8 PC patients
  - 2CR, 3PR, 1 SD

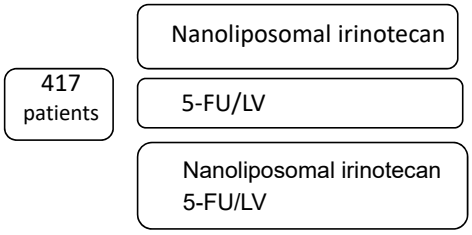
1. Hu, *CCR* 2018, 2. Le , *Science* 2017

Second-line treatment options in PC

Depending on the front-line regimen, options include:

- Gemcitabine
- Gemcitabine-*nab*-paclitaxel
- FOLFOX, FOLFIRI
- FOLFIRINOX
- 5-FU/LV-nanoliposomal irinotecan

Nanoliposomal irinotecan in PC patients previously-treated with gemcitabine: NAPOLI-1



Wang-Gillam, *Lancet* 2016

NAPOLI-1 results

	NI	5-FU/LV	NI + 5-FU/LV
Patients	151	149	117
Objective Response	6%	1%	16%
PFS (mo)	2.7	1.5	3.1
Median survival (mo)	4.9	4.2	6.1
QOL	No difference between arms		

Systemic therapy for advanced PC: Where are we now?

- FOLFIRINOX
  - Improves RR, PFS, OS in good PS pts
  - More toxic: patient selection and monitoring essential
- Gemcitabine + *nab*-Paclitaxel
  - Improves RR, PFS, OS
  - Not as active as FOLFIRINOX, slightly less toxic
- Gemcitabine
  - Cornerstone of care for many years
  - Improves quality of life, modestly improves survival

Systemic therapy for advanced PC: Where are we now?

- Gemcitabine + erlotinib
  - Marginally improves survival
- Nanoliposomal irinotecan + 5-FU/LV
  - Improves survival over 5-FU/LV alone
  - Is it any better than FOLFIRI?
- Maintenance Olaparib
  - Improves PFS in g*BRCA*m PC
- Pembrolizumab
  - Substantial activity in MMR-D tumors (<1% of PC)

Supportive care: Pain in advanced PC

- Occurs in >50-70% of PC pts
- Severe, epigastric, radiates to back
- Etiology:
  - Direct tumor invasion into nociceptors in pancreatic bed
  - Destruction of pancreatic tissue causing inflammation
- Mediated via celiac plexus

Wiebe, *Oncology* 2009

Supportive care: Celiac plexus neurolysis (CPN)

3 equivalent approaches:

- Percutaneous
- Endoscopic
- Surgical

In a 98 pt randomized trial, early CPN via EUS was superior to narcotics alone:

- Improved pain scores
- Trend to lower morphine use at 3 months

Most common CPN side effects:

- Diarrhea, hypotension, nausea, hemorrhage

Wiebe, *ASCO Ed Book* 2012 Wyse, *JCO* 2011

Trousseau's syndrome: Migratory superficial thrombophlebitis

- Associated with mucinous adenocarcinomas
- Not specific for pancreatic cancer

- Pro-coagulant-induced
- Relatively unresponsive to coumadin
- Manage with heparin

Many symptoms affect the nutritional status of PC patients

- Malignant gastroparesis (50%)
  - Slow gastric emptying w/o anatomic obstruction
  - From tumor infiltration of autonomic nerves or a para-neoplastic effect
  - Causes N/V, early satiety, weight loss, functional ileus
  - Treat with metoclopramide
- Gastric outlet obstruction (15%)
  - Stents are effective in most pts
- Small bowel obstruction
- Ascites
- Pancreatic endocrine insufficiency
  - > 50% of PC pts are diagnosed with DM or impaired glucose tolerance in the preceding 24 months

Wiebe, *Oncology* 2009

Pancreatic exocrine insufficiency:

A poorly recognized cause of malnutrition in PC pts

- Etiology:
  - Tumor blocks production and secretion of lipase
  - Inadequate delivery of lipase into gut
- Incidence:
  - 1 year post-pancreatectomy: >55%
  - Unresected head of pancreas tumors: >80%
- Symptoms:
  - Bloating, cramping, gas, pain when ingesting fatty foods
  - Frequent or loose stools
  - Frank steatorrhea occurs quite late

Wiebe, *ASCO Ed Book* 2012; Dominguez-Munoz, *Gastroenterol & Hepatol* 2011; Halloran, *Pancreatol* 2011

Pancreatic exocrine insufficiency: Management

- Empiric pancreatic enzyme replacement:
  - Start with 40-50K IU lipase per meal, half that with snacks
  - Low fat diet is <u>not</u> necessary
    - Results in insufficient intake of fat soluble vitamins
- Gastric acid inactivates lipase
  - Don't take on an empty stomach
    - Take <u>with</u>, not <u>before</u> meals!
  - Use with PPI or H2 blockade

Wiebe, *ASCO Ed Book* 2012; Dominguez-Munoz, *Gastroenterol & Hepatol* 2011

Pancreatic cancer: Conclusions

- Pancreatic cancer has the briefest survival of any solid tumor
- Genuine progress has recently been made for both metastatic and resectable patients who have a good performance status
- For so many other PC patients, our current treatments still have minimal impact on the natural history of this devastating disease

64

Mesothelioma

Hedy Lee Kindler, MD

August 19, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

64 – Mesothelioma

Hedy Lee Kindler, MD

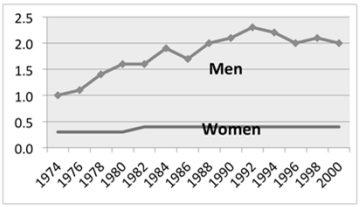
Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

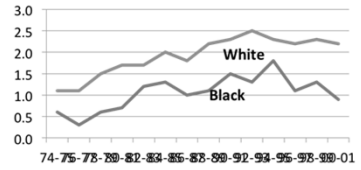
- N/A

Epidemiology of Mesothelioma

- Incidence:
  - 2,500-3,000 cases year in the US
  - 5,000 cases per year in Western Europe
  - An emerging problem in the developing world
- Onset 20 to 60 years following asbestos exposure
- Incidence has peaked:
  - US in 2000; Europe in 2018
- Male: female ratio 4:1
- In the US, a disease of the elderly
  - Median age is 74; 72% are > 65
- Less common in African-Americans



Mesothelioma incidence per 100,000 by GENDER



Mesothelioma incidence per 100,000 by RACE

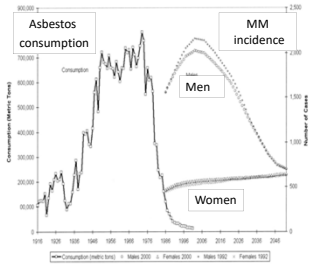
Etiology of Mesothelioma

Asbestos (70%)

- Occupational exposure
- Para-occupational exposure
  - Occurs in homes with an occupationally exposed worker
- Environmental exposure

Unknown (30%)

Relationship between asbestos consumption and MM incidence



20 to 50+ year latency following exposure

Asbestos, gender, and peritoneal MM

- In men
  - Asbestos causes ~60% of peritoneal mesothelioma
- In women
  - The attributable risk is lower[1]
- Prolonged, heavy asbestos exposure is more likely to cause peritoneal MM
  - In asbestos miners and insulators, the highest proportion of peritoneal MM occur in those with the greatest cumulative exposure[2]

1. Spirtas, *Occup Environ Med* 1994
2. Berry, *Br J Ca* 2012

What is asbestos?

- A general name for 6 types of naturally occurring minerals
- Key attributes:
  - High tensile strength, chemical/thermal stability, flexibility, low electrical conductivity, large surface area

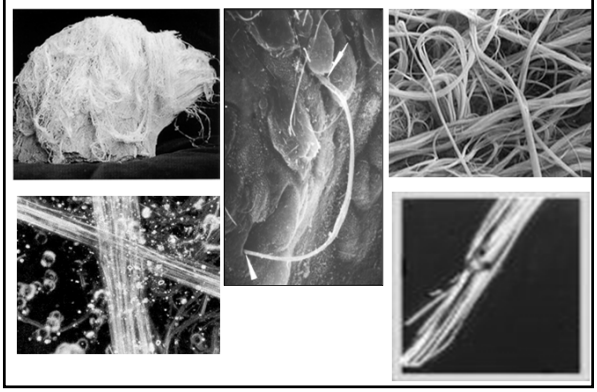
Serpentine Asbestos:

- Curly and pliable
  - Chrysotile

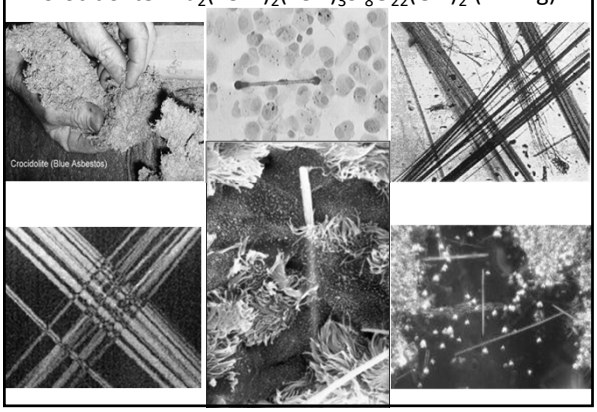
Amphibole Asbestos:

- Rod-like, less soluble in lung tissue
  - Actinolite, amosite, anthophyllite, crocidolite, tremolite

Chrysotile: $(Mg)_6\ (OH)_8Si_4O_{10}\ (\pm Fe)$



Crocidolite: $Na_2(Fe^{3+})_2(Fe^{2+})_3Si_8O_{22}(OH)_2\ (\pm\ Mg)$



Asbestos in History

Theophrastus, a student of Aristotle,
first described asbestos as:
'A substance resembling rotten wood that,
when doused with oil,
burns without being harmed'
On Stones, 300 B.C.E.

Asbestos: A brief history

- Embalmed bodies of Egyptian pharaohs were wrapped in asbestos cloth
- Pliny the Elder observed, "asbestos quarry slaves die young"
- Persians burned bodies in asbestos cloth to preserve the ashes
- 1890's: Rise of asbestos as a product
- 1900's: First asbestos-related diseases
- 1930's: Johns-Manville MDs document lung diseases in their workers
- 1960: Wagner observed a very high incidence of
- mesothelioma in S African asbestos workers
- 1964: Selikoff publishes study of asbestos workers with asbestosis, lung cancer and MM
- 1973: Peak consumption in US
- 2002: Last US mine closed

Asbestos in History

The causative relationship between asbestos and malignant mesothelioma was not recognized until 1960, when an unusually high incidence of the disease was noted in South African asbestos workers

Wagner, *Br J Ind Med* 1960

Occupational asbestos exposure

"Historical" asbestos occupations with ⇧ risk of MM

- Miners and millers
- Textile manufacturers
- Insulators
- Shipyard worker
- Construction
- "Secondary" or "bystander" occupations:
  - Carpenters, pipefitters, plumbers, electricians

Current: 1.3 million workers (OSHA estimate)

- Construction: abatement, demolition
- Janitors
- Brake and clutch repair (?)

In place asbestos exposure

Products (consumers/hobbyists and workers)

- Brake work: brake pads
- Construction and maintenance: paints, vinyl floor tiles, sheeting, adhesives, pipes, gaskets
- Asbestos protective equipment: fire-proof clothing for firemen, gloves for ceramics, stage curtains
- Appliances: hair dryers, broilers, toasters, cappuccino machines

Building-related (home, work and school)

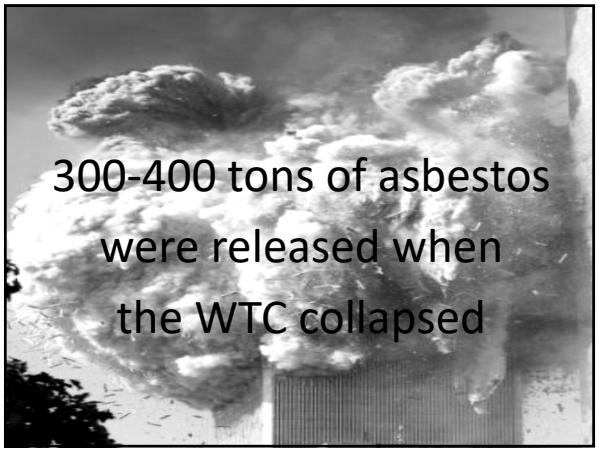
- Asbestos insulation, thermal pipes
- Schools and public buildings
  - EPA: ⅔ had damaged asbestos
  - Teachers rank high in occupations with MM cases

Building demolition/destruction

- WTC, Katrina

Asbestos and the World Trade Center

- Steel trusses supporting the twin towers were sprayed with hundreds of tons of asbestos-containing fire retardant
- The New York City Council banned further use of asbestos-containing sprays in 1971
- 39 floors of WTC 1 had already been sprayed; many products containing asbestos were used



Many WTC rescue workers had inadequate protection against asbestos

Asbestos and the EPA in 2019

- Contrary to common belief, asbestos has never been permanently banned in the US
- It is allowed in chemical manufacturing, gaskets, brake pads and brake linings
  - These uses were outlawed years ago in most other developed countries where asbestos was replaced by safer, economically viable alternatives.
- Under the current administration, the EPA released a new use rule for asbestos in 2019
  - This new rule creates loopholes that will permit continued and potentially expanded use of asbestos in the US

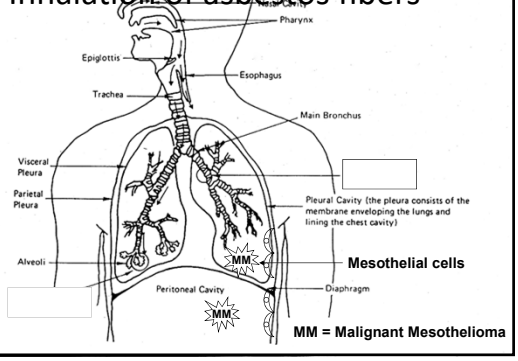
Landrigan, *NEJM* 2019

"A most reckless proposal"

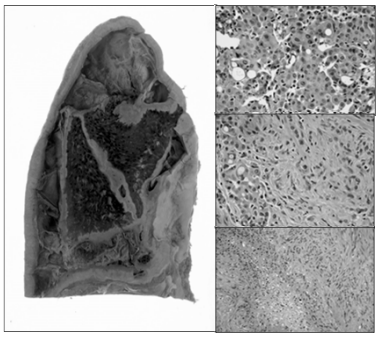
- The new rule:
  - permits continued use of asbestos in chemical manufacturing, gaskets, and brakes
  - allows asbestos mining to support such uses, which could lead to the reopening of domestic asbestos mines closed since 2002
  - permits continued importation of asbestos into the US
  - details a process whereby American industries can propose new uses of asbestos for review by EPA

Landrigan, *NEJM* 2019

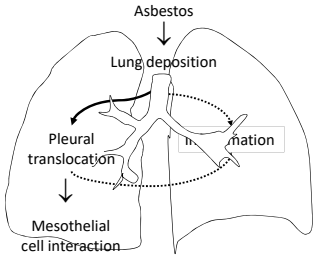
How do we get from this: Inhalation of asbestos fibers



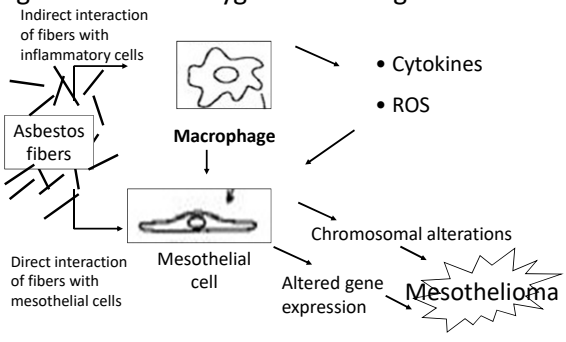
To this?



After inhalation, asbestos fibers trans-locate to the pleural space



Asbestos fibers cause persistent inflammation and cytokine production, and generate toxic oxygen and nitrogen radicals



Are there any other causes of mesothelioma?

50% of the people in 3 villages in Cappadocia, in Central Anatolia, Turkey, die of mesothelioma

The cemetery in Karain

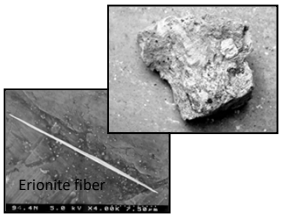
The Erionite Villages

Karain village (population ~ 600)

Tuzköy village (population ~ 1,400)

Like many other places in Cappodocia, these villages are characterised by ancient rock dwellings and caves dug in soft volcanic tuff

This was thought to be due to erionite in the houses. But nearby villages, built with stones from the same caves, had no mesotheliomas



Erionite is 300-800X more carcinogenic than chrysotile, and 100-500X more carcinogenic than crocidolite

Mesothelioma cases are clustered in specific homes, called 'the houses of death'

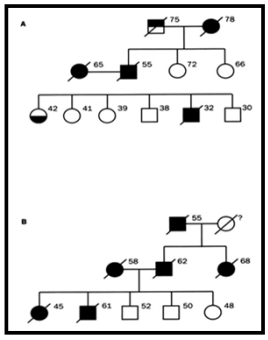
This is a house of the dead. Everyone died of mesothelioma

Next door, no one developed mesothelioma

There may be a genetic predisposition for mesothelioma

Analysis of a 6 generation pedigree of 526 individuals demonstrates autosomal dominant transmission of MM in these families

Hammady i-Roushdy, *Lancet* 2001



The search for a mesothelioma genetic susceptibility syndrome

- Only a small % of people heavily exposed to asbestos will develop MM (~5%)
- Yet MM clusters in some families
  - Is there a genetic predisposing factor?
- 2 US families studied:
  - No occupational asbestos exposure
  - Modest amounts of asbestos in their homes
  - Wisconsin family: 8 cancers, 5 MM
  - Louisiana family: 13 cancers, 7 MM

Testa, *Nature Genetics* 2011

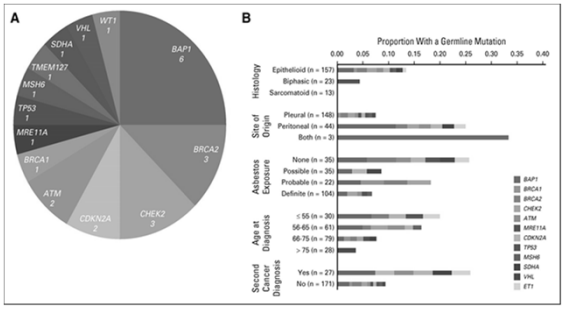
MM and the *BAP1* cancer syndrome

- These families have germline mutations in *BAP1*
  - BRCA1-associated protein
    - A tumor suppressor gene on 3p21
  - Predisposes to MM, uveal melanoma, cutaneous melanocytic tumors, RCC, and cholangiocarcinoma[1]
  - This is a gene-environment interaction
    - Mesothelioma is thought to predominate with asbestos exposure
- Somatic mutations of *BAP1*
  - Occur in 20-60% of MM[2]

1. Testa, *Nat Genetics* 2011 2. Bott, *Nat Genetics* 2011

12% of MM patients carry a germline mutation in a known cancer susceptibility gene

BAP1 accounts for only 25% of the mutations found



Panou, *JCO* 2018

Frequency of germline mutations in cancer susceptibility genes in MM

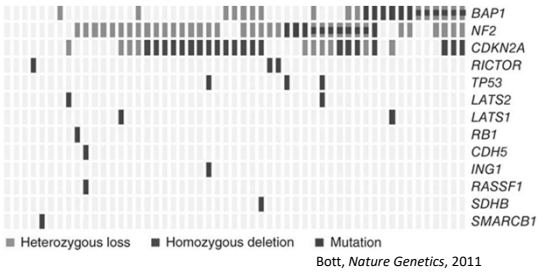
Specific clinical characteristics predict the presence of germline mutations:

- Peritoneal MM (25% had germline mutations)
- Minimal asbestos exposure
- Young age
- A 2nd cancer diagnosis

- These data:
  - Support clinical germline genetic testing for MM patients
  - Provide a rationale for additional investigation of the homologous recombination pathway in MM
    - PARP inhibitors are being evaluated in these patients

Panou, *JCO* 2018

The most common somatic genetic alterations in MM are tumor suppressors: BAP1, NF2, and CDKN2A



Bott, *Nature Genetics*, 2011

Does the SV-40 virus cause MM?

- DNA tumor virus
- Induces MM when injected into hamsters
- Mesothelial cells are very susceptible to SV40-mediated transformation[1]
- 60% of MM have SV-40-like DNA sequences
- 100% of MM patient sera have anti-Tag Ab[2]
  - Due to lab contamination of a related virus?
- 1955-63: polio vaccines made with SV-40 contaminated monkey kidney cells
  - Did SV-40 contamination cause an ↑ in MM?
  - Institute of Medicine: this cannot be determined

1. Bochetta, *PNAS* 2000 2. Carbone, *Oncogene* 1994

What is the relationship between cigarette smoking and mesothelioma?

SMOKING DOES NOT CAUSE MESOTHELIOMA!

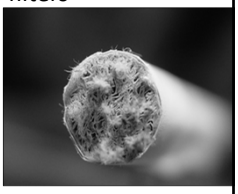
- Asbestos and smoking are synergistic for lung cancer, they are not synergistic for mesothelioma
- There is one exception, however…

"What is 'Micronite'? It's a pure, dust-free, completely harmless material that is so safe, so effective, it actually is used to help filter the air in hospital operating rooms."
Kent advertisement

Kent micronite cigarette filters

From 1952-56, Kent sold 11.7 billion cigarettes with "micronite" crocidolite filters

- 10 mg crocidolite per filter
- 80 billion asbestos fibers per filter
- In 1 year, a person smoking 1 ppd would inhale > 131 million crocidolite structures longer than 5 µm



Longo, *Cancer Research* 1995

Uncommon Causes of MM

- Previous radiotherapy
  - –For Hodgkin disease, breast cancer, seminoma, etc
- Collapsotherapy
  - –The induction of artificial pneumothorax or pneumoperitoneum for treatment of tuberculosis

Mesothelioma disease sites

Pleural	~80%
Peritoneal	~20%
Pericardial	Rare
Tunica vaginalis	Rare

Clinical Presentation

Pleural
- chest pain
- dyspnea
- cough
- weight loss
- fever
- night sweats

Peritoneal
- increased abdominal girth
- abdominal pain
- constipation
- anorexia
- umbilical hernia

Clinical presentation

Pericardial
- death (70% diagnosed post-mortem)
- dyspnea
- fever
- night sweats
- CHF
- constructive pericarditis
- pericardial effusion +/- tamponade
- acute MI

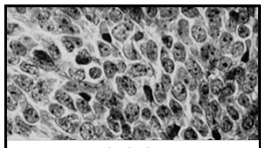
Tunica vaginalis
- unilateral testicular mass

Prognostic factors

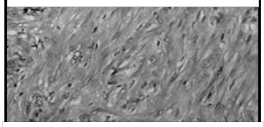
- stage
- pathologic subtype
- chest pain
- duration of symptoms
- age
- sex
- performance status
- weight loss
- platelet count
- WBC
- hemoglobin
- LDH

Pathology: The most important prognostic factor in MM

- Epithelial
  - 50-70% of MM
  - Best prognosis
- Sarcomatoid
  - 7-20% of MM
  - Worst prognosis
- Biphasic/mixed
  - 20-35% of MM
  - Intermediate prognosis



Epithelial MM
Median survival 17 months



Sarcomatoid MM
Median survival 6 months

Diagnosis is challenging

Diagnosis of MM requires
- An experienced pathologist
- Panel of at least 2 + and 2 - IHC stains
  - Specific panel depends on differential dx
- Common positive markers:
  - Calretinin, D2-40, CK 5/6, WT-1
- Common negative markers:
  - MOC-31, Ber-EP4, B72.3, CEA, PAX8, TTF-1, CDX-2

Cytology is usually not helpful

Husain, *Arch Pathol Lab Med* 2013

Sensitivity of diagnostic methods

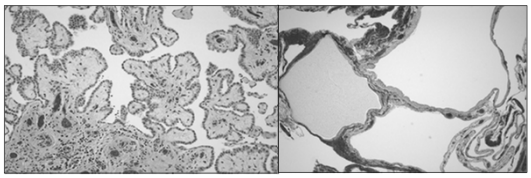
	% positive results
Fluid cytology	26%
Abrams needle biopsy	20.7%
Fluid cytology plus Abrams needle biopsy	38.7%
Thoracoscopy	98.4%

Boutin, *Cancer* 1993

Why do we call it "malignant" mesothelioma?

- Because there are several subtypes of benign (or borderline) mesothelioma

Well-differentiated papillary mesothelioma | Benign multicystic mesothelioma



2 pathologic subtypes of borderline malignant potential

Well-differentiated papillary mesothelioma (WDPM)

- Commonly presents as an asymptomatic incidental finding
- Often cured with resection alone

Benign multicystic mesothelioma (BMM)

- Consists of large grape-like cystic clusters
- Presents with an abdominal mass and abdominal pain, often in reproductive age women with a history of endometriosis

2 pathologic subtypes of borderline malignant potential

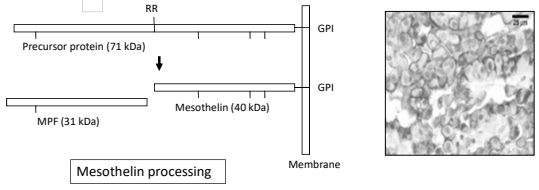
Both WDPM and BMM

- Much more common in the peritoneum
- Relatively indolent
- Occur principally in women
- Not attributable to asbestos
- Treated primarily with surgery
- Can be locally recurrent, especially BMM
- Rare transformation to malignant meso
  - For WDPM this may reflect initial misdiagnosis or sampling error

Biomarkers: Mesothelin

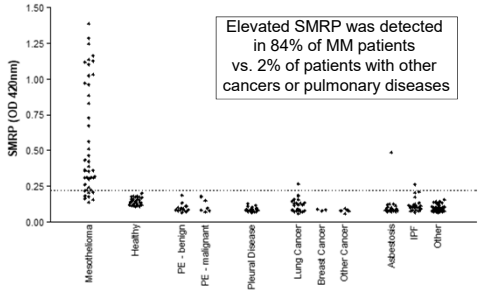
• A glycoprotein expressed on normal mesothelial cells of the pleura, pericardium and peritoneum

•Serum mesothelin-related protein (SMRP), the circulating product of mesothelin, is commercially available as MESOMARK



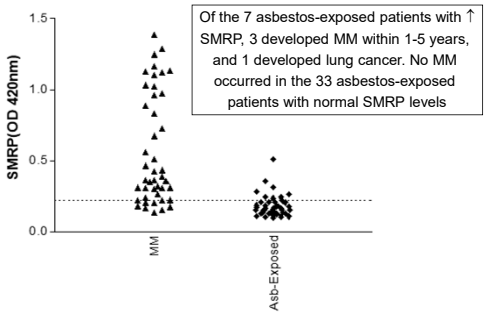
Hassan, *Clin Cancer Res*, 2004

SMRP is elevated in MM, but not in other pulmonary diseases



Robinson, *Lancet* 2003

SMRP is elevated in MM, and in asbestos-exposed individuals who subsequently develop MM



Robinson, *Lancet* 2003

Potential uses of SMRP

- Screening asbestos-exposed individuals
  - SMRP is elevated in asbestos-exposed individuals who subsequently develop MM
- Diagnosis
  - SMRP is ↑ in >60% of MM patients at presentation
- Determining prognosis
  - High SMRP levels are a poor prognostic factor
- Monitoring recurrence and treatment response
  - SMRP decreases following surgical resection and rises as the disease progresses
- Key Limitation
  - SMRP is only useful in epithelial MM

Other biomarkers for MM

Both are glycoproteins that mediate cell-matrix interactions

Osteopontin

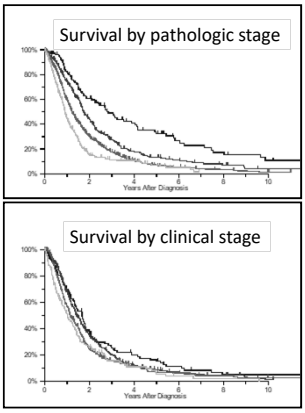
- ↑ in epithelial and sarcomatoid MM, as well as in other cancers, so less useful in discriminating MM from other diseases

Fibulin-3

- Significantly ↑ in plasma and effusions in MM pts compared with asbestos-exposed pts w/o MM
- Levels may correlate with MM prognosis
- May be useful in early detection

Staging in MM is problematic

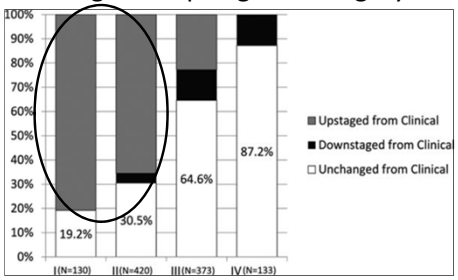
- There are numerous staging systems for pleural MM
  - All are surgically based
  - The IMIG/IASLC staging system is most widely used
- Some staging systems may predict survival in the resected patient
  - Most are imprecise in non-surgical patients
- Chemotherapy trials usually include patients with a range of stages, and prognoses



IMIG staging: Much better discrimination of survival by pathologic than clinical stage

This staging system is under revision

Most MM patients with an early clinical stage are upstaged at surgery



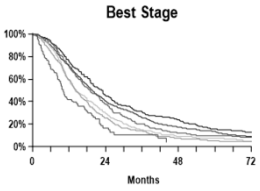
Differences between clinical and pathological staging in 1056 MM pts

Proposed new MPM stage groupings

	N0		N1/2 (new N1)		N3 (new N2)	
	v7	**v8**	**v7**	**v8**	**v7**	**v8**
T1	I (A,B)	**IA**	III	**II**	IV	**IIIB**
T2	II	**IB**	III	**II**	IV	**IIIB**
T3	II	**IB**	III	**IIIA**	IV	**IIIB**
T4	IV	**IIIB**	IV	**IIIB**	IV	**IIIB**
M1	IV	**IV**	IV	**IV**	IV	**IV**

Major changes:

- T1a, T1b consolidated into T1
- All ipsilateral LN now N1
- Contralateral, supraclavicular LN now N2



Rusch, *JTO* 2016

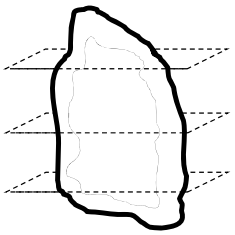
Mesothelioma is a difficult disease to measure reproducibly

- Bi-dimensional measurement is not usually feasible
- Uni-dimensional measurements of the pleural rind should be obtained at multiple areas in multiple levels on the thoracic CT scan

Measuring mesothelioma: Modified RECIST

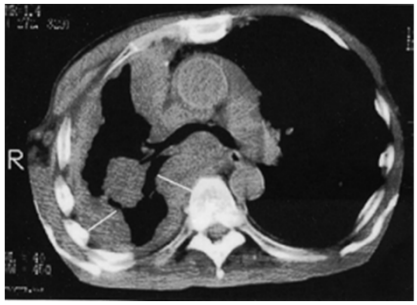
Select 3 CT sections per scan, at least 2 cm apart

2 thickness measurements per section



Byrne and Nowak, *Ann Oncol* 2004

Lesion measurement in mesothelioma



The role of surgery for MM is *very* controversial

- Surgery is rarely performed in some countries
  - In most of the US it is more widely accepted
- The goal is to remove all visible tumor
  - Surgery alone is not curative
- The optimal type of surgery is equally controversial
  - The decision is often driven more by surgeon bias than by data

Flores, *J Thor Cardiovasc Surg* 2008

The purpose of surgery for pleural MM

A maximal cytoreduction which is able to remove the disease down to levels which, at the end of the operation, hopefully leaves only microscopic residual disease and only minimal, or preferably no macroscopic disease

Surgical options for pleural MM

- Extrapleural Pneumonectomy (EPP):
  - En bloc resection of parietal, visceral pleura, ipsilateral lung, pericardium, diaphragm
- Extended P/D (E-P/D):
  - Parietal and visceral pleurectomy to remove all gross tumor, with resection of diaphragm and/or pericardium, the lung remains in place
- Pleurectomy/decortication (P/D):
  - Parietal and visceral pleurectomy to remove all gross tumor, without diaphragm or pericardial resection, the lung remains in place
- Partial pleurectomy (palliative):
  - Partial removal of parietal and/or visceral pleura for diagnosis or palliation, leaves gross tumor behind, the lung remains in place

Retrospective US analysis of 663 MM patients:
No statistical difference in survival by procedure at any individual tumor stage

	EPP	P/D
Operative mortality	7%	4%
Local recurrence	33%	65%
Distant recurrence	66%	35%
Overall Survival 14 months 5 year survival 12%		
Stage I	38 months	
Stage II	19 months	
Stage III	11 months	
Stage IV	7 months	

Flores, *J Thor Cardiovasc Surg* 2008

Requirements for surgical resection

Able to functionally tolerate maximal cytoreduction

- PFTs must predict adequate postop reserve
- Cardiology workup must include assessment of ventricular function

No disease outside ipsilateral hemithorax by "best practice" staging efforts

- PET-CT should be performed prior to surgery to rule out extra-thoracic disease
- Institutions vary in their staging approach, including mediastinoscopy, laparoscopy

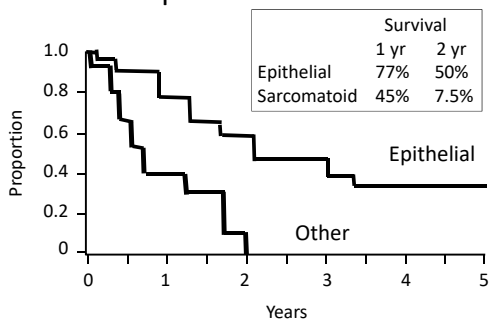
Prognostic indicators for surgical patients

Cox regression model of survival (n = 2,107)

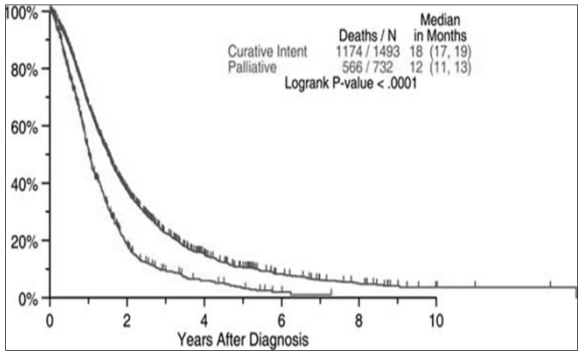
Variable	Hazard Ratio	p
II vs. I	1.16	0.1153
III vs. I	1.27	<0.0001
III vs. II	1.27	0.0002
IV vs. I	1.86	<0.0001
IV vs. III	1.26	0.0008
Other histology vs. epithelial	1.70	<0.0001
Male vs. Female	1.28	0.0002
Age, years 50-45 vs. <50	0.23	0.0058
65+ vs. <50	1.31	0.0006
65+ vs. 50-64	1.07	0.2500
Palliative vs. curative surgery	1.71	<0.0001

Rusch, *JTO* 2012

Survival by histology: Epithelial vs. other



Survival by surgical intent: Curative vs. palliative



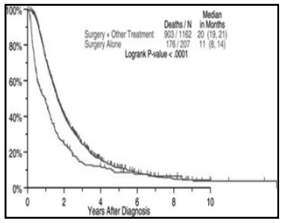
Prognostic indicators for surgical patients

Covariate	Hazard Ratio	95%CI	p
Tumor volume > 500 cm^3	2.02	1.18-3.47	0.0109
Anemia	1.99	1.19-3.33	0.0089
Adjuvant chemotherapy or radiotherapy	0.30	0.18-0.52	<0.0001

Gill, *AJR* 2012

Rationale for multimodality therapy in MM

- Maximal debulking surgery for MM rarely achieves a complete resection
- Retrospective IASLC database: longer survival with surgery + another treatment modality
  - Surgery alone:
    - 11 months
  - Surgery + another tx:
    - 20 months



Rusch, *JTO* 2012

No adequately powered randomized trials have been completed to evaluate this approach

Prospective multimodality trials in MM

N	Chemotherapy	Surgery	PFS (months)	Median survival (months)
19	Neo-adjuvant Gemcitabine/Cisplatin x 3	EPP	16.5	23
21	Neo-adjuvant Gemctabine/Cisplatin x 4	EPP	NR	19
61	Neo-adjuvant Gemcitabine/Cisplatin x 3	EPP	13.5	19.8
21	Neo-adjuvant Gemcitabine/Carboplatin x 3-4	EPP	16.3	25.5
77	Neo-adjuvant Pemetrexed/Cisplatin x 4	EPP	10.1	16.8
58	Neo-adjuvant Pemetrexed/Cisplatin x 3	EPP	13.9	18.4
35	Adjuvant Pemetrexed/Cisplatin x 3	P/D	15.8	30

The roles of radiation for MM

- Curative
  - Limited by tumor volume and normal tissue toxicity
- Palliative
  - 40-50 Gy effective for painful masses
- Prophylactic
  - 21 Gy in 3 fractions may prevent seeding from biopsy tracks (controversial)
- Adjuvant
  - Hemi-thoracic RT after EPP decreases local recurrence
  - Not generally feasible after P/D b/c pulmonary toxicity
  - IMRT after P/D is being evaluated in clinical trials
- Neo-Adjuvant
  - Pre-operative hemi-thoracic RT before EPP is highly experimental

Peritoneal MM outcomes: Past and present

- Historical series:
  - Untreated
    - Median survival ~6 months
- 1980s-90s:
  - Systemic chemotherapy or palliative surgery
    - Median survival <1 year
      - Range 9-15 months
- Contemporary series:
  - Aggressive locoregional treatment
    - Median survival approaches 5 years
      - Range 34-92 months

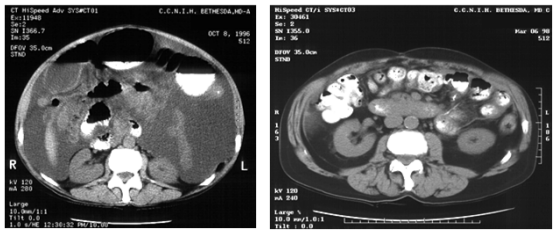
Rationale for aggressive loco-regional treatment of peritoneal MM

- Natural history
  - Remains confined to abdomino-pelvic cavity
  - Little invasion of underlying organs
  - No metastatic spread until advanced
- Aggressive loco-regional treatment is a preferred strategy
  - No level 1 evidence
  - Appears to improve survival over historical controls

Locoregional treatment for peritoneal mesothelioma

- Cytoreductive surgery (CRS)
  - Removes gross peritoneal disease
- Hyperthermic intraperitoneal chemotherapy (HIPEC)
  - Delivers high drug concentrations intra-operatively to microscopic residual tumor
  - Cisplatin, mitomycin, carboplatin, doxorubicin most commonly used
- Additional modalities may include
  - Early post-operative intraperitoneal chemotx (EPIC)
  - (Whole abdominal radiation)
  - Adjuvant or neo-adjuvant systemic chemotherapy

Most (~90%) of peritoneal MM patients obtain durable palliation of malignant ascites with CRS + HIPEC



Before CRS + HIPEC

18 months after CRS+ HIPEC

Determining extent of disease pre-operatively: The peritoneal cancer index (PCI)

PCI divides:

- Abdomen into a grid of 9 squares
- Small bowel mesentery into 4 quadrants

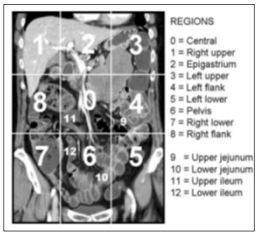
Tumor in each area is scored:

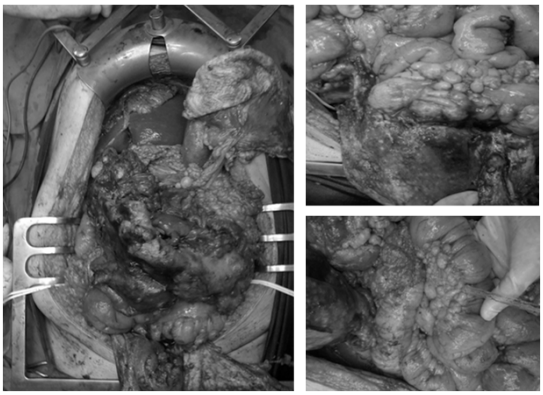
- Scale 0-3 (none to extensive)
- Up to a score of 39

PCI: a key prognostic indicator

Pre-op CT findings that predict adequate cytoreduction:

- No epigastric mass > 5 cm
- No loss of normal architecture of small bowel and its mesentery





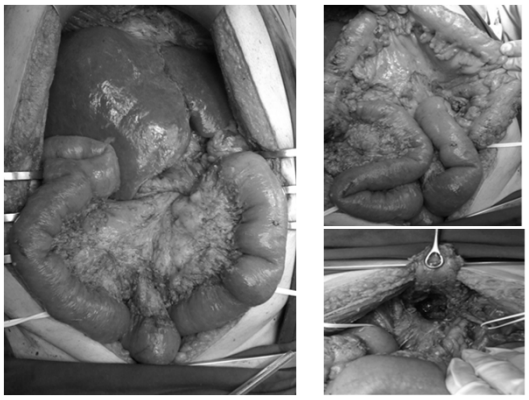
Courtesy of Marcello Deraco, Milan NCI

Determining the extent of disease post-op: Completeness of cytoreduction (CC) score

Quantifies residual disease after resection based on the size of the remaining tumor nodules

CC score	Size of remaining tumor nodules
CC-0	None
CC-1	< 2.5 mm
CC-2	2.5 mm-2.5 cm
CC-3	> 2.5 cm, or a confluence of tumor nodules at any site

The CC score is a key prognostic indicator for survival



Courtesy of Marcello Deraco, Milan NCI

Multivariate analysis of prognostic factors in peritoneal MM

Covariate	Significance
Gender	0.003
Pathological subtype	< 0.001
Completeness of cytoreduction	< 0.001

Proposed TNM Staging System Derived from Multi-institutional Registry

7 prognostic variables identified on univariate analysis from registry		
Age ≤ 50	Intrinsic	Not considered for preoperative staging
Female gender		
Epithelial subtype		
CC 0/1	Post-operative variable	
PCI 1-10	T	Useful for preoperative staging
No LN metastases	N	
No extra-abdominal metastases*	M	

T stage	PCI
T1	1-10
T2	11-20
T3	21-30
T4	31-39
N stage	0/1
M stage	0/1

Yan, *Cancer* 2011

*defined as penetrating the diaphragm or invading an abdominal wall scar

Proposed TNM System Stratifies Survival by Stage

Stage	TNM	Median survival (months)	1-year survival	5-year survival
I	T1 N0 M0	Not reached	94%	87%
II	T2-3 N0 M0	67	87%	53%
III	T4 or N1 or M1	26	66%	29%

Yan, *Cancer* 2011

Outcomes of CRS + HIPEC in Peritoneal MM

Center	Pts	Survival				Operative mortality (%)	Major morbidity (%)
		Overall (mo)	1-yr (%)	3-yr (%)	5-yr (%)		
Multi-institutional[1]	401	53	81	60	47	2.2	31
Milan[2]	83	44	78	56	50	2.4	28
DC[3]	62	79	84	58	50	2.9	27
Bethesda[4]	49	92	86	59	59	0	25

1. Yan 2009 2. Baratti 2010 3. Yan 2007 4. Feldman 2003

International MPeM Surgical Registry

Number of patients	405
Median age	50
Male	56%
Epithelial	79%
Mean PCI	20
CC 0/1	25%/21%
Mean surgical duration	8 hours
Median LOS	22 days
Peri-operative complications	46% (grade ¾ 31%)
Peri-operative mortality	2%
Median survival (range) Women Men	53 months (1-235) 119 months 36 months
3-year, 5-year survival	60%, 47%

Yan, *JCO* 2009

Pemetrexed + cisplatin

The benchmark regimen for mesothelioma

Single-blind, randomized phase III trial

456 patients

RANDOMIZE

Pemetrexed 500 mg/m^2
Cisplatin 75 mg/m^2 Q 21D

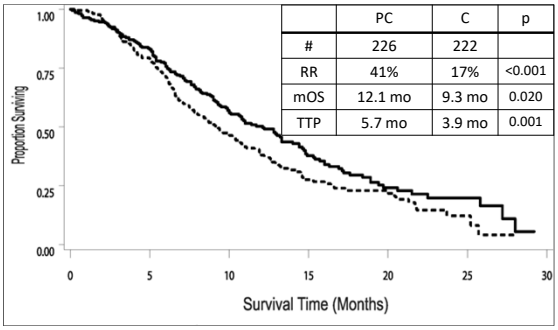
Primary endpoint: OS (HR 0.67)

Placebo
Cisplatin 75 mg/m^2 Q 21D

Pemetrexed is the only FDA-approved drug for MM

Vogelzang, *JCO* 2003

Pemetrexed + cisplatin: Results



	PC	C	p
#	226	222	
RR	41%	17%	<0.001
mOS	12.1 mo	9.3 mo	0.020
TTP	5.7 mo	3.9 mo	0.001

Vogelzang, *JCO* 2003

No drugs
have been approved
for mesothelioma
since this pivotal trial
was completed

Cisplatin or carboplatin?

Cisplatin is the regulatory standard

Carboplatin (AUC 5) + Pemetrexed

- Has similar activity
- Non-randomized data from Extended Access Database and single-arm phase II trials
- Commonly used in older patients

International Extended Access Program:
Similar outcomes when pemetrexed is combined with cis- or carboplatin

	Pemetrexed Cisplatin	Pemetrexed Carboplatin
Number of Patients	843	861
Response	26%	22%
Disease control rate	78%	76%
Time to progression	7.0 months	6.9 months
1 year survival	63%	64%
Grade ¾ neutropenia	24%	36%

No randomized trials compare these two regimens in MM patients

CALGB 30901: Is there a role for maintenance pemetrexed in MM?

63 pts

Pemetrexed
+
Cisplatin or Carboplatin
x 4-6 cycles

SD, PR or CR

RANDOMIZE

Pemetrexed until progression

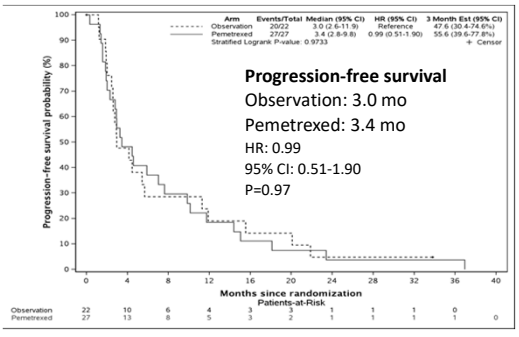
Stratification:
- Cisplatin vs. carboplatin
- Epithelial vs. other
- # cycles

Observation until progression

Primary endpoint: Progression-free survival

Dudek, *Clin Lung Ca* 2020

There is no role for maintenance pemetrexed in MM: CALGB 30901



Dudek, *Clin Lung Ca* 2020

The first positive randomized trial since pemetrexed was approved

MAPS: Open-label, randomized phase II/III trial of pemetrexed/cisplatin +/- bevacizumab

448 pts
Pleural MM
PS: 0-2
Chemo-naive
Age < 75

Pemetrexed
Cisplatin
Bevacizumab
x 6 cycles

Bevacizumab

Pemetrexed
Cisplatin

Surveillance

Primary endpoints:
Phase II: 6 mo PFS
Phase III: OS

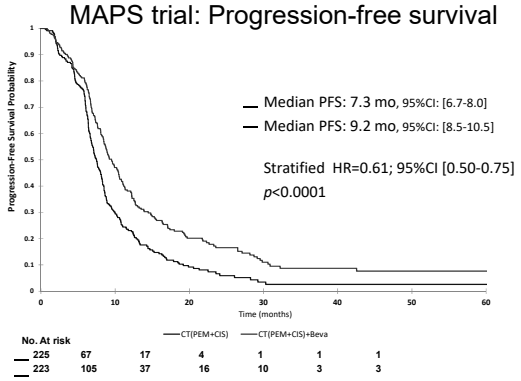
CT q 3 cycles—modified RECIST for MM

Stratification:
- Center
- Histology (epithelioid vs. non-epithelioid)
- PS (0-1 vs. 2)
- Smoking status

Zalcman, *Lancet* 2016

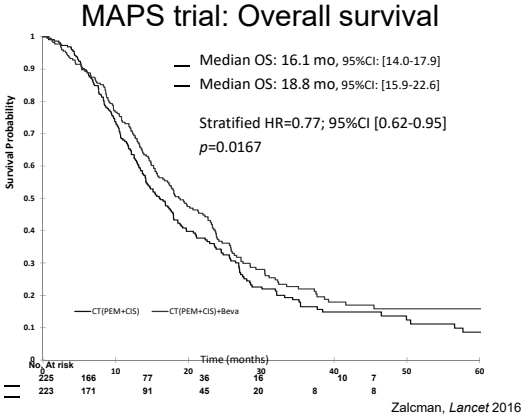
Statistics
Ph II: >25/50 non-PD at 6 mo to proceed to Ph III
Ph III: ↑median OS 13 to 17.3 mo, 3 yr OS 14.7 to 23.6%

MAPS trial: Progression-free survival



Zalcman, *Lancet 2016*

MAPS trial: Overall survival



Zalcman, *Lancet* 2016

MAPS: Results

	PC (N=225)	PCB (N=223)	HR
Response	Not reported		
PFS (mo)	7.3	9.2	HR 0.61
OS (mo)	16.1	18.8	HR 0.77
Grade ¾ toxicity	62%	71%	
Treatment discontinuation due to toxicity	6%	24%	P< 0.0001
QoL	No difference		

The MAPS trial in context

The addition of bevacizumab to pemetrexed + cisplatin:

- Significantly improves PFS
  - 7.3 vs. 9.2 mo, HR 0.61, p<0.0001
- Significantly improves OS
  - 16.1 vs. 18.8 mo HR 0.77, p=0.0167
- Yields an expected, manageable increase in toxicity
- Does not produce a detrimental effect on QOL
- Response: data not provided
- OS in the pem/cis control arm of MAPS was 4 months longer than in the pivotal Vogelzang trial (16.1 vs. 12.1 months)
  - Likely reflects patient selection for bevacizumab and the impact of subsequent pemetrexed/platinum retreatment

Do the results of the MAPS trial change the standard of care for mesothelioma?

- Though clearly a new treatment option, it is not a paradigm shift
- NCCN guidelines:
  - Pemetrexed/cisplatin/bevacizumab followed by maintenance bevacizumab is a first-line treatment option for patients with unresectable malignant pleural mesothelioma. This is a category 2A recommendation.
- Bevacizumab is not FDA-approved for mesothelioma

What about previously-treated MM?

No drugs are FDA-approved

Pemetrexed/platinum re-treatment:

- Durable disease control in pemetrexed-sensitive patients

Single-agent vinorelbine and gemcitabine:

- Widely used. Response rates are low, duration is brief

Immunotherapy:

- PD-L1 expression is common, higher in sarcomatoid histology, associated with worse prognosis independent of histology
- Tumor mutational burden is low
- NCCN guidelines include IO single-agent or combination therapy as 2nd/3rd- line treatment options
  - Based on multiple phase IB/II trials and the MAPS2 trial of nivo vs. nivo/ipi

RAMES: Randomized phase II study of gemcitabine with or without ramucirumab as 2nd-line treatment for MPM

N=164
- MPM with PD after platinum/pemetrexed 1st -line chemotherapy

Stratification:
- ECOG PS 0-1 vs. 2
- Age ≤ 70 vs. > 70
- Histologic subtype
- TTP

RANDOMIZE

Gemcitabine 1000 mg/m^2 **Placebo** D1, D8, Q 21 D

Gemcitabine 1000 mg/m^2 **Ramucirumab** 10 mg/kg D1, D8, Q 21 D

Primary endpoint: Overall survival

Pagano, *ASCO* 2020

RAMES: Results

		Gem-placebo	Gem-Ram	HR
N		81	80	
Survival	**Median overall**	**7.5 mo**	**13.8 mo**	**0.71**
	6-month	63.9%	74.7%	
	12-month	33.9%	56.5%	
	Epithelioid	8.8 mo	13.8 mo	
	Non-epithelioid	3.4 mo	13 mo	
	1st-line PFS ≤ 6 mo	11.5 mo	13.6 mo	
	1st-line PFS > 6 mo	7.1 mo	13.9 mo	
Progression-free survival (mo)		3.3 mo	6.2 mo	
Response rate		10%	6%	
Disease control rate		52%	73%	

Pagano, *ASCO* 2020

The standard of care for front-line systemic therapy of mesothelioma is about to change

CheckMate 743: Doublet IO vs. chemotherapy for previously-untreated MPM

N= 603

Key Eligibility criteria
- Unresectable pleural MM
- No prior systemic therapy
- PS 0-1

Stratification:
- Histology (Epithelioid vs. non-epithelioid)
- Gender

RANDOMIZE

Nivolumab 3 mg/kg Q 2 weeks **Ipilimumab** 1 mg/kg Q 6 wks x 2 years

Cisplatin or carboplatin + pemetrexed x 6 cycles

Primary endpoint: Overall survival

Secondary endpoints: ORR, DCR, and PFS by BICR
PD-L1[c] expression as a predictive biomarker

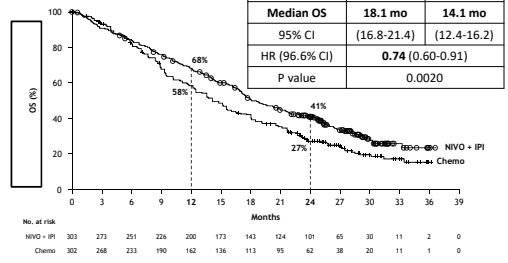
The DMC confirmed the primary endpoint of improved OS for NIVO + IPI vs chemo at the pre-specified interim analysis

Stats: To detect a HR of 0.72 with 90% power and 5% type-I error (2-sided)

Baas, WCLC 2020

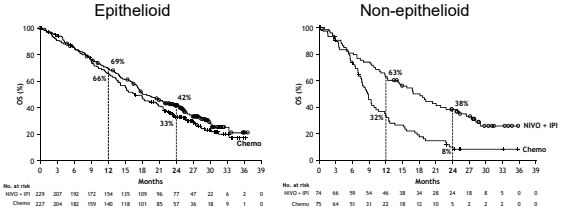
CheckMate 743: Overall survival

	Nivo-Ipi	Chemo
N	303	302
Median OS	**18.1 mo**	**14.1 mo**
95% CI	(16.8-21.4)	(12.4-16.2)
HR (96.6% CI)	**0.74** (0.60-0.91)	
P value	0.0020	



Baas, *WCLC* 2020

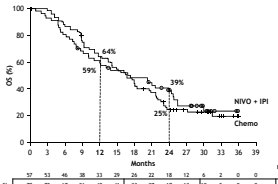
CheckMate 743 Overall survival by histology



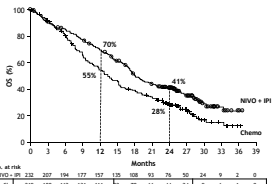
	Nivo-Ipi	Chemo		Nivo-Ipi	Chemo
N	229	227	N	74	75
Median OS (mo)	**18.7**	**16.5**	Median OS (mo)	**18.1**	**8.8**
(95% CI)	(16.9-22.0)	(14.9-20.5)	(95% CI)	(12.2-22.8)	(7.4-10.2)
HR (95% CI)	**0.86** (0.69-1.08)		HR (95% CI)	**0.46** (0.31-0.68)	

CheckMate 743
Overall survival by PD-L1 expression

PD-L1 < 1%



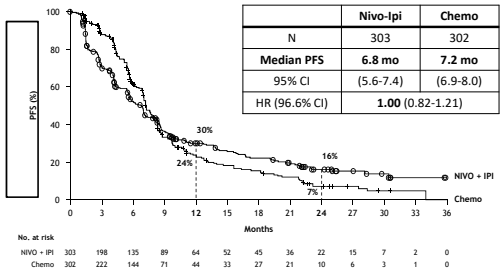
PD-L1 ≥ 1%



	Nivo-Ipi	Chemo
N	57	78
Median OS (mo)	**17.3**	**16.5**
(95% CI)	(10.1-24.3)	(13.4-20.5)
HR (95% CI)	**0.94** (0.62-1.40)	

	Nivo-Ipi	Chemo
N	232	219
Median OS (mo)	**18.0**	**13.3**
(95% CI)	(16.8-21.5)	(11.6-15.4)
HR (95% CI)	**0.69** (0.55-0.87)	

CheckMate 743:
Progression-free survival



	Nivo-Ipi	Chemo
N	303	302
Median PFS	**6.8 mo**	**7.2 mo**
95% CI	(5.6-7.4)	(6.9-8.0)
HR (96.6% CI)	**1.00** (0.82-1.21)	

CheckMate 743: Summary

		Nivo-Ipi	Chemo	HR
Survival	Median overall	18.1	14.1	0.74
	1-year	68%	58%	
	2-year	41%	27%	
Median overall survival	Epithelioid	18.7	16.5	0.86
	Non-epithelioid	18.1	8.8	0.46
	PD-L1 < 1%	17.3	16.5	0.94
	PD-L1 ≥ 1%	18.0	13.3	0.69
Progression-free survival (mo)		6.8	7.2	1.00
Response rate		40%	43%	
Duration of response (mo)		11.0	6.7	
Disease control rate		76.6%	85.1%	

CheckMate 743: Author's conclusions

- CheckMate 743 met its primary endpoint of statistically improved OS with NIVO + IPI vs. chemo at the pre-specified interim analysis
  - HR 0.74, *P* = 0.002; 2-year OS rates were 41% vs. 27%
- Survival benefit with NIVO + IPI vs. chemo was observed regardless of histology
- NIVO + IPI performed similarly in both histologies while chemo performed better in epithelioid histology, as expected
- PD-L1 data was descriptive in nature, precluding firm conclusions
- No new safety signals were observed
- This is the first positive randomized trial of dual immunotherapy in first-line treatment in MPM
- **NIVO+ IPI should be considered a new standard of care**

CheckMate 743 in Context

- Compared with pemetrexed/platinum, NIVO + IPI yields superior median, 1 and 2-year survival regardless of histology or PD-L1 expression
- CheckMate 743 clearly changes the standard of care for MPM patients with non-epithelioid histology
  - Median survival is dramatically improved: 18.1 vs. 8.8 mo, HR 0.46
  - Now, with doublet IO, epithelioid and non-epithelioid patients can achieve an equivalent survival of about 18 months
- For epithelioid histology and PD-L1 negative tumors, though NIVO + IPI is still favorable, the choice is less obvious
  - OS from NIVO + IPI is comparable to the bevacizumab arm of the MAPS trial (18.8 mo).
  - Would PCB have been a better control arm and a treatment option?
  - What is the role of chemoimmunotherapy?
- Further analyses are eagerly awaited

Moving treatment forward in MM: Key challenges

- MM is rare and regional
  - Trials can be challenging to accrue
  - Small market: less pharma and research funding
- Disease management fundamentals are unresolved
  - Controversy re: roles of surgery, RT, screening
  - Staging, radiologic measurement are problematic
  - New guidelines address some of these issues:
    - Staging (IASLC);[1-3] Imaging (mRECIST 1.1);[4] Diagnosis and treatment (ASCO)[5]

1. Nowak, *JTO* 2016 2. Rice, *JTO* 2016 3. Rusch, *JTO* 2016
4. Armato, *JTO* 2018 5. Kindler, *JCO* 2018

Mesothelioma: Where do we go from here?

- Prevention and screening
  - World-wide regulation of asbestos
  - Utilize current biomarkers, develop new ones
  - More thorough understanding of the role of germline mutations in the development of mesothelioma
- Systemic therapy
  - Pemetrexed has been the *only* FDA-approved drug since 2004
  - Combination IO is about to change the standard of care
- We are finally beginning to make progress against this terrible disease

65

Melanoma

F. Stephen Hodi, MD

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

65 – Melanoma

Stephen Hodi, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Advisory Committee/Board Member: Bristol-Myers Squibb, Merck
- Consultant: Sanofi, EMD Serono, Genentech and Novartis

Resolution

- Reviewed by peers and found to be unbiased.

Off-Label Usage

- Nivolumab, Ipilimumab, Pembrolizumab

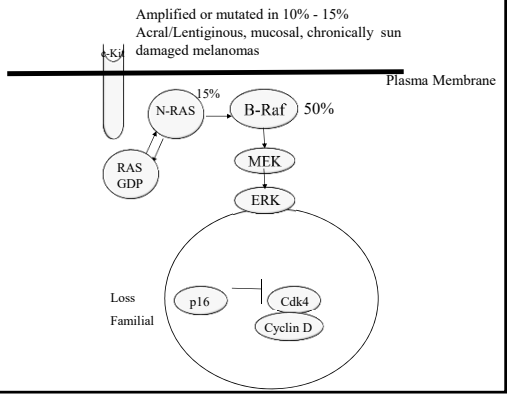
Epidemiology

- Incidence in US rising faster than any other cancer
- Approximately 60,000 new cases in US; 8,000 deaths
- Incidence varies by region
  - US: 15/100,000
  - New South Wales Australia: 1 in 20

Melanoma Risk Factors

- Outdoor leisure (RR 1-2)
- History of sunburn (RR 1.5-3)
- Intense intermittent sun (RR 2-3)
- Fair skin (RR 2-5), blonde or red hair (RR 1.5-5)
- Family History: 8-12%
- Five or more painful sunburns (RR 2-6)
- Sun Exposure
  - Degree and Intensity
  - Ultraviolet Radiation, especially UV-B (290-320 nm)

Molecular Changes

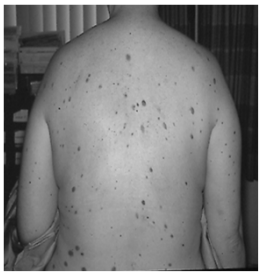


Clinical Features of Cutaneous Melanoma

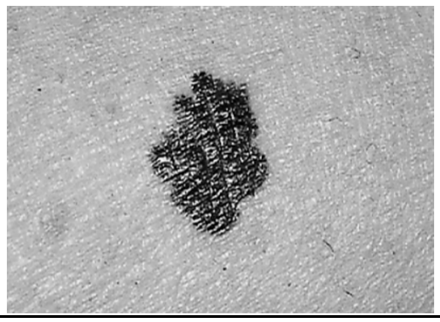
- A: Asymmetry
- B: Border
- C: Color
- D: Diameter

Any changing lesion

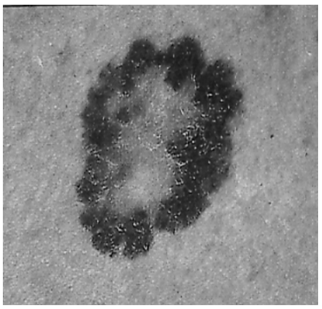
Dyplastic Nevus Syndrome



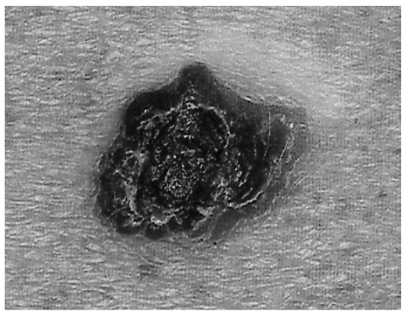
Superficial Spreading Melanoma



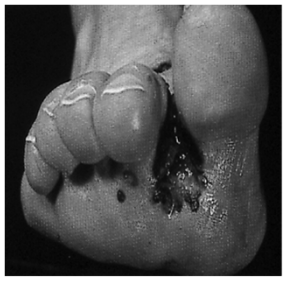
Spontaneous Regression in Primary Melanoma



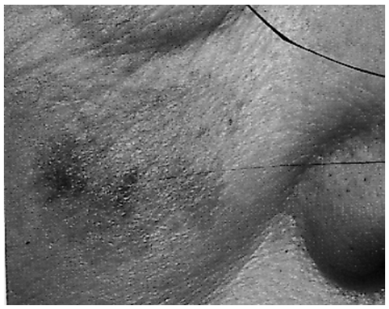
Nodular Melanoma



Acral Melanoma

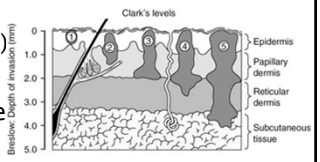


Lentigo Maligna Melanoma



Prognostic Features

- Thickness (mm)
- Ulceration
- Mitoses (per mm2)
- Anatomic location
- Histologic subtype
- LVI
- Microsatellites



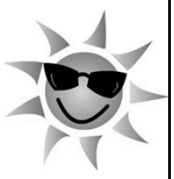
Sabiston Textbook of Surgery, 17th ed., 2004 Saund

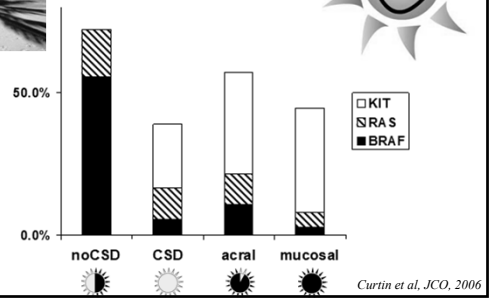
MAP/PI3: Genetic Variations

Correlation with Causative Factor

Sun Exposure

CSD–chronic sun damage





Curtin et al, JCO, 2006

Melanoma Surgical Margins

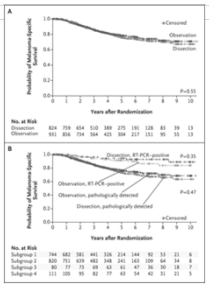
- *In situ:* 0.5 cm
- Primary <1.0 mm: 1 cm
- Primary >1.0 mm: 2 cm
- Anatomy must be taken into consideration for surgical margins, e.g. face
- Randomized trials have not shown a benefit for larger surgical procedures

Sentinel Lymph Node Sampling

- Indication: Melanoma > 1mm or melanoma < 1 mm with ulceration or Clark's level IV or V (20% will have positive SLN)
- No evidence that SLN improves survival
- Important prognostic indicator
- Requires surgical expertise for accurate results (sensitivity and specificity)
- Recommendation for completion lymphadenectomy has changed

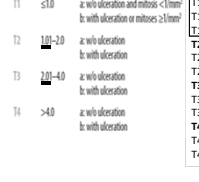
Morton et al NEJM, 2006

Completion Lymph Node Dissection Does Not Improve Survival in Patients with Positive Sentinel Lymph Node



Faries MB et al. N Engl J Med 2017;376:2211–2222.

AJCC 8th Edition T Categories



T Category	Thickness	Ulceration Status
TX (Primary tumor thickness cannot be assessed)		
T0 (No evidence of primary tumor)		
Tis (Melanoma *in situ*)		
T1	**≤1.0 mm**	**Unknown or unspecified**
T1a	<0.8 mm	Without ulceration
T1b	<0.8	With ulceration
T1b	≥0.8–1.0 mm	With or without ulceration
T2	**>1.0–2.0 mm**	**Unknown or unspecified**
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	**>2.0–4.0 mm**	**Unknown or unspecified**
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0	With ulceration
T4	**>4.0 mm**	**Unknown or unspecified**
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual, 8th Ed. 2017.

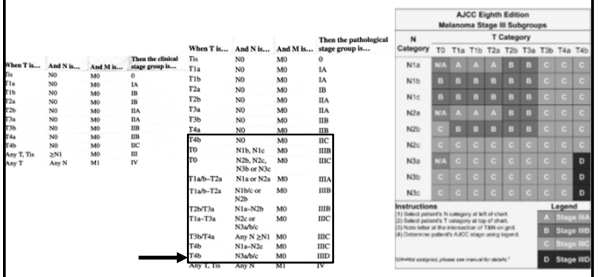
AJCC 8th Edition N Categories

N Category	Number of tumor-involved regional lymph node(s)	Presence of in-transit, satellite and/or microsatellite metastases
N0	No regional metastases detected	None
N1		
N1a	1 clinically occult (i.e., detected by SLN biopsy)	None
N1b	1 clinically detected	None
N1c	No regional lymph node disease	Yes
N2		
N2a	2–3 clinically occult (i.e., detected by SLN biopsy)	None
N2b	2–3, at least 1 of which clinically detected	None
N2c	1 clinically occult or clinically detected	Yes
N3		
N3a	4 or more clinically occult (i.e., detected by SLN biopsy)	None
N3b	4 or more, at least 1 of which clinically detected, or presence of any number of matted nodes	None
N3c	2 or more clinically occult or clinically detected	Yes

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual, 8th Ed. 2017.

Microsatellites, Satellite Metastases, and In-transit Metastases are now part of each N category

AJCC 8th Edition Clinical and Pathological Stage Groups



Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual, 8th Ed. 2017.

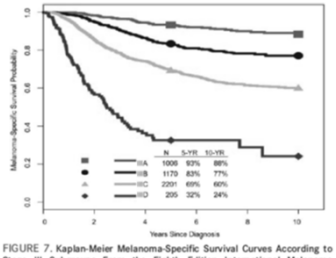


FIGURE 7. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage III Subgroups From the Eighth Edition International Melanoma Database.

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual, 8th Ed. 2017.

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual, 8th Ed. 2017.

M Category: Important Changes

- New fourth M category M1d: Distant metastasis to CNS
  - Poorest prognosis
  - Poor response to novel therapies
  - Exclusion from clinical trials
- Serum LDH levels are now part of each M category
  - Suffix (0) if normal
  - Suffix (1) if elevated
  - No suffix implies unknown

Gershenwald J et al. "Melanoma of the Skin". Chapter in AJCC Cancer Staging Manual, 8th Ed. 2017.

Staging work-up

Stage I/II

- CXR
  - Additional imaging if specific signs/symptoms
- CBC with diff, hepatic panel, LDH
- Full skin exam

Stage III/IV

- CT C/A/P or PET/CT whole body
  - Additional imaging if specific signs/symptoms
- Brain MRI with and without gadolinium
- CBC with diff, hepatic panel, LDH
- Full skin exam

Adjuvant Therapy

- High risk patients: thick primary melanomas $\geq$ 4mm or node positive disease; 25-75% chance of dying from melanoma
- Multiple chemotherapy trials
  - Overall not improve survival
- Multiple biologics investigated

Interferon

- High dose IFN -interferon alpha 2b
  - 20 MU/M2 IV induction, 5 days/week followed for 4 weeks
  - 10 MU/M2 sc three times per week for 11 months
  - 3 of 3 trials RFS benefit, 2 of 3 OS benefit, meta-analysis no OS benefit
- Pegylated IFN
  - Sylatron-FDA for stage III melanoma
  - Dose- 6 mcg/kg/wk SC for 8 doses, followed by 3 mcg/kg/wk for up to 5 years
  - 7.6 yrs follow-up: PEG-IFN sustained RFS benefit, but not OS
  - N1 patients had better benefit in RFS and trend OS
  - Ulcerated N1: benefit all endpoints
  - Prospective Trial EORTC 18081: PEG-IFN vs. Observation in ulcerated primary >1mm, 1000 pts.
- Careful patient selection
- Supportive measures key
  - Antipyretics
  - Nutritional and fluid support
  - Antidepressants
- Appropriate monitoring of patients and dose reduction for toxicity (LFTs and CBC)

Stage IV Melanoma

- Median Survival: 11 months
  - Wide Range: Dependent upon site(s) of disease, LDH
- Treatments:
  - Chemotherapy
  - Cytokines
  - Biochemotherapy
  - Vaccines/Immunotherapy
  - Targeted Small Molecules
  - Combinations

Single Agent Chemotherapy

- Dacarbazine (DTIC): approved single agent
  - RR 8-25%
  - CRs 2%
  - 31% durable
  - Temozolomide
- Nitrosoureas: BCNU, CCNU RR 12-17%
- Taxanes: RR15-20%
- Platinum compounds: RR 20%

LeJeune et al., Buzaid et al.

IL-2 in Melanoma

- 374 patients at NCI Surgery Branch
- 15.5% response rate (58/374)
- 5.1% CR, 10.4% PR
- Skin only metastases RR 53.6% (15/28)
- Skin and lymph node RR 32.5% (26/80)
- All other sites of disease RR 9.2% (32/348)
- Patient selection likely influences RR

Phan et al., JCO 2001

Combinations with Chemotherapy does not improve OS

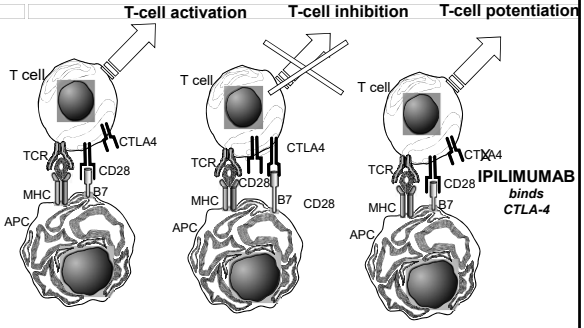
Regimen	RR	CR	Median Survival
DTIC	9.9%	0%	6.3 months
Dartmouth (CVD/Tam)	16.8%	0%	7.7 mos
P value		0.13	0.52

Chapman et al., JCO 1999

Chemotherapy vs. Biochemotherapy

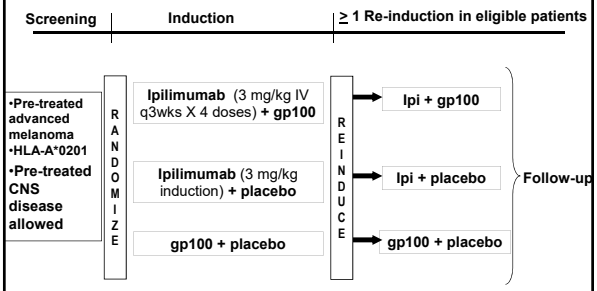
- Three randomized studies presented at ASCO 2003
- Varying chemo/biochemo doses and regimens
- Biochemotherapy better RR, more toxicity, no statistically significant difference in survival

Ipilimumab: Mechanism of Action

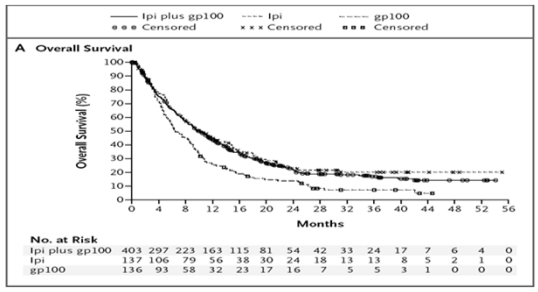


Phase II: 20-30% durable disease control

MDX010-20: Study Design



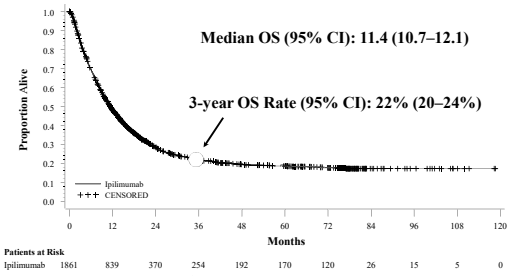
Hodi NEJM 2010



Survival Rate	Ipilimumab + gp100	Ipilimumab alone	gp100 alone
1-yr	44%	46%	25%
2-yr	22%	24%	14%

N ENGL J MED 363;8 NEJM.ORG AUGUST 19, 2010

Primary Analysis of Pooled OS Data: 1861 Patients



ECCO 2013

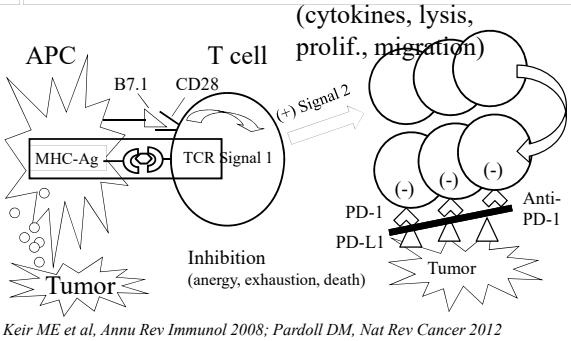
Ipilimumab

- FDA approved 2011
- Indication- stage IV melanoma or unresectable stage III melanoma.
- Approved dose- 3 mg/kg IV over 90 minutes q 3 weeks for a total a 4 doses
- Silent regarding maintenance, NCCN guidelines
- Reinduction; approximately 35% response

Ipilimumab
Assessment of response

- Conventional response criteria may not adequately assess the effect of immunotherapy
- Anti-tumor responses may be delayed and scans may show progression before response (immune mediated response criteria)

Role of PD-1 in Suppressing Antitumor Immunity



Keir ME et al, Annu Rev Immunol 2008; Pardoll DM, Nat Rev Cancer 2012

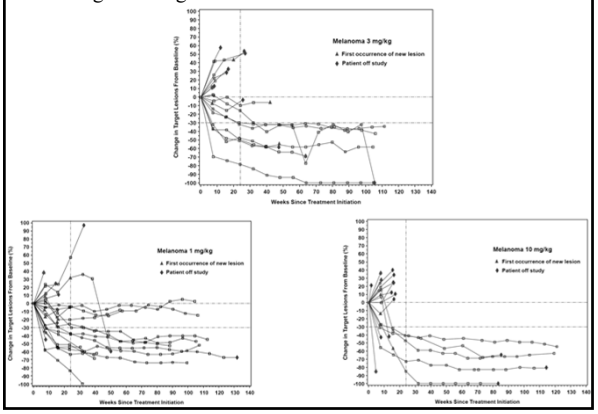
Nivolumab-Related Adverse Events

Drug-Related Adverse Event	All Grades		Grades 3-4	
	Tot Pop*	MEL	Tot Pop	MEL†
	No. (%) of Patients, All Doses			
Any adverse event	207 (70)	82 (79)	41 (14)	21 (20)
Fatigue	72 (24)	30 (29)	5 (2)	2 (2)
Rash	36 (12)	21 (20)	—	—
Diarrhea	33 (11)	18 (17)	3 (1)	2 (2)
Pruritus	28 (9)	15 (14)	1 (0.3)	—
Nausea	24 (8)	9 (9)	1 (0.3)	1 (1)
Appetite ↓	24 (8)	7 (7)	—	—
Hemoglobin ↓	19 (6)	7 (7)	1 (0.3)	1 (1)
Pyrexia	16 (5)	5 (5)	—	—

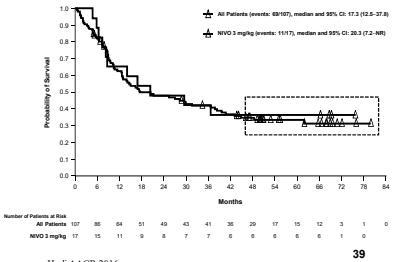
*AEs occurring in ≥5% of the total population.
†Common grade 3-4 AEs also included lymphopenia (3 pts) and abdominal pain and lipase increased (2 each). An additional 27 grade 3-4-related AEs were observed and one or more occurred in a single patient.

Topalian et al. NEJM 2012

Changes in Target Lesions Over Time in Melanoma Patients



Nivolumab Overall Survival at 5 Years of Follow-up



Hodi AACR 2016

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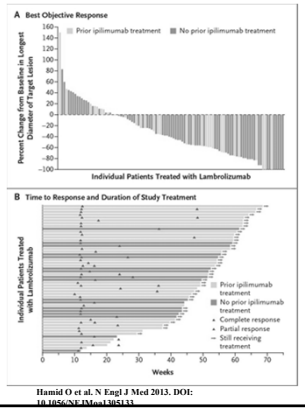
Antitumor Activity of MK-3475



Hamid O et al. N Engl J Med 2013. DOI: 10.1056/NEJMoa1305133

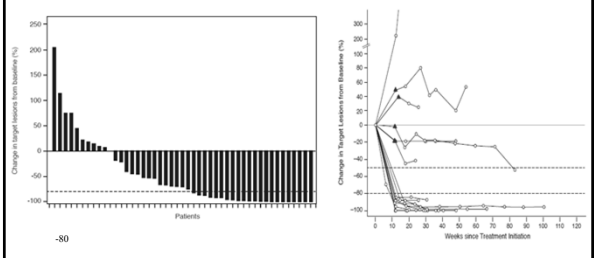
Immunotherapy: Toxicity = irAE

- Occur in approximately 60% of patients
- Grade 3/4 in approximately 10-15% of patients
- Any organ system can be involved
  - Gastrointestinal-enterocolitis, abdominal pain, diarrhea, bowel perforation (e.g. CTLA-4)
  - Pulmonary - pneumonitis (e.g. PD-1)
  - Endocrinopathy-thyroid (TSH before cycle), pituitary, adrenal insufficiency
  - Hepatitis-elevated AST or ALT or bililrubin
  - Dermatitis-rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis
  - Neurologic-neuropathy, Guillain-Barré
  - Other- ocular manifestations

Checkpoint Blockade
Treatment of immune adverse reactions

- ☐ Rule out infections or other etiologies
- ☐ Corticosteroids-
  - High grade: IV methylprednisolone
  - PO
  - Steroids tapered slowly over one month
  - Rarely need infliximab

Ipilimumab + Nivolumab Best Responses in All Evaluable Patients



-80

Wolchok et al. NEJM 2013

Treatment-Related Select Adverse Events Occurring in ≥1 Patient

Select Adverse Event	Concurrent Regimen All Cohorts (n=53)		Sequenced Regimen All Cohorts (n=33)	
Number of Patients (%)	All Gr	Gr 3–4	All Gr	Gr 3–4
Pulmonary	3 (6)	1 (2)	1 (3)	0
Renal	3 (6)	3 (6)	0	0
Endocrinopathies	7 (13)	1 (2)	3 (9)	2 (6)
Uveitis	3 (6)	2 (4)	0	0
Skin	37 (70)	2 (4)	8 (24)	0
Gastrointestinal	20 (38)	5 (9)	3 (9)	0
Hepatic	12 (23)	8 (15)	1 (3)	0
Infusion reaction	1 (2)	0	0	0
Lipase	10 (19)	7 (13)	4 (12)	2 (6)
Amylase	8 (15)	3 (6)	1 (3)	1 (3)

CA209-067: Study Design

CA209-067: Study Design

45

Randomized, double-blind, phase III study to compare NIVO+IPI or NIVO alone to IPI alone*

Unresectable or Metastatic Melanoma
- Previously untreated
- 945 patients

Randomize 1:1:1

Stratify by:
- *BRAF* mutation status
- AJCC M stage
- Tumor PD-L1 expression <5% vs ≥5%*

N=314: NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N=316: NIVO 3 mg/kg Q2W + IPI-matched placebo

N=315: IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

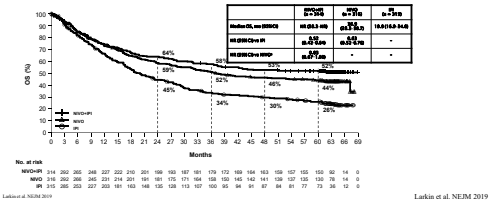
Treat until progression or unacceptable toxicity

Co- Primary endpoints: PFS and OS vs IPI
Secondary endpoints: ORR, NIVO vs NIVO+IPI (OS and PFS)*, Safety

Database lock: Sept 13, 2016 (median follow-up ~30 months in both NIVO-containing arms)

**The study was not powered for a comparison between NIVO and NIVO+IPI*

Checkmate 067: Randomized, Double-blind, Phase III Study to Compare NIVO+IPI or NIVO alone to IPI alone



Larkin et al. NEJM 2019

Larkin et al. NEJM 2019

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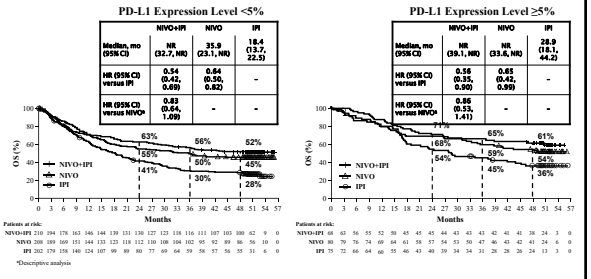
OS by Tumor PD-L1 Expression, 5% Cutoff



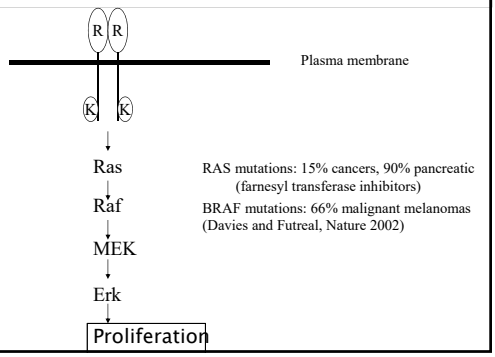
*Descriptive analysis

Hodi et al. Lancet Oncology 2018

Conclusions

- Blockade of the PD-1 pathway represents a new immune therapy for patients with melanoma
- Preliminary data correlating PD-L1 expression in pretreatment tumor biopsies with clinical outcomes will be further explored
- Pembrolizumab, Nivolumab, Nivolumab plus Ipilimumab approved
- NCCN recommendation PD-1 first line
- Combinations continue to be developed

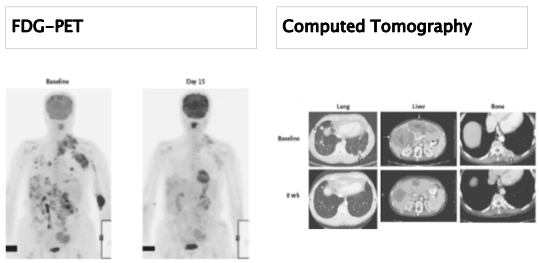
Downstream signaling events: The MAPK pathway



RAS mutations: 15% cancers, 90% pancreatic (farnesyl transferase inhibitors)

BRAF mutations: 66% malignant melanomas (Davies and Futreal, Nature 2002)

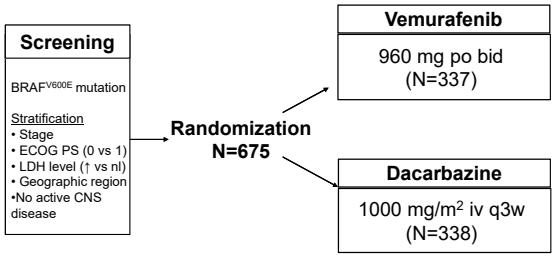
Vemurafenib: V600E BRAF Specific



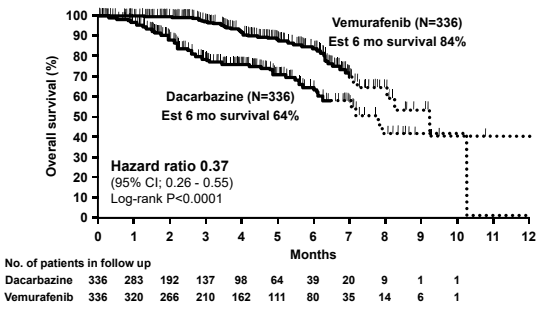
Vemurafenib

- ORR of 53%
- OS at 6 months 77% (95% CI: 70, 85)
  12 months 58% (95% CI: 49, 67)
- Median duration of response 6.7 months
- 960 mg BID is manageable, with most AEs being reversible with dose modification or interruption

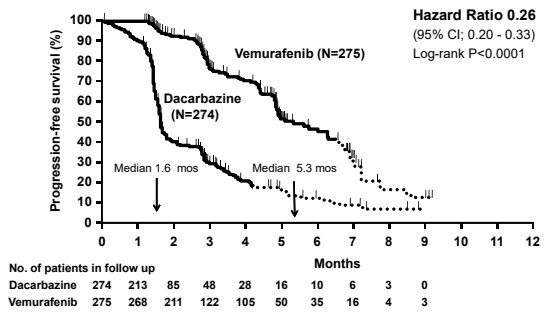
Phase III BRIM3 Study design



Overall survival (Dec 30, 2010 cutoff)



Progression-free survival (Dec 30, 2010 cutoff)

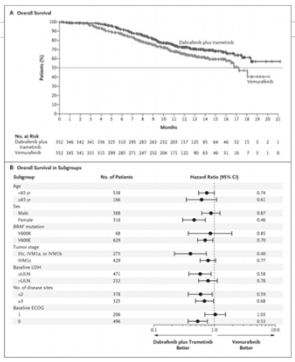


Selective B-Raf Inhibitors in Patients with Metastatic Melanoma: Safety

- Side effects:

Rash, arthritis, diarrhea, squamous cell skin cancer, pancreatitis keratoacanthoma, photosensitivity, LFTs, prolonged QTc. Visual changes.

BRAFi + MEKi: Overall Survival Improved Dabrafenib (BRAFi) + Trametinib (MEKi)

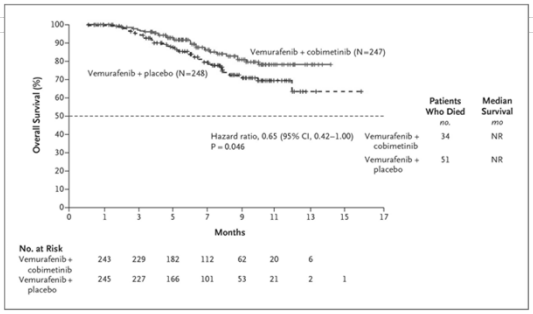


•Increased incidence of pyrexia

•Decreased incidence of skin manifestations of BRAFi

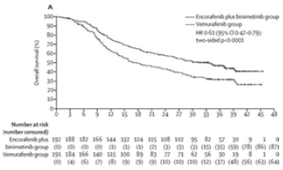
Robert C et al. N Engl J Med 2015;372:30-39.

Vemurafenib (BRAFi) + Cobimetinib (MEKi) Improves Survival



Larkin J et al. N Engl J Med 2014;371:1867-1876.

Encorafenib plus Binimetinib versus Vemurafenib (COLUMBUS):



Check CPK

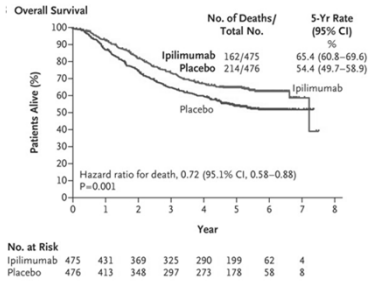
Dummer et al. Lancet Oncology 2018

Targeting BRAF Mutant Melanoma

- Selective BRAF inhibitors are a breakthrough for melanoma.
- Benefit seen in all subgroups and baseline characteristics
- Combination of BRAF and MEK inhibition improves survival
- Pyrexia and less skin toxicity with BRAFi + MEKi combination
- Not indicated for wild type BRAF
- Side effects: rash, arthritis, diarrhea, squamous cell skin cancer, keratoacanthoma, photosensitivity, LFTs, prolonged QTc

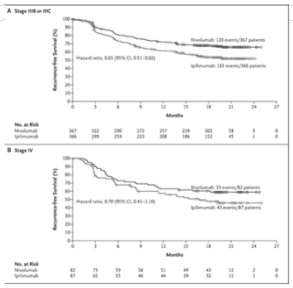
Does the benefit of immune and targeted therapies in the metastatic setting offer benefit for adjuvant patients?

Overall Survival



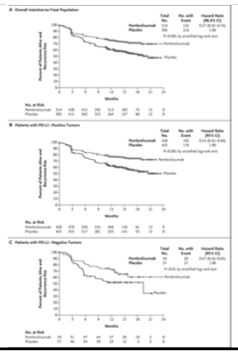
Eggermont et al NEJM 2016

Nivolumab vs. Ipilimumab
Recurrence-free Survival, According to Disease Stage.



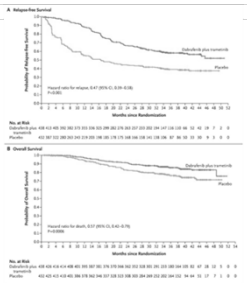
Weber J et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1709030

Pembrolizumab vs Placebo



Eggermont et al. NEJM 2018

Dabrafenib plus Trametinib
Relapse-free Survival and Overall Survival.



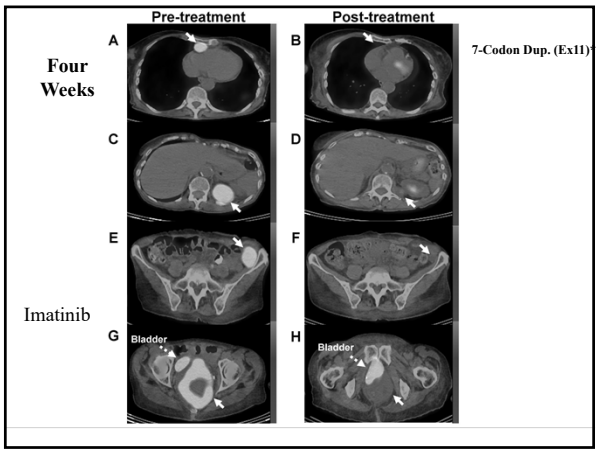
Long GV et al. N Engl J Med 2017. DOI: 10.1056/NEJMoa1708539

Treatment options for patients with Stage III melanoma

- Observation
- IFN
- Participation in a clinical trial
- Ipiluminab (anti-CTLA4) clinical trials
  - EORTC Ipilimumab vs. observation
  - ECOG study Ipilimumab vs. high dose IFN
- Nivolumab, Pembrolizumab
- Dabrafenib plus Trametinib

Mucosal and Acral Melanomas

- Clinical behavior different than cutaneous melanomas
  - Non Risk Factors for Cutaneous Melanomas
- Mucosal Melanoma
  - Vaginal, Anal, Sinus, Oropharynx
  - 400-600 Cases per year
- Acral (Non-Hair Containing Skin) Melanoma
  - Palms, Soles, and Nailbeds
  - 5% Melanomas
- 15-20% with KIT mutation and/or amplification



Imatinib in KIT Melanoma

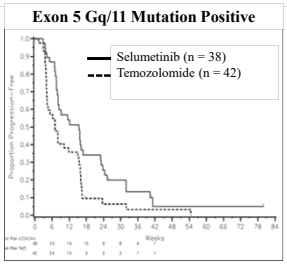
- Phase II studies
- 8-12% KIT mutational rate of tumors
- Mutation +/- amplification
- RR 24%
- TTP 3 months
- PFS 9 months for patients who experience SD/PR

Guo et al JCO 2011; Carvajal et al JAMA 2011; Hodi et al. JCO 2013

Ocular Melanoma

- Most common extra-cutaneous melanoma
- Most commonly involving choroid and ciliary body; conjuntival lesions are rare
- Recurrence over 5-10 years; surveillance not well defined
- Improving understanding of genetics (not BRAF)
  - In contrast to cutaneous lesions, 50% GNAQ mutations, 20% GNA11 mutations (G-coupled proteins)
- Local therapy: enucleation vs. external beam/radioactive rings

Ocular Melanoma: PFS is Improved with Selumetin (MEKi)



15.4 weeks (95% CI, 8.1 – 16.9) vs 7.0 weeks (95% CI, 4.3 – 11.9)

HR 0.55 (95% CI, .34 - .87)
p = 0.011

Carvajal *et al.*, JAMA 2014

Treatment for Stage IV Disease: *Summary*

- Immune modulation
  - CTLA-4 blockade
  - PD-1 blockade
  - Anti-CTLA-4 + anti-PD-1
- Improved genetic understanding
  - BRAFi + MEKi
  - KIT
- Combinatorial Approaches

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Carcinoid Tumors, Carcinoid Syndrome and Pancreatic Neuroendocrine Tumors

Diane Reidy, MD

August 20, 2020

Carcinoid Tumors, Carcinoid Syndrome and Pancreatic Neuroendocrine Tumors

Diane Reidy, MD

Thursday, August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

66 – Carcinoid Tumors, Carcinoid Syndrome and Pancreatic Neuroendocrine Tumors

Diane Reidy-Lagunes, MD, MS

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **None**

Agenda

- NETs and heterogenity
- Use of pathology and genetics to guide management
- Systemic therapy options in 2020
- A role for biomarkers to guide NET therapy (or lack thereof)
- "Legend" = important point

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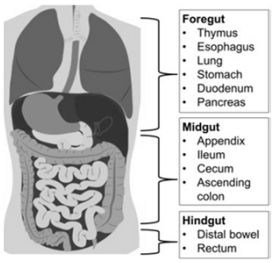
NET Pearls: Location matters!
Treatment and prognosis driven by where the tumor starts



Oronsky et al. (2017), *Neoplasia*

Pathology grading – most important prognostic tool but with problems

Uses differentiation status, cytologic grade

	Well-differentiated (NET)		Poorly-differentiated (NEC)
Tumor grade	1	2	3
Ki-67 index (%)	<3	3-20	>20
Mitotic count (per 10 HPF)	<2	2-20	>20

WHO, World Health Organization; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; HPF, high-power field

Kartalis et al. (2015), *Ann Gastroenterol*

WHO Classification of Pancreatic NE Neoplasms (2017)

Well differentiated NE tumor*

Grade	Mitoses	Ki-67 Index
G1	<2 / 10 HPF	<3%
G2	2-20 / 10 HPF	3-20%
G3**	>20 / 10 HPF	>20%

*Organoid architecture, "well differentiated" cytology, absence of non-neuroendocrine carcinoma components, may have components of G1 or G2, usually strong immunoexpression of general NE markers

**mitoses >20/10 HPF but usually <30/HPF; Ki 67 >20% but usually <55%

Poorly differentiated NE carcinoma*

Grade	Mitoses	Ki-67 Index
G3**	>20 / 10 HPF	>20%

*Small cell carcinoma and large cell NE carcinoma; less organoid architecture, classic cytology of small cell and large cell NE CA, absence of G1 or G2 NE components, may have non-neuroendocrine carcinoma components, less diffuse immunoexpression of general NE markers

**mitoses >20/10 HPF and usually >30/10 HPF; Ki67 >20% and usually >55%

Symptoms of Neuroendocrine Tumors

- 85% of tumors are non-functional!
- A nonfunctional tumor can become functional –always assess for new symptoms particularly at progression
- Hormone w/u driven by clinical symptoms
  - Midgut and Lung
    - Carcinoid syndrome –flushing and diarrhea (24 hour 5hiaa, serum 5hiaa)
  - Pancreatic NETs
    - VIP
    - Insulin, Proinsulin
    - Gastrin
    - Glucagon
    - ACTH
    - Carcinoid syndrome –flushing, diarrhea (rare)- 24 hour 5hiaa, serum 5hiaa

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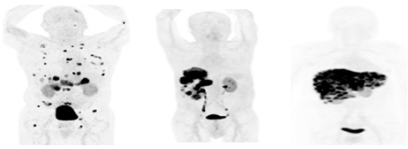
Diagnostic Work-Up

- Cross-sectional imaging (CT Triphasic or MRI)
- Functional Imaging x1 (Somatostatin scintigraphy –i.e. Octreotide scan or Ga68DOTATATE)
- Biopsy
- Biomarkers? Unlikely to help
- Role of EUS? Capsule Endoscopy? Yield is low

Evolving Diagnostic imaging GA68 DOTATATE



Ga 68 DOTATATE improved sensitivity compared to octreotide imaging

Radioactive diagnostic agent indicated for localization sst positive disease

Beware of comparing apples to oranges! Ga68 should not be compared to cross-sectional imaging to define extent of disease

Question 1

16 year-old boy has a resected 0.8 cm tumor of the appendix found incidentally at the time of acute appendicitis. Does any further work-up need to be done

A) Yes
B) No

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Answer: NO

- Review of 200 patients at MSK suggest there is no role for right hemicolectomy or any other imaging for carcinoid <1.0 cm
- NCCN recommendations tumors >2.0 cm should be considered for right hemicolectomy
- Tumors between 1-2 cm with meso-appendiceal involvement might have LN involvement; in our data set NO patients with carcinoid of the appendix recurred (even with LN Involvement)

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Question 2

75 year-old man has bilobar liver lesions and 3 cm RLQ mass in terminal ileum. The liver lesion is biopsied to be well differentiated low grade NET. He experiences flushing and diarrhea. He is started on octreotide LAR with improvement of his symptoms. He develops sudden onset acute n/v/abdominal pain and is found to be pSBO at the site of the primary tumor. What does the anesthesiologist have to worry about?

A) Cardiac history and risk for carcinoid heart
B) Carcinoid Crisis
C) Epinephrine surge and risk of hypertensive emergency
D) All of the above
E) none of the above
F) A+B

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Genetics: Sequencing of NETs

Mutations in well differentiated panNETs

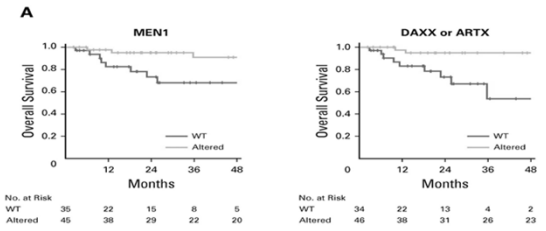
- Whole-exome sequencing → targeted sequencing
- Early stage (59%), metastatic (41%)
  - Chromatin remodeling genes (MEN1/DAXX/ATRX)
  - mTOR pathway (PTEN, TSC2)

*Better prognosis with MEN1 + DAXX/ATRX mutated status

Jiao et al. (2011), *Science*

Jiao et al Science, 2011

Next-generation sequencing of pancreatic NETs



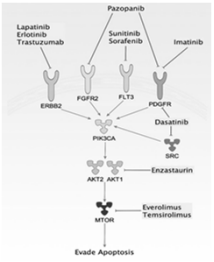
Raj et al. (2018), *JCO Precision Oncology*

Raj et al JCO PO, 2018

15

Exome sequencing in small intestine NETs (SI-NETs)

- 48 SI-NETs (70% G1, 30% G2)
- Integrated analysis: recurrent alterations (chromatin remodeling, DNA damage, apoptosis, RAS signaling, axon guidance)
- Most frequent alterations along mTOR pathway (33%)



Banck et al. (2013), *J Clin Invest*

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Multidisciplinary Treatment for Advanced NETs

Surgery

Nonsurgical Liver-Directed Therapy
- Embolization (+/- chemotherapy)

Medical Treatment
- SSAs
- IFN-α (carcinoid- toxic)
- Cytotoxic chemotherapy (pNET)
- Biologic targeted agents (pNET)
- PRRT (carcinoid)

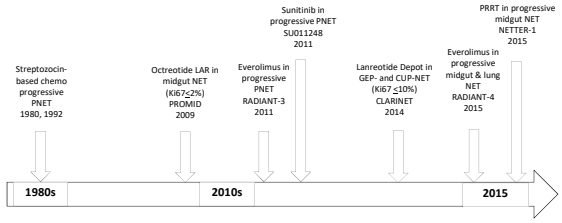
Role of Liver Directed Therapy

- Response rates similar across all embolization types (bland embolization, Y90 Radioembolization, Chemoembolization)
- No randomized controlled trials to know which is better
- Drug eluting beads have high rate of abscesses and bilomas
- Radioembolization for large bulky disease may be safer but could be risks with PRRT
- Largely dependent on the comfort level of Interventional Radiologist

Kennedy, et al American Journal of Clinical Oncology. 31(3):271-279, June 2008; Chamberlain et al Cancer, 2006; Gupta et al Cancer 2007

Systemic Treatment in Advanced NETs

NET therapy: Key Advances through Level 1 Evidence



Moertel et al. (1980), *N Engl J Med*; Moertel et al. (1992), *N Engl J Med*; Rinke et al. (2009), *J Clin Oncol*, Yao et al. (2011), *N Eng J Med*; Raymond et al. (2011), *N Eng J Med*; Caplan et al. (2014) *N Eng J Med*; Yao et al. (2016), *Lancet*; Strosberg et al. (2015), *ESMO Annual Meeting*

Systemic Treatment Options for Advanced NETs

Pancreatic NET	Extra-Pancreatic NETs
Lanreotide	Lanreotide, Octreotide – GI
Everolimus	Everolimus (non-functional GI, lung)
Sunitinib	^{177}Lu-Dotatate
Alkylating agents (streptozocin, temozolomide); platinum, 5FU	
^{177}Lu-Dotatate	

- Activity of sunitinib in pancreatic NET was established in patients without prior everolimus
- Activity of VEGF pathway inhibitors in advanced carcinoid tumors has not been established

Somatostatin Analogs

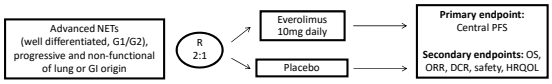
What we know

- No data to use a different somatostatin analog upon disease progression
- No data comparing octreotide and lanreotide
- No data to use beyond progression in nonfunctional patients

Presented by:

"Carcinoid" GI and Lung NETs: Targeted Trials

RADIANT-4



Yao et al. (2016), *Lancet*

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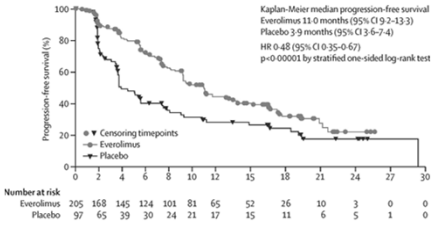
RADIANT-4 results: PFS (central review)



Yao et al. (2016), *Lancet*

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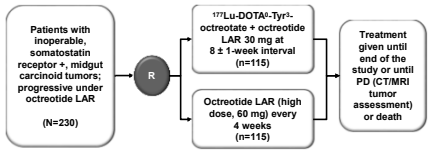
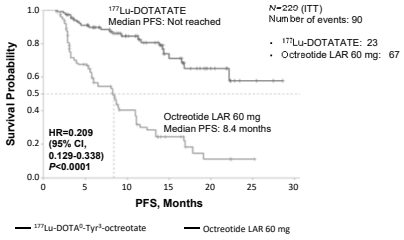
NETTER-1: Phase 3 Study Design
Role of PRRT



Primary Endpoint	Secondary Endpoints
PFS according to RECIST criteria (objective tumor response)	Safety and tolerability

A study comparing treatment with ^{177}Lu-DOTA^{0}-Tyr^{3}-octreotate to octreotide LAR in patients with inoperable, progressive, somatostatin receptor positive midgut carcinoid tumours (NETTER-1). ClinicalTrials.gov website. https://www.clinicaltrials.gov/ct2/show/NCT01578239?term=NETTER&rank=1. Accessed 10/2/2015.
Ruszniewski P, et al. ESMO. 2015 (abstr 6LBA).

NETTER-1 Study Results: Progression-Free Survival



Ruszniewski P, et al. ESMO. 2015 (abstr 6LBA).

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Side Effects Lu177-DOTATATE

- Nausea
- Lymphopenia
- Anemia
- Hair loss
- MDS/leukemia 1-2% risk

Strosberg et al NEJM 2017, Bodei et al, Eur J Nuc Med, 2014

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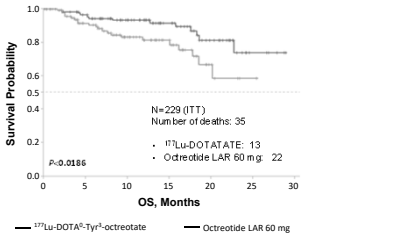
NETTER-1 Study Results: Interim OS Analysis



Ruszniewski P, et al. ESMO. 2015 (abstr 6LBA).

30

Carcinoid Syndrome

- Treat the disease!
  - Embolization and other systemic approaches
- Somatostatin Analogs

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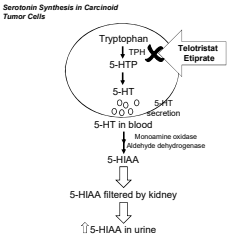
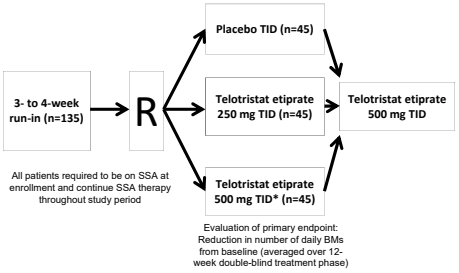
Telotristat Etiprate
A Tryptophan Hydroxylase (TPH) Inhibitor



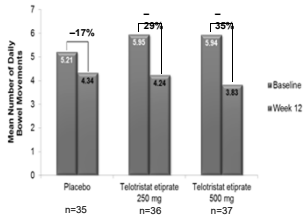
- Telotristat etiprate is a novel oral inhibitor of TPH, the rate-limiting enzyme in serotonin biosynthesis
- Two early-stage clinical studies of telotristat etiprate demonstrated a favorable safety profile and evidence of clinical activity in carcinoid syndrome
- Both preclinical and clinical studies suggested that telotristat etiprate is associated with minimal CNS activity

Study Design Phase III Telestar



TELESTAR: Reduction in Mean Daily Bowel Movement Frequency at Baseline and Week 12

All patients continue SSA therapy throughout study period. Data include only patients for whom both baseline and Week 12 assessments were available.



SSA, somatostatin analog.

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Pancreatic NETs:
Targeted and cytotoxic therapies

Summary

Parameter	Everolimus (RADIANT-3)	Sunitinib
No. of patients	410	171
	Low-intermediate grade	Low grade
Design	Phase III multicenter RCT	Phase III multicenter RCT
Intervention	10mg Everolimus QD	37.5mg Sunitinib QD
Control	Placebo	Placebo
Crossover	Yes	No
Primary outcome - PFS	**11 months vs. 4.6 months**	**11.4 months vs. 5.5 months**
Secondary - OS	NS	NS
CR/PR	5% vs 2%	9% vs 0%
SD	73% vs 51%	63% vs 60%

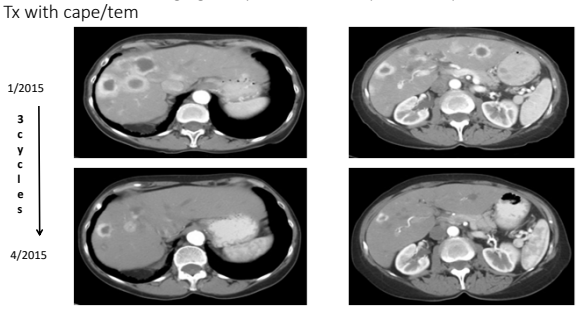
Raymond et al. (2011), *N Engl J Med*; Yao et al. (2011), *N Engl J Med*

Cytotoxic chemotherapy in pancreatic NETs

- Streptozocin – very toxic
- ECOG randomized phase II cape/tem versus tem alone > Capecitabine + temodar greater PFS 22.7 months versus 14 months temodar alone
- Platinum drugs-higher grade tumors
- Sequencing of therapy needs to be addressed

Kunz et al 2018 ASCO

Well differentiated, high grade pancreatic NET (Ki-67 30%)
Tx with cape/tem



Biomarkers to guide NET therapy

Biomarkers in NETs: What we know

- NCCN guidelines do not limit use of SSA to NETs that are SSTR positive
  - But it is likely that SSA treatment only benefits patients whose tumors harbor the SSTR
- To date, all studies have failed to identify a NET patient cohort more likely to benefit from everolimus
- SSTR expression on imaging studies predicts response to PRRT

Janson et al. (1994), *Eur J Endocrinol*; Mehta et al. (2015), *Medicine*; Qian et al. (2016), *Pancreas*; Zatelli et al. (2016), *Endocr Relat Cancer*

40

A word on poorly differentiated NEC

- Poorly differentiated NEC are treated with platinum- based therapy
- Platinum/etop or platinum/irinotecan are reasonable first line treatment options
- A PET DOTATATE is NOT HELPFUL as it should not drive management – even if positive, PRRT is ONLY approved for well differentiated NET and not NEC

Walenkamp et al Cancer Treat Rev. 2009;35(3); Cancer Sci. 2014 Sep;105(9):1176-81. Epub 2014 Sep 6.

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Conclusions

- Pathologic and molecular (genetics) features are important to characterize NET biology
- Through Level 1 evidence, treatment landscape is broadening
- Many therapies to consider that were not available 10 years ago
  - Role for biomarkers in NETs remains limited
- Takes a team approach!

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Esophageal Cancer

David Ilson, MD, PhD

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

67 – Esophageal Cancer

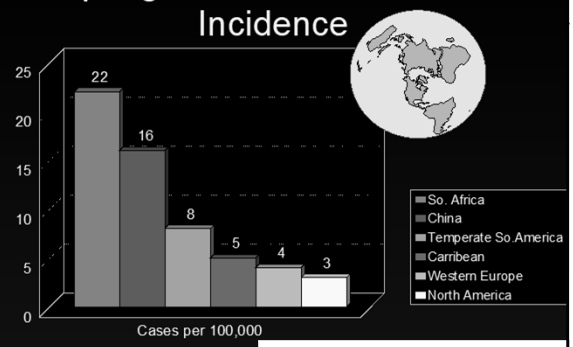
David H. Ilson, MD, PhD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Consulting: AMGEN, Bayer, Lilly, Pieris, Roche/Genentech, Astra Zeneca, Bristol Myers Squibb, Astellas, Merck, Taiho**

Esophageal Cancer: Worldwide Incidence



MSKCC dhi 1999

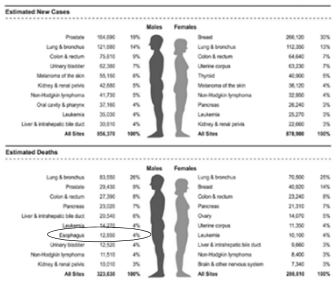
Sixth Leading Cancer Death

Esophageal Carcinoma US Incidence in 2020

- **18,440 cases**
- **Decline in Gastric Cancer Incidence**
- **Increase in Esophageal , GE JX, cardia adeno**
- **OS improvement, 1975-77, 1984-86, 1999-2006**
  - 5% ➔ 10% ➔ 19%

Siegel et al, CA 70: 7-30; 2020

Esophagus Cancer, U.S., 2018



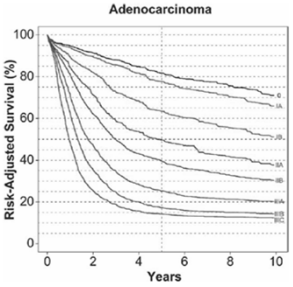
7th Cause of Cancer Death in Men

Siegel et al, CA 68: 7; 2018

Gastric and Esophageal Cancer: AJCC 7 Staging

Gastric	Esophageal Adeno
T1a: lamina propria/ musc mucosa	**T1a: intramucosal**
T1b: submucosal	**T1b: submucosal**
T2: muscle	**T2: muscle**
T3: transmural to adventitia	**T3: transmural / adventitia**
T4a: into serosa / peritoneum (old T3)	**T4a: pleura**
T4b: into adjacent organ	**T4b: aorta**
N1: 1-2nodes	**N1: 1-2 nodes**
N2: 3-6 nodes	**N2: 3-6 nodes**
N3a: 7-15 nodes	**N3: 7+ nodes**
N3b: 16+ nodes	**M1: distant metastases**
M1: distant metastases	**Stage IAB: T1-2N0 (grade)**
Stage I: T1N0-1, T2N0	**Stage IIAB: T3N0,T1-2N1,T2N0 (gr)**
Stage II: T3N0, T2N1, T1N2,	**Stage IIIAB: T3N1-2, T4aN0, T1-2N2**
Stage III: T3N1-2, T4N0, T2N2	**Stage IIIC: N3, T4aN1-2, T4b**
Stage IV: T4N1, M1	**Stage IV: M1**

AJCC 7 Staging: Survival in over 4600 pts with esophageal and GEJ cancer



T2-T3 or N+

Rice Cancer 2010

Esophageal Cancer Epidemiology

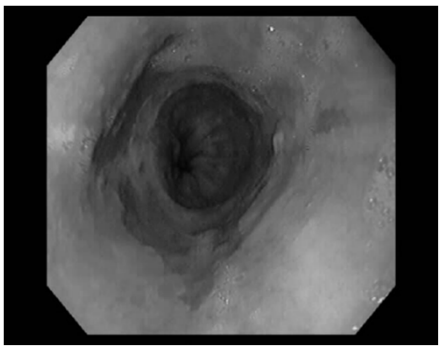
- **Squamous Cancer**
  - Alcohol , tobacco abuse
  - Lye Ingestion
  - Achalasia
- **Esophageal Webs (Plummer Vinson Syndrome)**
- **Tylosis**: autosomal dominant ➔ 17q
- Fanconi Anemia, Bloom Syndrome
- **Micronutrient Deficiency (China):**
  - Lowest serum selenium: highest risk of esophageal or gastric cancer

Blot JNCI 85: 1483; 1993

Esophageal Cancer Epidemiology

- **Adenocarcinoma**
  - Reflux
  - Barrett's esophagus
  - Obesity, Tobacco Abuse
  - Familial Barrett's Esophagus
    - No validated candidate genes

Barrett's Esophagus: Endoscopic Appearance



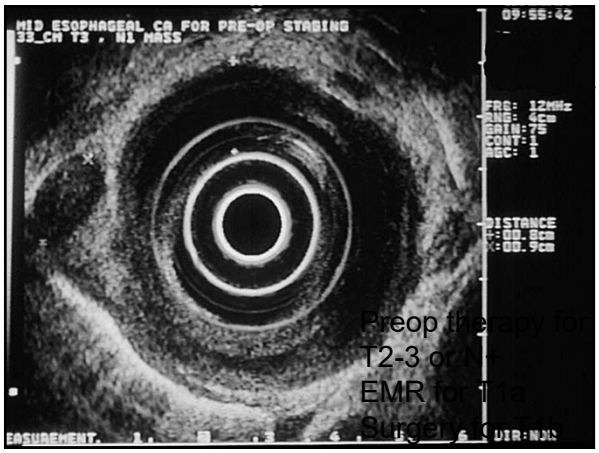
Esophageal Cancer Epidemiology

- **Barrett's Esophagus**
  - Squamous epithelium replaced with intestinal columnar epithelium
  - Found in 10% of endoscopies for GERD
    - Prevalence 1.6%
  - 1-2% risk of adenoca over 10 yrs
  - Screening EGD every 2 years
- **Surgery for High Grade Dysplasia**
  - Old teaching
    - 10% per year risk of cancer
    - 30% coincident cancer
  - PDT in medically inoperable patients
  - RFA emerging as a therapy alternative to surgery
  - RFA now also considered for low grade dysplasia

Shaheen et al NEJM 360: 2277-88;2009

Esophageal Cancer Selection of Neoadjuvant Patients

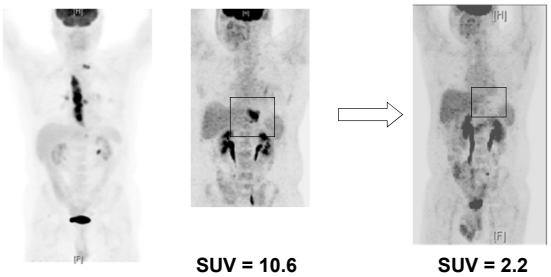
- **High Risk Patients**
- **Western pts are T3 / N+**
- **CT scan / Barium Swallow limited accuracy**
- **Endoscopic Ultrasound (EUS)**
- **PET Scan**



PET SCAN:
1) Staging: 15% occult mets
2) Determine Response to Preop Chemo

Supraclavicular LN = Stage IV

Response to Preop Chemo



SUV = 10.6

SUV = 2.2

Esophageal Cancer: Adjuvant Therapy

- **Survival with surgery alone: 20-40%**
- **Adjuvant trials in esophageal cancer have evaluated preop therapy**
  - Preop Chemotherapy
  - Preop Chemo + radiotherapy
    - Most common U.S. practice

Esophageal and GEJ Cancer: Mixed Results preop Chemo

- **MAGIC (ECF): 13% ↑ OS at 5 yr (120/503 pts eso + GEJ)**
  - No increase in RO resection rate
  - Fewer pts on the preop chemo arm went to surgery
  - ITT R0: 66-69%
- **FFCD / FNLC (CF): 14% ↑ OS at 5 yr (180/224 pts eso + GEJ)➔no epirubicin**
  - Improved R0 resection rate by 11%

Cunningham NEJM 355: 11; 2006, Ychou J Clin Oncol 29: 1715; 2011

Esophageal and GEJ Cancer: Mixed Results preop Chemo

- **Preop chemo CF failed:**
  - U.S. INT 113 (CF): 450 pts: No impact on OS, R0 (59-62%)
  - MRC 0E0-2 (CF): 800 pts
    - 5 years: 6% OS increase, Impact due to increase in R0 (54% ➔ 60%)
  - MRC OEO-5 (CF x 2, ECX x 4): 900 pts
    - CF = ECX, no benefit from epi
    - Poor rates of R0 resection: 60-67%
    - EUS, PET, laparoscopic staging
  - FLOT 4
    - FLOT superior to ECF as preop chemo, GEJ/gastric

Alllum J Clin Oncol 2009, Kelsen NEJM 1988, Cunningham Lancet Oncol 2018; Al Batran Lancet Oncol 2019

Contemporary Trials

Trial	Regimen	Eso / GEJ	R0
OEO5	ECX x 4	907	66%
	CF x 2		59%
STO3	ECX + / - Bev	680	69% (61-75%)
FLOT4	ECX	201	77%*
	FLOT	200	84%*
CROSS	Surgery	141	69%**
	Carb/Pac/RT	134	92%**

*GEJ + Gastric

**AC + Squam

Alderson Lancet Oncol 2017; Cunningham Lancet Oncol 2017; Al-Batran Lancet Onco 2019 Van Hagen NEJM 2012

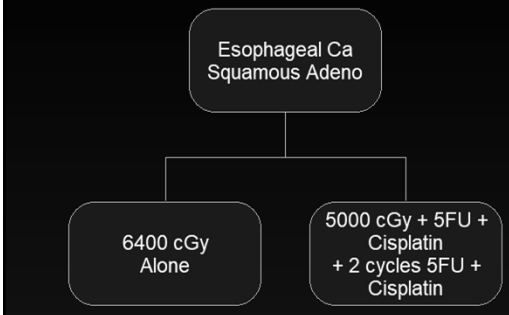
Margin Status with Preop ECF/X Depends on Location: STO3

	Patients	% R0
Total Resected	834	
Esophageal	116	66%
Type 1	102	61%
Type 2	148	72%
Type 3	157	75%
Stomach	304	87%
Eso/GEJ	523	69%

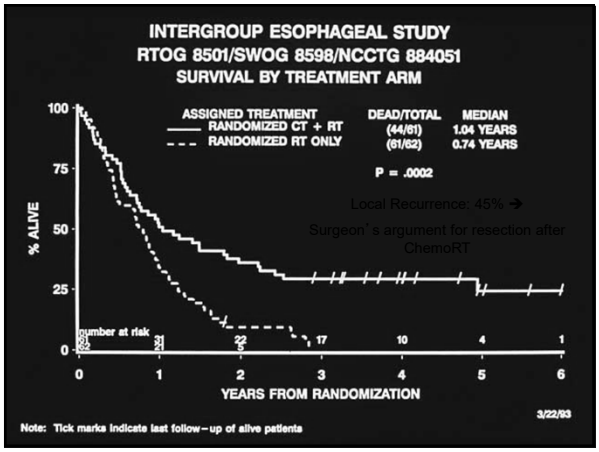
Cunningham Lancet Oncol 2017

Chemoradiotherapy: Esophageal Cancer

RTOG Trial 85-01: Non operative Tial

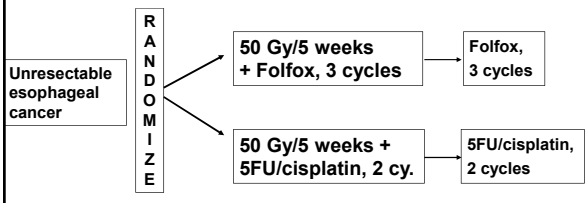


mskcc dhi 1999



Prodige 5 - ACCORD 17 trial design

Conroy ASCO 2012



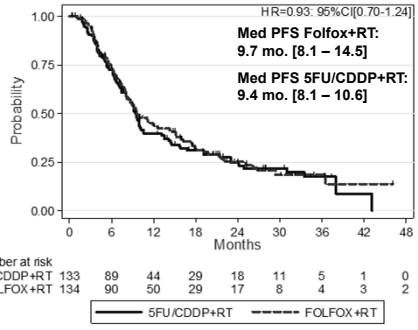
Stratification :

- adenocarcinoma vs squamous-cell vs adenosquamous
- pretreatment weight loss < 10% vs ≥ 10%
- performance status: 0 vs 1 vs 2
- center

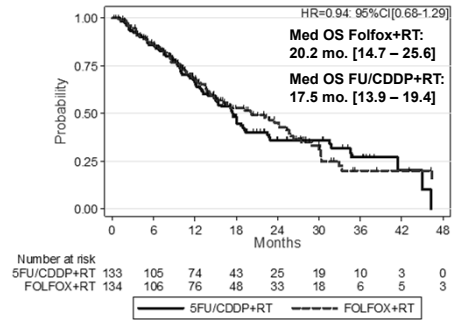
Tumor characteristics

Characteristics	Folfox N=134	5FU/cisplatin N=133	p
Tumor type			
Adenocarcinoma	19 (14.2%)	18 (13.5%)	NS
Squamous-cell carcinoma	114 (85.1%)	115 (86.5%)	
Adenosquamous	1 (0.7%)	-	
TNM classification			
Stage I	0 (0%)	1 (0.7%)	NS
Stage II A	31 (21.1%)	31 (23.3%)	
Stage II B	10 (7.5%)	7 (5.3%)	
Stage III	67 (50.0%)	72 (54.1%)	
Stage IV A	8 (6.1%)	8 (6.1%)	
Stage IV B	4 (3.1%)	4 (3.1%)	

Progression-Free Survival



Overall Survival

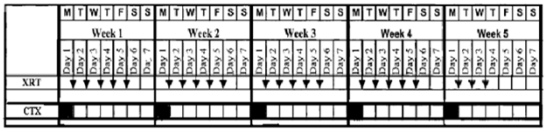


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.J. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*



- **Paclitaxel 50mg/m² + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29**
- **Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy**
- **Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)**

Van Hagen et al NEJM 366: 2074; 2012

CROSS: Major Results

- **EUS staged patients**
- **T3N0-1: 75%, median age 60**
- **74% Adenocarcinoma**
- **93% received all courses chemotherapy**
  - 23% had > = grade 3 toxicity from pre-op therapy
- **Post-operative morbidity and mortality almost identical (mortality 3.7-3.8%)**

Resection rate and resection margins

Resection rate of all randomized patients

Surgery alone	CRT + surgery
186/188 (99%)	168/178 (95%)

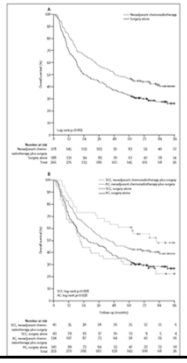
Resection margins

	Surgery alone	CRT + surgery	
R0	**111/161 (69%)**	**148/161 (92%)**	**p<0.002**

R0 = no tumor within 1 mm of the resection margins

CROSS study

Overall Survival Improved with Chemo RT + Surgery



- 5-year survival 47% versus 34%
- Median survival 48.6 versus 24 months, HR 0.68, p = 0.003)
  - Squamous HR 0.48 (p = 0.008)
  - Adeno HR 0.73 (p = 0.038)
- Squamous path CR 49%, Adeno 23% (p = 0.008)
- Local and Distant Recurrence reduced (16%, 9% Δ)

Shapiro J, Lancet Oncol 16: 1090; 2015

Preop Chemo vs Chemo RT: Stahl

- EUS, laparoscopy staged pts
- Siewert I-III, T3-4 adenocarcinoma

Arm	Pts	R0	pCR	N0	Median Survival	3 yr OS	Local Control
Chemo	59	70%	2%	37%	21 mos	28%	59%
Chemo RT	60	72%	16%	64%	33 mos	47% P = 0.07	77% P = 0.06

Stahl J Clin Oncol: 27: 836; 2009

Ongoing Randomized Trials of Preop Chemo + / - RT

- **ESOPEC (NCT 92509286)**
  - FLOT vs CROSS, Eso and GEJ, 438 pts
- **NEO-Aegis (NCT 0172645)**
  - ECF/X, FLOT vs CROSS, Eso and GEJ, 366 pts
- **TOPGEAR (NCT 01924819)**
  - Perioperative ECF/X, FLOT
  - + / - Preoperative RT
  - GEJ and Gastric cancer, 752 pts
- **CRITICS 2**
  - FLOT vs CROSS vs DOC ➔ CROSS

Esophageal Cancer and the Role of Surgery?

- **Adenocarcinoma**
  - Low rate of pathologic complete response after chemo RT (23% CROSS trial)
  - Surgery considered for most patients
    - Chemo RT alone: Elderly, co morbidities
    - Delay surgery in responders, use as a salvage procedure

Esophageal Cancer: Predictive Accuracy of post ChemoRT Endoscopy

- **137 pts: Cisplatin based chemo RT ➔ surgery**
  - ➔ EGD and biopsy ➔ Surgery
- **104 pts (76%) negative biopsy post therapy**
  - Poor Predictor: Only 35% had pathologic CR at surgery
- **A negative biopsy better predictor for squamous cell carcinoma (p <0.001)**

Sarkaria JCO 24: Abs 4024, 182, 2006

Chemo RT or Chemo RT ➔ Surgery only in Responding Patients: FFCD 9102

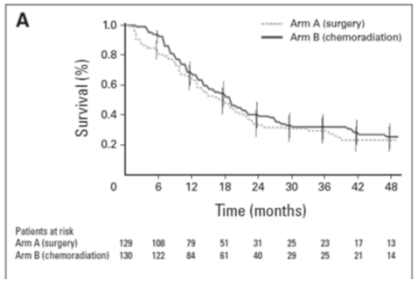
455 pts, 259 responders randomized: Non responders excluded.

Author	Pt No.	Histol.	Therapy	Med. Surv.	O.S.	Local Control
Bedenne	259	Squam	Chemo RT + S	17.7 mos	34% 2 yr	66%
		Squam	Chemo RT	19.3 mos	40% 2 yr	57%

Treatment Mortality S 9.3% CRT 0.8%

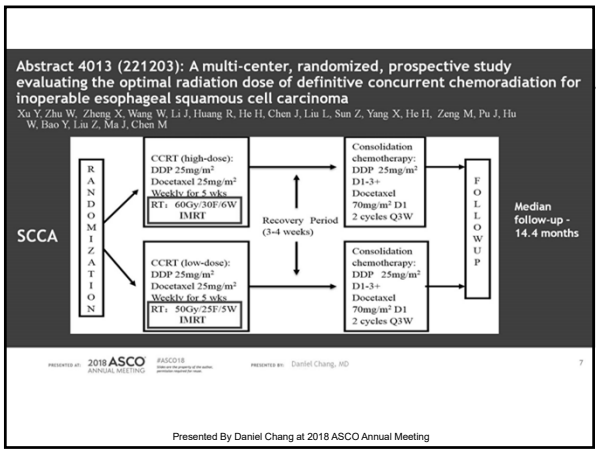
Bedenne et al JCO 25: 1160; 2007

OS in Responding Patients: CRT + / Surgery

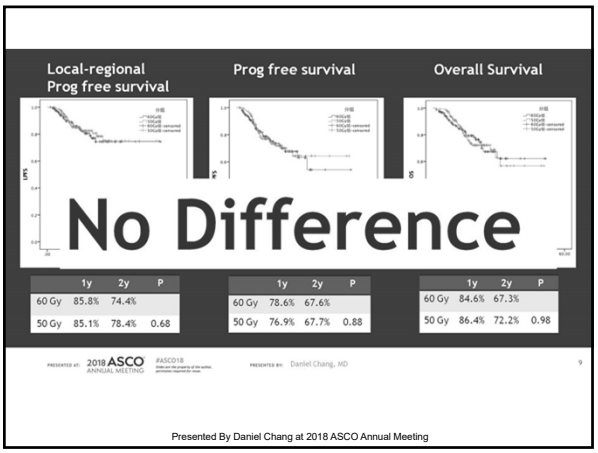


Combined Modality Therapy
Higher RT Doses

- **Increasing RT Dose: RTOG 94-05**
  - 6480 vs 5040 Gy RT
  - + 5-FU + Cis
  - No benefit for ↑RT
- **Brachytherapy: RTOG 92-74**
  - 50.4 Gy + 5-FU + Cis
  - + Brachy (15 Gy) + 5-FU + Cis
  - 18% Fistula
  - No increase in local control



Presented By Daniel Chang at 2018 ASCO Annual Meeting



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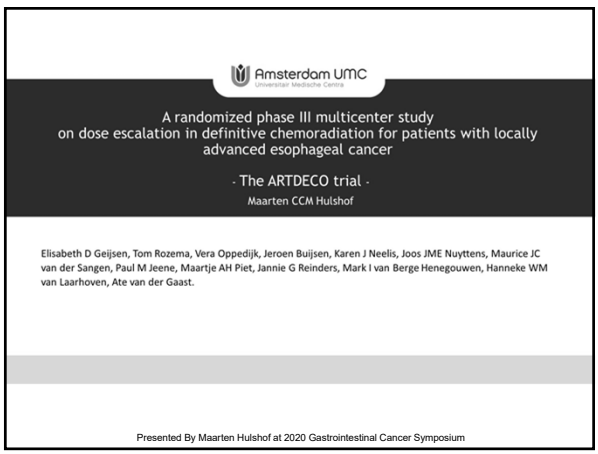
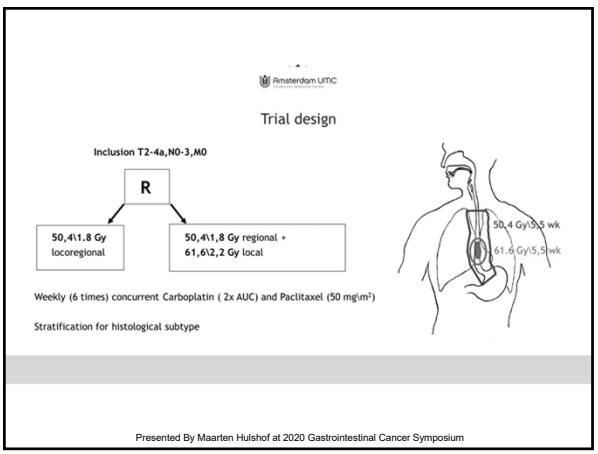


Presented By Maarten Hulshof at 2020 Gastrointestinal Cancer Symposium



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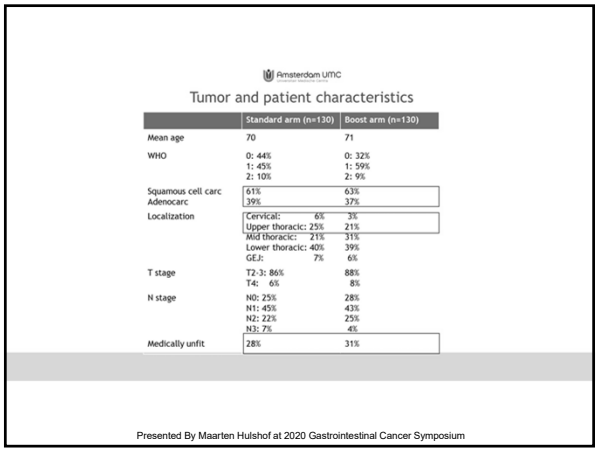

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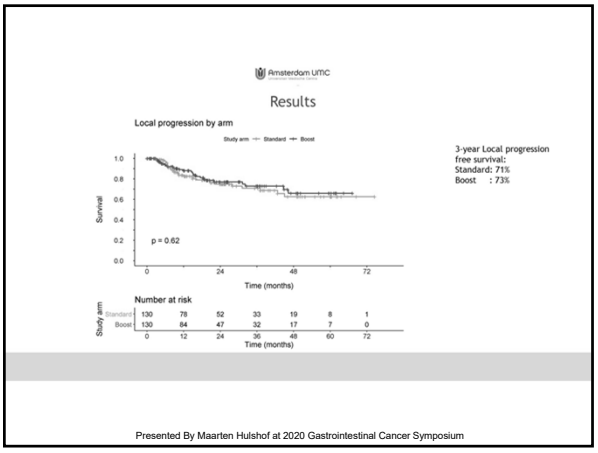

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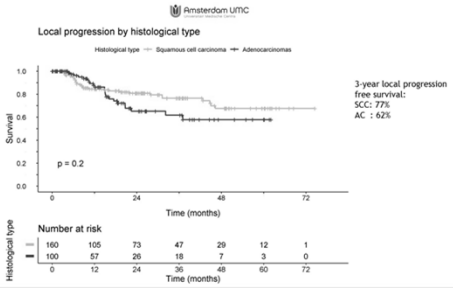

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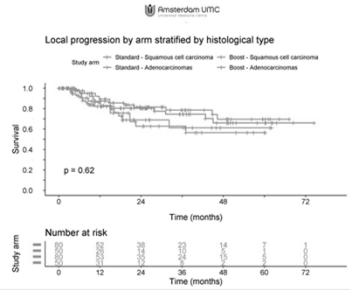

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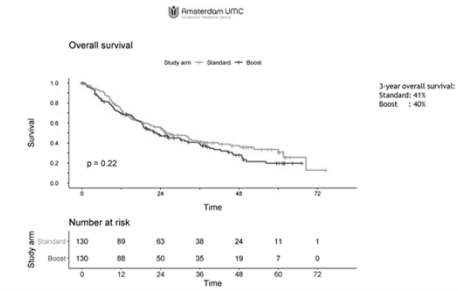
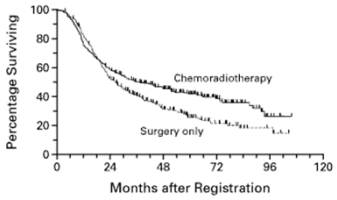


Presented By Maarten Hulshof at 2020 Gastrointestinal Cancer Symposium

Esophageal Cancer: Preop Chemo, RT, or Both? Conclusions

- **Esophageal, GEJ Adeno**
  - Preop ECF (CF) improves survival and is feasible
    - FLOT superior to ECF
    - Poor rates of R0 resection for CF, ECF
  - Preop RT + Chemo: superior OS, more path CR's, superior R0 resection
- **Esophageal Squamous**
  - RT + Chemo:
    - As primary therapy without surgery is acceptable
    - Surgery after chemo RT: in selected patients
      - Improved local control → no improvement in survival
    - No benefit for higher RT doses

Post Op ChemoRT: Gastric INT 116

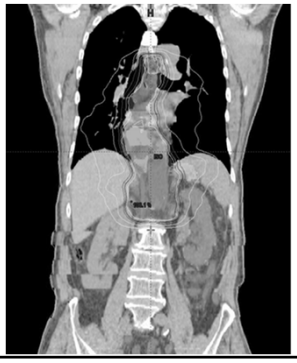


- **20% were GE JXN tumors**
- **Similar survival benefit in this subset**
- **Post Op Chemo RT in GE JXN cancer**

Overall Survival

Macdonald NEJM 345: 725-730; 2001

Post-op Chemoradiation: GE junction: Larger post op RT field poorly tolerated



Management of Residual Disease

- Pre or post op therapies marginal benefits: 60-80% of pts still die
- Survival improvements ranging from 0% to 6-14%
- Pts with no treatment effect and significant residual disease post surgery have a poor outcome
- Standard of care after preop chemoRT and surgery is observation alone

National Cancer Database: Observation versus Adjuvant Chemo post ChemoRT/Surgery

- Propensity matched analysis from a 10,086 pt database
- 732 pts getting post op chemo vs 3660 observation
- OS difference of 6 months (34 to 40 mos)
- 5 yr OS difference of 4%
- Selection bias despite propensity matching
- Poor tolerance of post op therapy

Mokdad et al JAMA Oncol 4: 31-38; 2018

New Agents In Combined ChemoRT

- Carbo + Paclitaxel + RT, surgery: Cross trial, new standard
- SWOG S0-356: Oxaliplatin + 5-FU + XRT: preop
  - 27% path CR in adenocarcinoma, OS 33 months
- French Trial, nonoperative chemort: 5-FU Cisplatin = FOLFOX during RT, squamous cancers

Leichman J Clin Oncol 29: 4555; 2011; Conroy Lancet Oncol 15: 3015; 2014

Metastatic Disease: Patient Selection for Chemotherapy

- Apply regimens for gastric cancer (NCCN)
- 2 drug regimens are preferred
  - FOLFOX, CAPE-OX, FOLFIRI, CAPE-CIS
- 3 drug regimens adding docetaxel (DCF, mDCF, FLOT)
  - No survival benefit for Doc + S-1/Cisplatin (JCOG 1013)
  - No survival benefit in patients 65 or older: FLOT
  - Epirubicin adds no benefit (NCCN)

Advanced Esophagogastric Cancer Chemotherapy: What Regimen to Use?

	Oxali: EOX or EOF	Cape: ECX or EOX	XP	FLO	FOLFIRI	FUFIRI	S-1 Cis	DCF	ECF
Pts	489	513	160	109	209	170	305	221	126
%RR	44%	45%	41%	34%	39%	32%	54%	36%	45%
TTP, months	6.7	6.5	5.6	5.5	5.3	5.0	6.0	5.6	7.4
OS, months	10.9	10.4	10.5	10.7	9.5	9.0	13.0	9.2	8.9

Cunningham NEJM 358:36;2008, Kang Annals Oncol 20:666;2009, Al-Batran JCO 26:1435;2008, Dank Annals Oncol 19:450;2008 Koizumi Lancet Oncol 9:215;2008, Van Cutsem JCO 24:4991;2006, Webb JCO 15:61;1997

Does Epirubicin add Benefit? CALGB 80403-ECOG 1206 Trial: FOLFOX = ECF

- 245 pts with esophageal and GEJ adeno (222) or squamous (23)
- Cetuximab + 3 chemo regimens
- RR primary endpoint
- FOLFOX = ECF, fewer dose changes or stopping therapy for toxicity

	ECF	FOLFOX	IRINO-CIS
Number	63	66	71
RR%	60%	53%	45%
PFS	7.1 m	6.8 m	4.9 m
OS	11.6 m	11.8 m	8.6 m

Enzinger J Clin Oncol 34: 2016

Gastric Cancer Targeted Agents Used in GEJ and Esophageal Adenocarcinoma

- **Add trastuzumab to first line chemotherapy in HER2 positive adenocarcinoma**
- **Add ramucirumab to second line paclitaxel**
- **Pembrolizumab for third of later line therapy in PDL-1 + adenocarcinoma at > = 1%**
- **Clinical trials for gastric include GEJ but not esophageal adenocarcinoma**
  - GEJ and esophageal AC are genomically similar
- **GEJ and esophageal AC are rarely MSI high or EBV +**

Four EsophagoGastric Cancer Genomic Subsets Emerge: TCGA

- **Genomically unstable**
  - 95% of GEJ and esophageal tumors
  - High rate of p53 mutation, amplification of RTK's
  - HER2 30% (EGFR, FGFR, MET)
- **Microsatellite instability (MSI): < 1% in Esophageal and GEJ cancers**
- **Genomically stable: rare GEJ cancer**
- **High Epstein-Barr virus burden: rare GEJ cancer**
- **Squamous cancers: genomically distinct from AC**
  - More closely resemble squamous aerodigestive cancers
  - p53 mutation common

Nature Genetics 24: 2903; 2014

NRG ONCOLOGY
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Trastuzumab With Trimodality Treatment For Esophageal Adenocarcinoma with HER2 Overexpression: A Multicenter Randomized Phase III Trial, NRG Oncology/RTOG 1010

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Treatment

- RT: 5040 cGy in 180 cGy daily fractions (28 fx over 5 ½ weeks)
- Chemotherapy: Paclitaxel, 50 mg/m^2, and carboplatin AUC = 2, weekly for 6 weeks.
- Trastuzumab
  - 4 mg/kg week 1
  - 2 mg/kg/weekly x 5 during ChemoRT
  - 6 mg/kg for 1 dose prior to surgery
  - 6 mg/kg every 3 weeks for 13 treatments after surgery

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NRG ONCOLOGY™

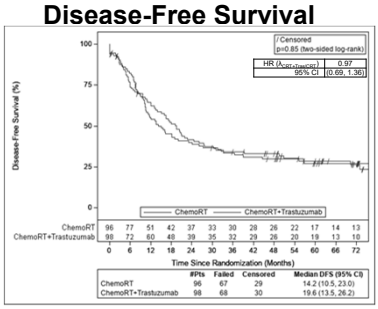
Patient or Tumor Characteristic

	ChemoRT + Trastuzumab (n=98)		ChemoRT (n=96)	
Median Age (min-max) years	63 (40-80)		65.5 (24-83)	
Sex				
Male	85	87%	79	82%
Female	13	13%	17	18%
Zubrod Performance Status				
0	62	63%	62	65%
1	34	35%	31	32%
2	2	2%	3	3%
T stage, clinical				
T1	1	1%	4	4%
T2	18	18%	17	18%
T3	79	81%	75	78%
Presence of Adenopathy				
No	38	39%	38	40%
Yes adenopathy, but celiac absent	48	49%	48	50%
Yes adenopathy and celiac present ≤ 2 cm	12	12%	10	10%

NRG/RTOG 1010

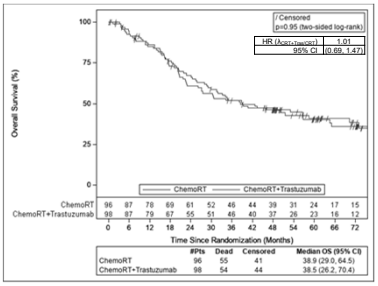
NRG ONCOLOGY™

Disease-Free Survival



NRG ONCOLOGY™

Overall Survival



NRG ONCOLOGY™

Surgery and Pathologic Complete Response (pCR)

	ChemoRT + Trastuzumab (n=98)	ChemoRT (n=96)	Chi-squared p-value
Surgery			
Yes	**82 (84%)**	**78 (81%)**	
No (progression, mets, death)	5 (5%)	8 (8%)	
No (other)	11 (11%)	10 (10%)	
pCR			0.71
Yes	22 (27%)	23 (29%)	
No	60 (73%)	55 (71%)	

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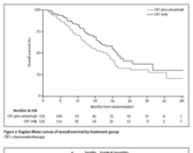
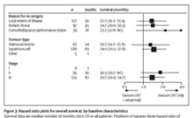
NRG ONCOLOGY™

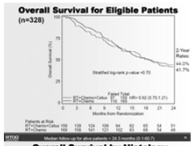
EGFr: Definitive Cetuximab + Chemo RT

- **SCOPE-1**
- **Cape-Cis ➔ Cape-Cis-RT + / - Cetuximab**
- **258 pts (65 AC,188 SCC)**



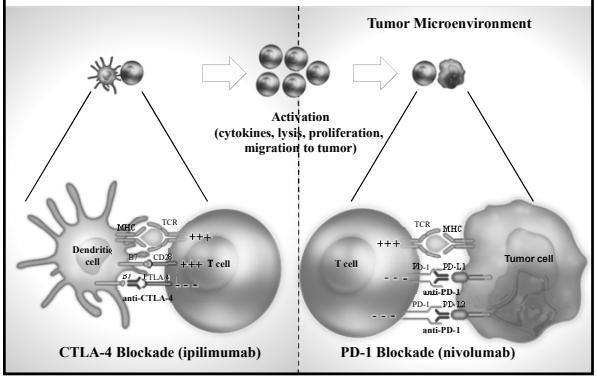


- **RTOG 0436**
- **Pac-Cis-RT + / - Cetuximab**
- **328 pts (203 AC,125 SCC)**

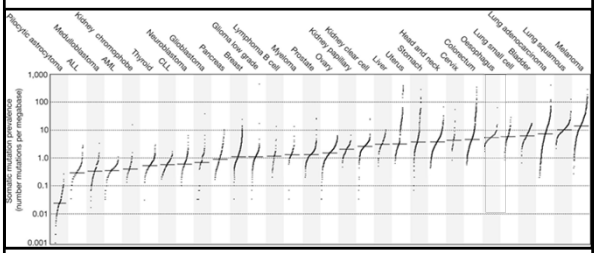


Crosby Lancet 14: 627; 2013 Suntha JCO 32: 2014 (suppl 3; abstr LBA6

Blocking CTLA-4 and PD-1



Somatic Mutation Prevalence



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

Esophageal Cancer Immunotherapy

- **Phase II activity of pembro, nivo, durvalumab, avelumab RR 10-15% or less**
  - Esophageal Squamous and Adeno
  - Similar to activity in gastric cancer
    - 3rd line pembro approved in PDL-1+, MSI high adenocarcinoma
- **GEJ cancers: included in gastric cancer phase III trials**
  - ATTRACTION 2: + Nivolumab vs BSC
  - KEYNOTE 61 and 62: negative trials
    - Paclitaxel vs Pembro 2nd line
    - Chemo vs or + Pembro 1st line
  - +3Rd line pembro approved in PDL-1 + , MSI high
- **Phase III:**
  - KEYNOTE 181: MD choice chemo vs Pembro in 2nd line esophageal and GEJ cancer, + squamous CPS 10%
  - Attraction 3: Paclitaxel vs Nivolumab in 2nd line squamous cancer + regardless of PDL-1

Pembrolizumab Versus Chemotherapy as Second-line Therapy for Advanced Esophageal Cancer: The Phase 3 KEYNOTE-181 Study

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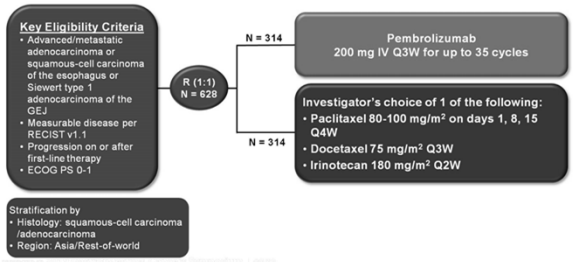
Phase 3 KEYNOTE-181 Study (NCT02564263)



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Baseline Characteristics (ITT)

Characteristic, n	Pembrolizumab N = 314	Chemotherapy N = 314
Median age, years (range)	63 (23-84)	62 (24-84)
≥65 years	139 (44.3)	133 (42.4)
Male	273 (86.9)	271 (86.3)
Asia	121 (38.5)	122 (38.9)
Rest of World	193 (61.5)	192 (61.1)
ECOG PS 1	187 (59.6)	197 (62.7)
Squamous-cell carcinoma	198 (63.1)	203 (64.6)
Adenocarcinoma	116 (36.9)	111 (35.4)
PD-L1 CPS ≥10[a]	107 (34.1)	115 (36.6)
Metastatic disease	290 (92.4)	286 (91.1)
0-1[b] prior therapies	305 (97.1)	310 (98.7)
≥2 prior therapies	9 (2.9)	4 (1.3)

[a]6 patients in pembrolizumab and 3 in chemotherapy group were not evaluable; [b]2 patients in pembrolizumab group had 0 prior therapies; Data cutoff: October 15, 2018.

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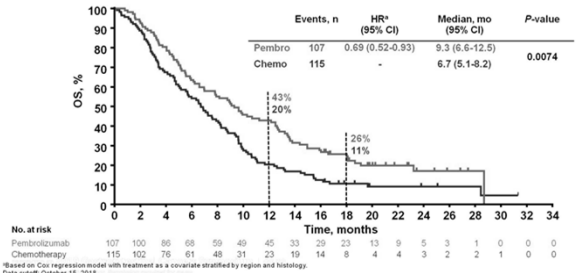
Overall Survival (PD-L1 CPS ≥10)



[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

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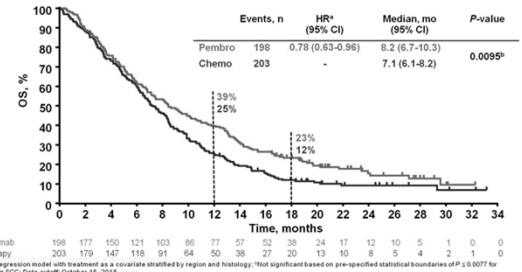
Overall Survival (SCC)



[a]Based on Cox regression model with treatment as a covariate stratified by region and histology; [b]Not significant based on pre-specified statistical boundaries of $P \leq 0.0077$ for superiority of OS in SCC; Data cutoff: October 15, 2018.

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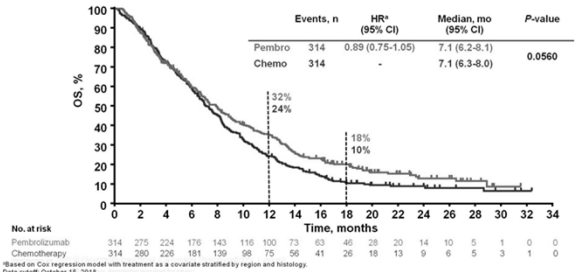
Overall Survival (ITT)



[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

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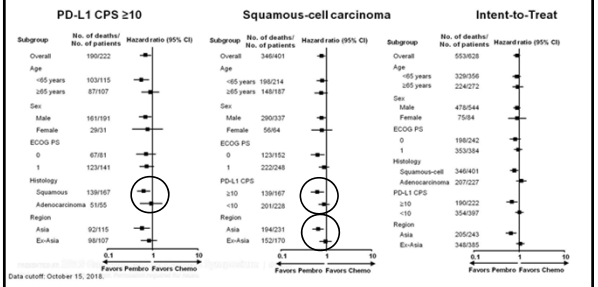
OS in Key Subgroups



Data cutoff: October 15, 2018.

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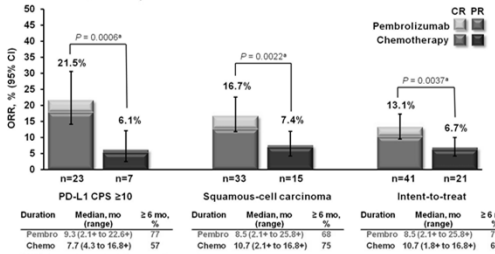
Response Rate and Duration
(RECIST v1.1, BICR)



Duration	Median, mo (range)	≥ 6 mo, %
PD-L1 CPS ≥10		
Pembro	9.3 (2.1+ to 22.6+)	77
Chemo	7.7 (4.3 to 16.8+)	57
Squamous-cell carcinoma		
Pembro	8.5 (2.1+ to 25.8+)	68
Chemo	10.7 (2.1+ to 16.8+)	75
Intent-to-treat		
Pembro	8.5 (2.1+ to 25.8+)	72
Chemo	10.7 (1.8+ to 16.8+)	62

*Nominal; one-sided.
Data cutoff: October 15, 2018.

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BARCELONA 2019 ESMO congress

Nivolumab Versus Chemotherapy in Advanced Esophageal Squamous Cell Carcinoma: The ATTRACTION-3 Study

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Abstract Number 2389

ATTRACTION-3

ATTRACTION-3 Study Design

- ATTRACTION-3 is a randomized, open-label, phase 3 study of nivolumab versus docetaxel or paclitaxel in patients with ESCC[a]

Key eligibility criteria
- Unresectable advanced or recurrent ESCC
- Refractory to or intolerant of 1 prior fluoropyrimidine/ platinum-based therapy
- ECOG performance status 0 or 1

R 1:1

Stratification[b]:
- Region
- No. of organs with metastases
- PD-L1 expression

Nivolumab 240 mg IV Q2W[c]

Docetaxel 75 mg/m² IV Q3W[c] **or paclitaxel** 100 mg/m² IV QW × 6 weeks, then 1 week off[c]

Primary endpoint:
- OS

Other key endpoints:
- PFS, ORR, DCR, TTR, DOR, HRQoL, and safety

- Of 419 patients randomized, 417 received ≥ 1 dose of the assigned treatment
- At data cutoff (November 2018), minimum follow-up was 17.6 months[d]

[a]ClinicalTrials.gov number, NCT02569242; [b]Region (Japan vs rest of world), number of organs with metastases (≤ 1 vs ≥ 2), and PD-L1 expression (≥ 1% vs < 1%); [c]Until documented disease progression, discontinuation due to toxicity, withdrawal of consent, or study end; [d]Time from randomization of the last patient to data cutoff.
DCR, disease control rate; DOR, duration of response; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; Q2W, once every 2 weeks; Q3W, once every 3 weeks; QW, every week; R, randomization; TTR, time to response.

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ATTRACTION-3

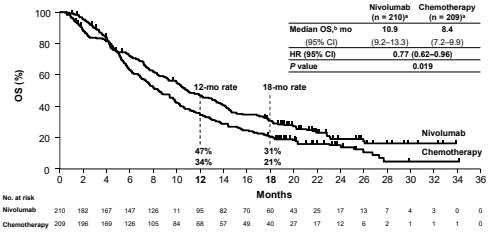
Baseline Characteristics

	Nivolumab N = 210[a]	Chemotherapy N = 209[a,b]
Median age (range), years	64 (37–82)	67 (33–87)
Male, n (%)	179 (85)	185 (89)
Race, n (%)		
Asian	201 (96)	200 (96)
White	9 (4)	9 (4)
ECOG performance status, n (%)		
0	101 (48)	107 (51)
1	109 (52)	102 (49)
Disease stage[c] (TNM classification), n (%)		
II–III	8 (7)	13 (11)
IV	94 (88)	100 (83)
Prior therapies, n (%)		
Surgery	111 (53)	94 (45)
Radiotherapy	153 (73)	142 (68)
Systemic anticancer therapy	210 (100)	208 (100)
Tumor PD-L1 expression,[d] n (%)		
< 1%	109 (52)	107 (51)
≥ 1%	101 (48)	102 (49)
History of smoking, n (%)		
Never	30 (14)	32 (15)
Former	159 (76)	147 (70)
Current	21 (10)	30 (14)

[a]Intent-to-treat population; [b]Docetaxel, n = 65 and paclitaxel, n = 144; [c]Summarized at randomization for patients with non-recurrent ESCC (nivolumab, n = 107 and chemotherapy, n = 120). Disease stage could not be classified for 5 patients in the nivolumab arm and 7 patients in the chemotherapy arm; [d]Evaluated using IHC 28-8 pharmDx assay.
TNM, tumor, node, and metastases.

ATTRACTION-3

Overall Survival



	Nivolumab (n = 210)[a]	Chemotherapy (n = 209)[a]
Median OS,[b] mo	10.9	8.4
(95% CI)	(9.2–13.3)	(7.2–9.9)
HR (95% CI)	0.77 (0.62–0.96)	
P value	0.019	

- Nivolumab provided superior OS, with a 23% reduction in the risk of death and a 2.5-month improvement in median OS, versus chemotherapy

[a]Intent-to-treat population; [b]Minimum follow-up: 17.6 months.
CI, confidence interval; mo, months.

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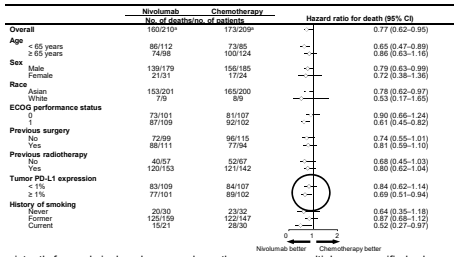
ATTRACTION-3

Overall Survival by Subgroups



	Nivolumab No. of deaths/no. of patients	Chemotherapy No. of deaths/no. of patients	Hazard ratio for death (95% CI)
Overall	160/210[a]	173/209[a]	0.77 (0.62–0.95)
Age			
< 65 years	86/112	73/85	0.65 (0.47–0.89)
≥ 65 years	74/98	100/124	0.86 (0.63–1.16)
Sex			
Male	139/179	156/185	0.79 (0.63–0.99)
Female	21/31	17/24	0.72 (0.38–1.36)
Race			
Asian	153/201	165/200	0.78 (0.62–0.97)
White	7/9	8/9	0.53 (0.17–1.65)
ECOG performance status			
0	73/101	81/107	0.90 (0.66–1.24)
1	87/109	92/102	0.61 (0.45–0.82)
Previous surgery			
No	72/99	96/115	0.74 (0.55–1.01)
Yes	88/111	77/94	0.81 (0.59–1.10)
Previous radiotherapy			
No	40/57	52/67	0.68 (0.45–1.03)
Yes	120/153	121/142	0.80 (0.62–1.04)
Tumor PD-L1 expression			
< 1%	83/109	84/107	0.84 (0.62–1.14)
≥ 1%	77/101	89/102	0.69 (0.51–0.94)
History of smoking			
Never	20/30	23/32	0.64 (0.35–1.18)
Former	125/159	122/147	0.87 (0.68–1.12)
Current	15/21	28/30	0.52 (0.27–0.97)

- OS consistently favored nivolumab versus chemotherapy across multiple pre-specified subgroups, including tumor PD-L1 expression

[a]Intent-to-treat population.

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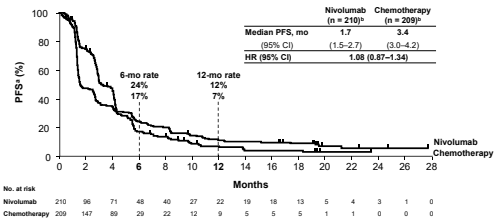
ATTRACTION-3

Progression-Free Survival



- An overall hazard ratio of 1.08 suggests no meaningful difference in PFS between nivolumab and chemotherapy

[a]Per investigator assessment; [b]Intent-to-treat population.

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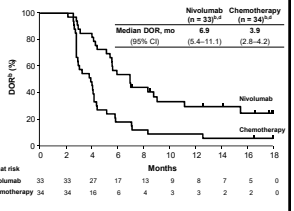
Response and Disease Control

	Nivolumab N = 171[a]	Chemotherapy N = 158[a]
ORR,[b] n (%)	33 (19)	34 (22)
95% CI	14–26	15–29
P value	0.63	
Best overall response,[b,c] n (%)		
Complete response	1 (1)	2 (1)
Partial response	32 (19)	32 (20)
Stable disease	31 (18)	65 (41)
Progressive disease	94 (55)	51 (32)
Not evaluable	13 (8)	8 (5)
DCR,[b] n (%)	64 (37)	99 (63)
95% CI	30–45	55–70
Median TTR[b] (range), months	2.6 (1.2–6.5)	1.5 (1.2–5.6)
Patients with ongoing response,[b] n/N (%)	7/33 (21)	2/34 (6)

Duration of response



- Nivolumab and chemotherapy had comparable ORRs; however, responses were more durable with nivolumab

[a]Randomized patients who had target lesion measurements at baseline; [b]Per investigator assessment based on Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1; [c]Percentages may not add up to 100% due to rounding; [d]No. of responders.

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Esophageal Cancer: Summary

- **Poor survival with Surgery Alone (20-30%)**
- **Neoadjuvant Therapy in Esophageal and GEJ Cancer**
  - Adenocarcinoma
  - Periop Chemo CF; FLOT is superior
  - Preop Chemo + RT, Carbo Paclitaxel preferred
    - Press release + adjuvant Nivo
- **Squamous Cancer: Primary Chemo + RT, selective use of surgery**

Esophageal Cancer: Summary

- **Metastatic Disease**
  - Gastric cancer chemo
  - Platinum + FU +/- third drug
    - ECF, DCF, mDCF, FLOT standards
    - Epirubicin may not benefit
  - Two drug alternatives (FOLFOX, FOLFIRI, Cape-Cis or Oxali) less toxic
  - Oxaliplatin, capecitabine = Cis, 5-FU
  - Second Line: taxane or irinotecan
- **Targeted therapies**
  - Trastuzumab in HER2+ esophageal
  - Ramucirumab or Ram + Paclitaxel second line esophageal/GEJ
  - Pembrolizumab: in MSI high, PDL-1 + GEJ and eso adeno 3rd line
  - Nivolumab, Pembro (CPS 10) approved in esophageal squamous cancers 2hd line

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Gastric Cancer

David Ilson, MD

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

68 – Gastric Cancer

David H. Ilson, MD, PhD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

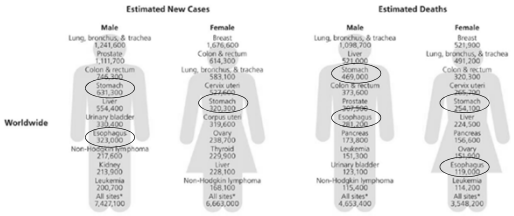
- **Consulting: AMGEN, Bayer, Lilly, Pieris, Roche/Genentech, Astra Zeneca, Bristol Myers Squibb, Astellas, Merck, Taiho**

Esophageal and Gastric Carcinoma US Incidence in 2020

- **27,600 cases**
- **Decline in Distal Gastric Cancer Incidence**
- **Increase in Esophageal , GE JX, cardia adeno**
- **OS improvement, 1975-77, 1984-86, 1999-2006**
  - 16% ➔ 18% ➔ 27%

Siegel et al, CA 70: 7-30; 2020

Global Incidence of Gastric + Esophageal Cancer: 2012



Gastric 5th in Global Incidence, 3rd in Global Mortality
Esophagus + Gastric = Lung Cancer in Global Mortality

Torre L, Bray F, Siegel R et al. CA Cancer J Clin 65: 87-108; 2015

Global Incidence of Gastric Cancer: 2012

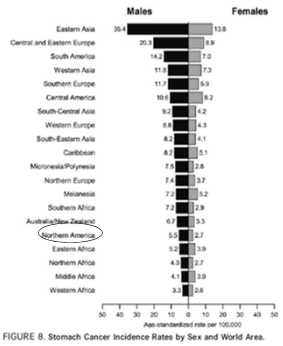


FIGURE 8. Stomach Cancer Incidence Rates by Sex and World Area.
Torre L, Bray F, Siegel R et al. CA Cancer J Clin 65: 87-108; 2015

Gastric and Esophageal Cancer: AJCC 7th Edition Staging

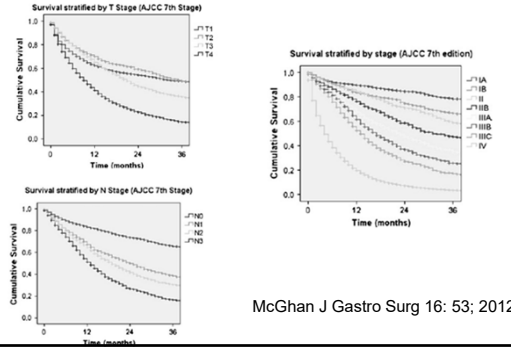
Gastric

- **T1a: lamina propria/ musc mucosa**
- **T1b: submucosal**
- **T2: muscle**
- **T3: transmural to adventitia**
- **T4a: into serosa / peritoneum (old T3)**
- **T4b: into adjacent organ**
- **N1: 1-2nodes**
- **N2: 3-6 nodes**
- **N3a: 7-15 nodes**
- **N3b: 16+ nodes**
- **M1: distant metastases**
- **Stage I: T1N0-1, T2N0**
- **Stage II: T3N0, T2N1, T1N2,**
- **Stage III: T3N1-2, T4N0, T2N2**
- **Stage IV: T4N1, M1**

Esophageal Adeno

- **T1a: intramucosal**
- **T1b: submucosal**
- **T2: muscle**
- **T3: transmural / adventitia**
- **T4a: pleura**
- **T4b: aorta**
- **N1: 1-2 nodes**
- **N2: 3-6 nodes**
- **N3: 7+ nodes**
- **M1: distant metastases**
- **Stage IAB: T1-2N0 (grade)**
- **Stage IIAB: T3N0,T1-2N1,T2N0 (gr)**
- **Stage IIIAB: T3N1-2, T4aN0, T1-2N2**
- **Stage IIIC: N3, T4aN1-2, T4b**
- **Stage IV: M1**

AJCC Staging: Survival in over 13,000 pts with gastric cancer, SEER database



McGhan J Gastro Surg 16: 53; 2012

Factors Associated With Increased Risk of Developing Stomach Cancer

- **Nutritional/environmental**
  - Salted or smoked foods
  - High dietary nitrates
  - Low intake of fruits, vegetables, and vitamin A and C consumption
  - Low serum selenium
- **Social**
  - Low socioeconomic status
  - **Tobacco use**
- **Medical**
  - Prior gastric surgery
  - *Helicobacter pylori* infection
    - Cag-1
  - Gastric atrophy and gastritis
  - Pernicious anemia

Factors Associated with Risk of Developing Stomach Cancer

- **Hereditary Diffuse Gastric Cancer**
- **Mutation in CDH-1/E-cadherin gene**
  - **Calcium dependent cell adhesion protein**
- **Autosomal dominant**
- **Multifocal, diffuse cancers, young age**
- **Lobular breast cancer**
- **Prophylactic gastrectomy for carriers**
  - **Gastric ca develops in 3 of 4 carriers**

Hopkins Nature 392: 402; 1998 Huntsman NEJM 344: 1904; 2001

Factors Associated with Risk of Developing Stomach Cancer

- **HNPCC: nonpolyposis CRC (Lynch Syndrome)**
  - DNA mismatch repair gene mutations, 4 loci, auto dominant
- **FAP: polyposis colorectal ca**
  - APC gene mutation, auto dominant
- **Juvenile Polyposis, Peutz-Jeghers Syndromes**
- **BRCA**

Hopkins Nature 392: 402; 1998 Huntsman NEJM 344: 1904; 2001

Staging of Gastric Cancer

- **Endoscopy and biopsy**
- **CT scan chest, abdomen pelvis to assess for metastasis**
- **Endoscopic ultrasound considered to assess T stage**
- **If T3 or N+ on EUS consider laparoscopy**
  - 20-30% have occult peritoneal metastases or positive cytology on washings ➔ Stage IV disease
- **PET scan**
  - May ID occult mets in 15%
  - Not sensitive for peritoneal disease
  - Diffuse cancers often not PET avid

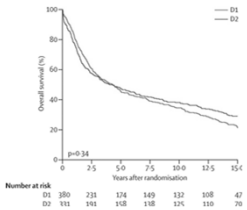
U.S. National Database: Gastric Cancer Surgical Outcome: 1985-1996

- **50,169 pts**
- **28% 5 year survival**
- **Surgical Staging:**
  - 27% had no or unknown LN's
  - 56% had < = 15 LN's
  - only 18% had > 15 LN's
- **Less than a D1 resection common in the U.S.**
- **D1: Greater and lesser curvature nodes**
- **D2: + celiac, gastrohepatic, splenic nodes**

Hundahl, Cancer 88:921; 2000

Optimal Surgery for Gastric Cancer?

- **D2 resection is the standard of care in Asia**
- **Increasingly in the West D2 resection is considered the standard**
- **Update of Dutch D1 vs D2 resection at 15 years supports D2**



Songun I et al Lancet Oncol 11: 439; 2010

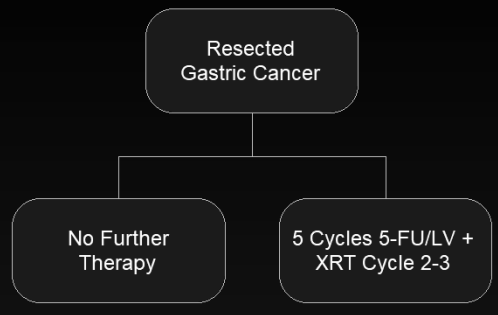
Adjuvant Therapy in Gastric Cancer Improves OS

- **Post op RT + chemo (U.S.), less than a D1-2 resection**
  - 5FU-LV + RT, INT 116:
    - 10% ↑ 5 yr OS, HR 0.65
- **Pre and post op chemo (U.K.) without RT**
  - ECF, MAGIC:
    - 13% ↑ 5 yr OS, HR 0.75
  - FLOT is superior to ECF
- **Post op chemo (Asia): 2 trials, 2000 pts, D2 resection, no RT**
  - S-1 (Oral 5-FU), ACTS-GC:
    - 10% ↑ 5 yr OS, HR 0.67 (2011 update)
  - Cape-Oxali , CLASSIC Trial:
    - 9% ↑ 5 yr OS, HR 0.66
  - S-1 + Docetaxel > S-1 Stage III JACCRO GC-07: 913 pts, 16.4% increase in 3-year RFS
  - S-1 + Oxali > S1 in node positive disease, no benefit for RT, ARTIST 2

Macdonald NEJM 345:725; 2001 Cunningham NEJM 355: 11; 2006 Sasako JCO 29: 4387; 2011 ; Noh Lancet Oncol 15: 1389;

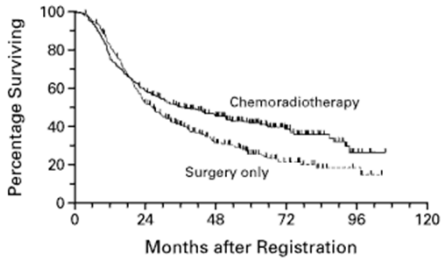
U.S. Intergroup 116 (SWOG 9008)

Gastric Cancer: Adjuvant 5-FU + RT



Macdonald NEJM 345: 725-730; 2001

Overall Survival: INT 116



Macdonald NEJM 345: 725-730; 2001

INT 116: Gastric Cancer Conclusions

- **Biggest impact in decreasing local recurrence**
  - 29% reduced to 19% with FU/RT
- **Surgical resection: 54% had less than a D1 resection**
  - Only 10% had a D2 resection
- **Standard of care for gastric cancer in <D1 resection**

Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4): A multicenter, randomized phase 3 trial

Al-Batran SE, Homann N, Schmalenberg H, Kopp HG, Haag GM, Luley KB, Schmiegel WH, Folprecht G, Probst S, Prasnikar N, Thuss-Patience P, Fischbach W, Trojan J, Koenigsmann M, Pauligk C, Goetze TO, Jaeger E, Lindig U, Kasper S, Hozaeel W, Meiler J, Schuler MH, Hofheinz RD for the German Gastric Study Group at AIO

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FLOT4 Study Design

Deutsche Krebshilfe | AIO

Randomized, multicenter, investigator-initiated, phase II/III study

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

STRATIFICATION

R

n=716

FLOT x4 - RESECTION - FLOT x4

FLOT: docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

ECF/ECX x3 - RESECTION - ECF/ECX x3

ECF/ECX: Epirubicin 50 mg/m2, d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

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FLOT Regimen

- T docetaxel d1 50 mg/m² iv inf.
- O oxaliplatin d1 85 mg/m² iv inf.
- L leucovorin d1 200 mg/m² iv inf.
- F 5-FU d1 2.600 mg/m² iv 24h inf.
  - repeated every 2 weeks

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Baseline 1

	ECF/ECX N=360		FLOT N=356	
Age				
median	62	-	62	-
< 60	160	44%	155	44%
60-69	113	31%	116	33%
>=70	87	24%	85	24%
Sex				
male	265	74%	268	75%
female	95	26%	88	25%
ECOG PS				
0	254	71%	246	69%
1	103	29%	109	31%
2	3	1%	1	<1%
Location				
GEJ Siewert type 1	85	24%	80	23%
GEJ Siewert type 2 or 3	115	32%	118	33%
Stomach	160	44%	158	44%

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Baseline 2

	ECF/ECX N=360		FLOT N=356	
cT-stage				
T1	2	1%	3	1%
T2	59	16%	49	14%
T3	253	70%	267	75%
T4	33	9%	28	8%
unclear	13	4%	9	3%
cN-stage				
N-	70	19%	77	22%
N+	290	81%	279	78%
Barrett's Carcinoma*				
yes	54	15%	53	15%
no	297	83%	301	85%
unclear or unknown	4	1%	2	1%
missing	5	1%	0	-

*Baseline data were supplemented by data form surgical specimen

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Surgery 1

	ECF/ECX (360)	FLOT (356)	P-value
Enrolled	360 (100%)	356 (100%)	
Proceeded to surgery	340 (94%)	345 (97%)	
Rate of resectional tumor surgery (ITT)	313 (87%)	336 (94%)	0.001
Rate of margin-free (R0)-resection (ITT)	276 (77%)	300 (84%)	0.011
Type of surgery			
transthoracic esophagectomy	98 (27%)	109 (31%)	
gastrectomy with or without transhiatal esophagectomy	199 (55%)	208 (58%)	
multivisceral resection	10 (3%)	15 (4%)	
other resectional tumor surgery	6 (2%)	4 (1%)	
palliative (non-curative) resection	6 (2%)	0 (0%)	
non-resectional surgery	22 (6%)	9 (3%)	
no surgery	19 (5%)	11 (3%)	

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Histopathology (ypTN)

ypT-stage	ECF/ECX (360)	FLOT (356)	P-value§
≤T1	53 (15%)	88 (25%)	0.001
T2	44 (12%)	44 (12%)	
T3	175 (49%)	165 (46%)	
T4	47 (13%)	37 (10%)	
NA*	41 (11%)	22 (6.2%)	

ypT-stage	ECF/ECX (360)	FLOT (356)	P-value§
N0	146 (41%)	174 (49%)	0.029
N1	44 (12%)	55 (16%)	
N2	54 (15%)	47 (13%)	
N3	73 (20%)	57 (16%)	
NA*	43 (12%)	23 (7%)	

*NA, not applicable and include patients who could not be staged due to no operation, non-resectional surgery, or tumor regression
§Chi-Square Test

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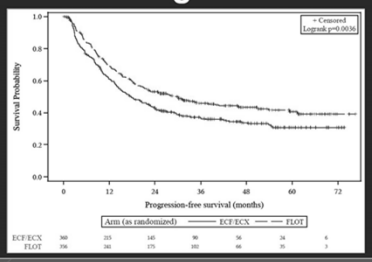
FLOT4: Progression-Free Survival



	ECF/ECX	FLOT
mPFS 18 months months	[15-22]	30 [21-41]
HR	0.75 [0.62-0.91] p=0.004 (log rank)	
PFS rate*	ECF/ECX	FLOT
2y	43%	53%
3y	37%	46%
Projected PFS rates	31%	41%

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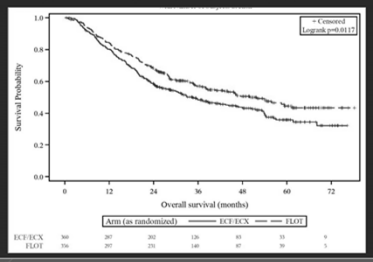
FLOT4: Overall Survival



	ECF/ECX	FLOT
mOS months	[27-46]	35 months [38-na]
HR	0.77 [0.63 - 0.94] p=0.012 (log rank)	
OS rate*	ECF/ECX	FLOT
2y	59%	68%
3y	48%	57%
Projected OS rates	36%	45%

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CLASSIC: Surgery vs XELOX after D2

Surgically (D2) resected Stage II, IIIA, or IIIB GC, 6 weeks prior to randomization

No prior chemotherapy or radiotherapy

n=1035

RANDOMIZATION 1:1†

n=520

8 cycles of XELOX (6 months)

Capecitabine: 1,000mg/m² bid, d1–14, q3w
Oxaliplatin: 130mg/m², d1, q3w

Observation: No adjuvant therapy

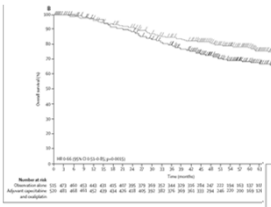
n=515

- **Primary endpoint: 3-year DFS‡**
- **Secondary endpoints: overall survival and safety profile**

†Stratified by stage and country with age, sex, and nodal status as covariates
‡GASTRIC project: 3-year DFS and 5-year overall survival are strongly associated, Burzykowski et al. ASCO 2009

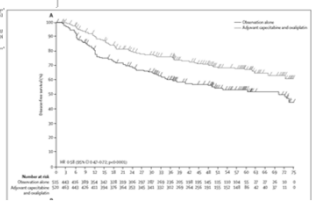
Noh et al Lancet Oncol 15: 1389-1396; 2014

CLASSIC: Surgery vs XELOX after D2



5 yr DFS: 68% vs 53%, HR 0.58, P < 0.001

5 yr OS: 78% vs 69%, HR 0.66, P = 0.0015



Noh et al Lancet Oncol 15: 1389-1396; 2014

ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC)

Se Hoon Park,[1] Dae Young Zhang,[2] Boram Han,[2] Jun Ho Ji,[3] Tae Gyu Kim,[3] Sung Yong Oh,[4] In Gyu Hwang,[5] Jung Hoon Kim,[6] Dong Bok Shin,[7] Do Hoon Lim,[1] Kyoung Mee Kim,[1] Ji Yeong An,[1] Min-Gew Choi,[1] Jun-Ho Lee,[1] Tae Sung Sohn,[1] Jae-Moon Bae,[1] Sung Kim,[1] Seung Tae Kim,[1] Jeeyun Lee[1] and Won Ki Kang[1]

[1]Sungkyunkwan University, Samsung Medical Center, Seoul, Korea; [2]Hallym University Medical Center, Anyang, Korea; [3]Samsung Changwon Hospital, Changwon, Korea; [4]Dong-A University, Busan, Korea; [5]Chung-Ang University, Seoul, Korea; [6]Gyeongsang National University, Jinju, Korea; [7]Gachon University Gil Hospital, Incheon, Korea.

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Adjuvant chemoRadioTherapy In Stomach Tumor 2

- 900 patients with D2 resected gastric adenocarcinoma
- pStage II to III, LN+
- Stratified by (1) stage, (2) type of surgery (STG *v* TG), (3) Lauren classification

RANDOMIZATION

- Adjuvant Chemotherapy with S-1 (S-1 for one year)
- Adjuvant Chemotherapy with SOX (S-1/oxaliplatin for 6 mo)
- Adjuvant Chemoradiotherapy (SOX x2 → S-1/RT → SOX x4)

- Primary endpoint: DFS
- S-1: 40-60 mg bid 4/2 wks q6wks
- SOX: S-1 40 mg/m² bid 2/1 wks q3wks + oxaliplatin 130 mg/m² D1
- S-1/RT: S-1 40 mg bid daily concurrently with RT 45 Gy for 5 wks

1 *ClinicalTrials.gov*, NCT0176146

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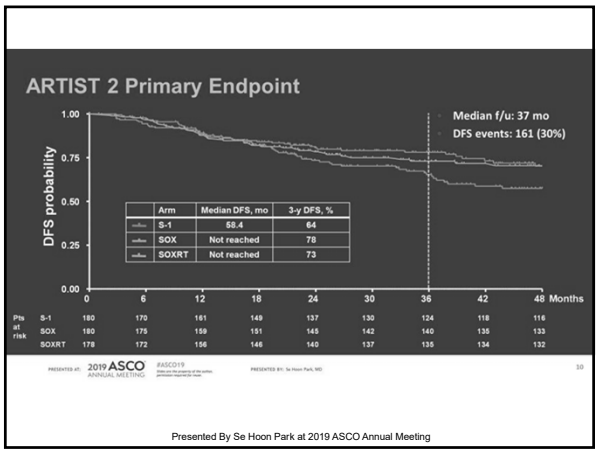

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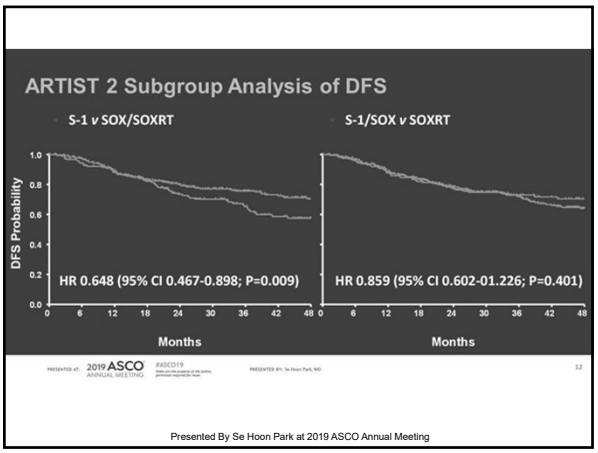

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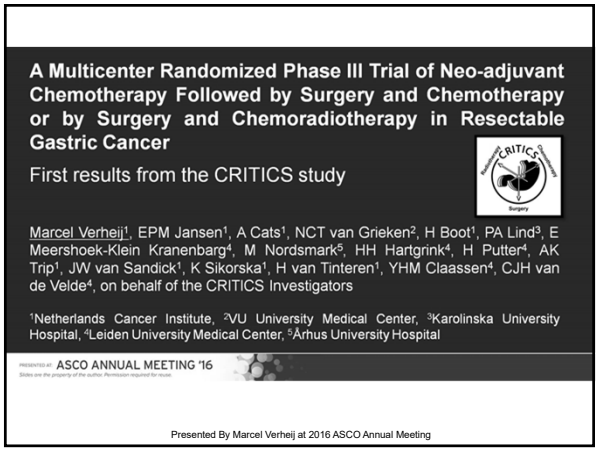

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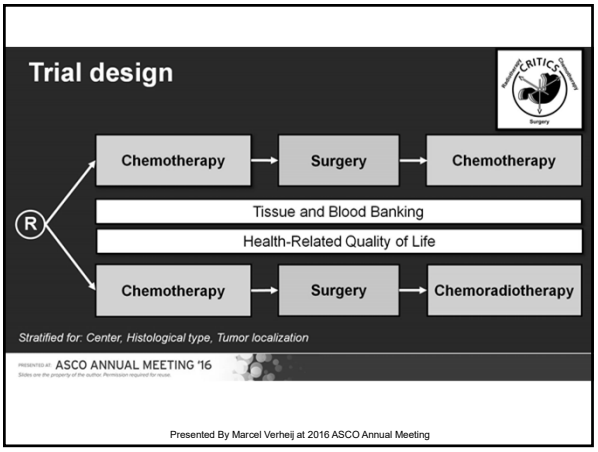

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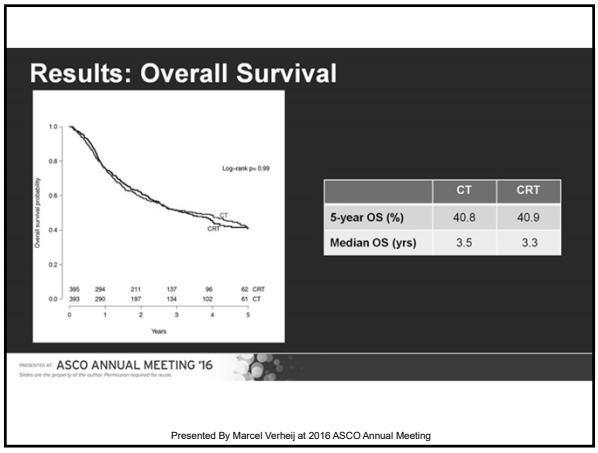
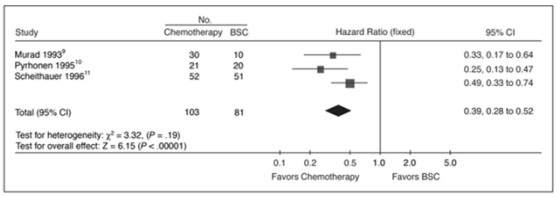


Presented By Marcel Verheij at 2016 ASCO Annual Meeting

What is the role of RT?

- **Gastric Cancer: Extent of Surgery Dictates Need for RT**
- **Higher rates of local recurrence with less than D1-D2**
- **Post op RT + 5-FU/LV: less than a D1 resection**
- **Gastric Cancer: Periop (FLOT) or Post op Chemo (CAPEOX) without RT with D2 resection**

Metastatic Disease: Best Supportive Care vs Chemotherapy



Wagner J Clin Oncol 24: 2903; 2006

Metastatic Disease: Patient Selection for Chemotherapy

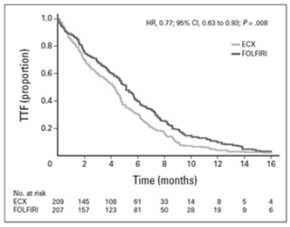
- **2 drug regimens are preferred**
  - FOLFOX, CAPE-OX, FOLFIRI, CAPE-CIS
- **3 drug regimens adding docetaxel (DCF, mDCF, FLOT)**
  - No survival benefit for Doc + S-1/Cisplatin (JCOG 1013)
  - No survival benefit in patients 65 or older: FLOT
  - Epirubicin adds no benefit (NCCN)

Advanced Esophagogastric Cancer Chemotherapy: What Regimen to Use?

	Oxali: EOX or EOF	Cape: ECX or EOX	XP	FLO	FOLFIRI	FUFIRI	S-1 Cis	DCF	ECF
Pts	489	513	160	109	209	170	305	221	126
%RR	44%	45%	41%	34%	39%	32%	54%	36%	45%
TTP, months	6.7	6.5	5.6	5.5	5.3	5.0	6.0	5.6	7.4
OS, months	10.9	10.4	10.5	10.7	9.5	9.0	13.0	9.2	8.9

Cunningham NEJM 358:36;2008, Kang Annals Oncol 20:666;2009, Al-Batran JCO 26:1435;2008, Dank Annals Oncol 19:450;2008 Koizumi Lancet Oncol 9:215;2008, Van Cutsem JCO 24:4991;2006, Webb JCO 15:61;1997

Does Epirubicin add benefit? FOLFIRI vs ECX



- **416 patients**
- **1/3 GEJ, 2/3 Gastric**
- **RR 39% vs 38%**
- **PFS 5.3 vs 5.8 months**
- **OS 9.5 vs 9.7 months**
- **TTF, toxicity favored first line FOLFIRI over ECX**

Gimbaud J Clin Oncol 32: 3520; 2014

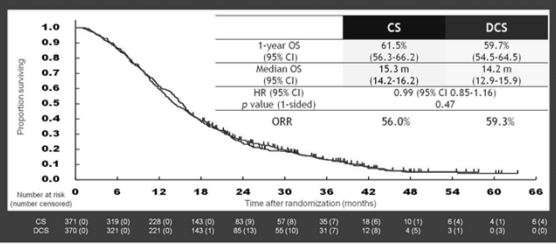
Abstract #4009: Phase III study comparing triplet chemotherapy with S-1 and cisplatin plus docetaxel versus doublet chemotherapy with S-1 and cisplatin for advanced gastric cancer (JCOG1013)

Yasuhide Yamada, Narikazu Boku, Junki Mizusawa, Satoru Iwasa, Shigenori Kadowaki, Norisuke Nakayama, Mizutomo Azuma, Takeshi Sakamoto, Kohei Shitara, Tatsuya Okuno, Keisho Chin, Akira Nozaki, Masaki Nakamura, Hiroki Hara, Hiroshi Katayama, Haruhiko Fukuda, Takaki Yoshikawa, Takeshi Sano, Mitsuru Sasako, Masanori Terashima

Stomach Cancer Study Group of Japan Clinical Oncology Group (JCOG), Japan

Presented By Joseph Chao at 2018 ASCO Annual Meeting

Primary Endpoint: Overall survival (OS)



	CS	DCS
1-year OS (95% CI)	61.5% (56.3-66.2)	59.7% (54.5-64.5)
Median OS (95% CI)	15.3 m (14.2-16.2)	14.2 m (12.9-15.9)
HR (95% CI)	0.99 (95% CI 0.85-1.16)	
p value (1-sided)	0.47	
ORR	56.0%	59.3%

Presented By Joseph Chao at 2018 ASCO Annual Meeting

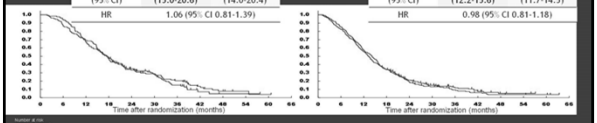
Key Secondary Endpoint: OS according to histological type

Intestinal type (n=259)

	CS	DCS
Median OS (95% CI)	17.5 m (15.0-20.6)	17.5 m (14.0-20.4)
HR	1.06 (95% CI 0.81-1.39)	

Diffuse type (n=482)

	CS	DCS
Median OS (95% CI)	14.2 m (12.2-15.6)	13.3 m (11.7-14.5)
HR	0.98 (95% CI 0.81-1.18)	



Overall survival was significantly shorter in the diffuse type (median, 13.7 months, 95% CI 12.5-14.6) than in the intestinal type (17.5 months, 15.7-18.9; HR 1.38, 95% CI 1.17-1.62).

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Presented By Joseph Chao at 2018 ASCO Annual Meeting

Second Line Chemo Gastric Phase III Trials ➔ Taxanes and Irinotecan Improve Survival

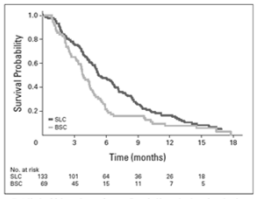


Fig 2. Kaplan-Meier estimates for overall survival in randomly assigned patients. BSC, best supportive care; SLC, salvage chemotherapy.

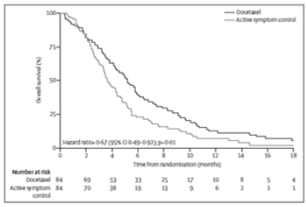


Figure 2: Kaplan-Meier plot of overall survival

Docetaxel/Irinotecan vs BSC

Docetaxel vs BSC

Ford H ***Lancet Oncol 15:78; 2014;*** **Kang JH** ***J Clin Oncol 30:1513; 2012***

TAGS: TAS-102 Gastric Study[a]

Patients with mGC
(including GEJ cancer)
- ≥2 prior regimens:
  - Fluoropyrimidine
  - Platinum
  - Taxane and/or irinotecan
  - HER2 inhibitor, if available, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 y in Japan)

Target sample size: 500

R 2:1

FTD/TPI (TAS-102) + BSC (n=337)
35 mg/m² BID orally on days 1–5 and 8–12 of each 28-day cycle

Placebo + BSC (n=170)
BID orally on days 1–5 and 8–12 of each 28-day cycle

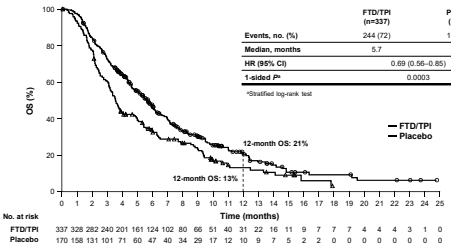
End points
- Primary:
  - OS
- Key secondary:
  - PFS, safety
- Other secondary:
  - ORR
  - DCR
  - QOL
  - Time to ECOG PS ≥2

- Treatment until progression, intolerable toxicity, or patient withdrawal
- Multicenter, randomized, double-blind, placebo-controlled, phase III study
  - Stratification: ECOG PS (0 vs 1), region (Japan vs ROW), prior ramucirumab (yes vs no)
  - Sites: 18 countries, 110 sites; enrollment: February 2016 – January 2018
  - Data cutoff date: March 31, 2018
  - Target 384 events allowed detection of HR for death of 0.70 with 90% power at 1-sided type 1 error of 0.025

BID, twice daily; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ORR, overall response rate; PFS, progression-free survival; QOL, quality of life; ROW, rest of world; [a]NCT02500043

45

Primary Endpoint – OS



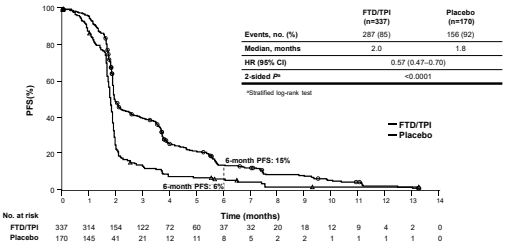
	FTD/TPI (n=337)	Placebo (n=170)
Events, no. (%)	244 (72)	140 (82)
Median, months	5.7	3.6
HR (95% CI)	0.69 (0.56–0.85)	
1-sided *P*[a]	0.0003	

[a]Stratified log-rank test

ITT population

46

Secondary Endpoint – PFS



	FTD/TPI (n=337)	Placebo (n=170)
Events, no. (%)	287 (85)	156 (92)
Median, months	2.0	1.8
HR (95% CI)	0.57 (0.47–0.70)	
2-sided *P*[a]	<0.0001	

[a]Stratified log-rank test

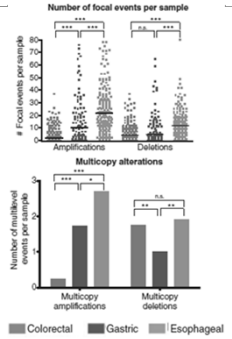
ITT population

47

TCGA: Gene Amplification in Esophagogastric Cancer

296 Esophageal / Gastric Cancers, 190 CRC

- **Amplified genes in 37% Gas / Eso tumors**
  - EGFR
  - HER2
  - MET
  - FGFR1-2
  - KRAS
- **Targetable Receptors and Receptor Tyrosine Kinases**

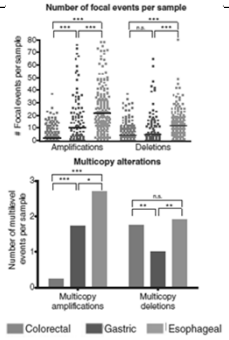


Dulak AM et al Can Res 72: 4383; 2012

Gene Amplification in Esophagogastric Cancer

296 Esophageal / Gastric Cancers, 190 CRC

- **Amplified genes in 37% Gas / Eso tumors**
  - EGFR: failed
  - HER2: mixed
  - MET: failed
  - FGFR1-2: ongoing
  - KRAS
- **Targetable Receptors and Receptor Tyrosine Kinases**



Dulak AM et al Can Res 72: 4383; 2012

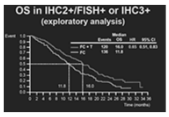
Four Genomic Subsets: Therapeutic Implications of TCGA

- **Genomically unstable**
  - RTK directed therapy: HER2 only success
- **MSI**
  - Immune checkpoint inhibitors: approved for refractory MSI high solid tumors
- **Genomically stable**
  - Not clearly targetable
- **Epstein-Barr virus**
  - PIK3CA, immune checkpoint inhibitors

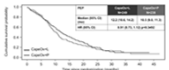
Nature 24: 2903; 2014

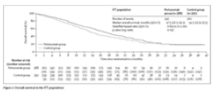
HER2: Esophagogastric Cancer is not Breast Cancer

- **Trastuzumab + first line activity**
  - TOGA: Cape-Cis + trastuzumab improved RR, PFS, OS
- **First Line Lapatinib (LOGIC) + Cape / Oxaliplatin**
  - No difference in OS
  - 12.2 vs 10.5 mos (HR 0.91)
- **Pertuzumab (JACOB) failed to improve OS + Trastuzumab / Cisplatin / FP**
  - 780 pts
  - OS 17.5 vs 14.2 mos (HR 0.84, p = 0.056)



Primary Endpoint: Overall Survival

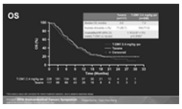


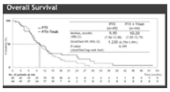


Bang Lancet 376: 687; 2010, Hecht JCO 34: 443; 2016, Tabernero Ann Oncol 28: 2017

HER2 Targeted Agents: Second Line

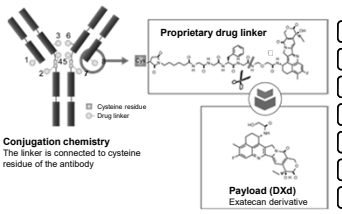
- **Second line: trastuzumab emtansine (TDM-1) no better than a taxane in 345 pts (OS 7.9 vs 8.6 mos, HR 1.15)**
- **T-ACT: phase II tras continuation**
  - 90 pts first line Tras
  - Paclitaxel + / - Tras
  - PFS primary endpoint
  - No difference PFS, OS
- **De novo and acquired HER2 resistance are likely**





Bang Lancet 376: 1302; 2010, Makiyama J Clin Oncol 38: 2018 (suppl, Abst 4011)

Trastuzumab Deruxtecan Structure and Mechanism of Action[1]



- Payload with a different MOA
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio

- Trastuzumab deruxtecan (DS-8201a) designed with goal of improving critical attributes of an ADC

1. Iwata H et al. *J Clin Oncol.* 2018;36(15 suppl):2501-2501.

PeerView.com

DESTINY-Gastric01: Phase 2 Trial of Trastuzumab Deruxtecan in Advanced HER2+ Gastric Cancer[1]

Patients must have
- Pathologically documented locally advanced or metastatic gastric or GEJ cancer
- Progression on and after ≥2 prior regimens
- Adequate tumor sample
- Measurable disease based on RECIST 1.1

N = ~220

- **Experimental**: Trastuzumab deruxtecan (IV infusion every 3 weeks)
- **Active comparator:** Physician's choice of irinotecan 150 mg/m^2 biweekly or paclitaxel 80 mg/m^2 weekly
- **Exploratory:** Trastuzumab deruxtecan (IV infusion every 3 weeks) in max 20 pts with naïve HER2 IHC 2+/ISH- disease
- **Exploratory:** Trastuzumab deruxtecan (IV infusion every 3 weeks) in max 20 pts with naïve HER2 IHC 1+ disease

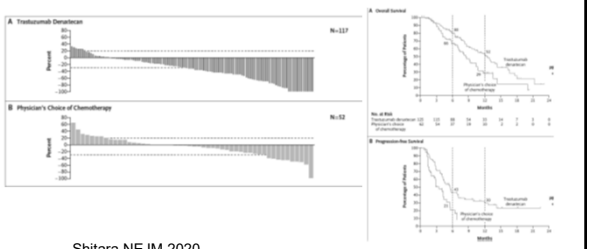
Outcomes

Primary: % of participants in the experimental and active comparator groups with objective response
Secondary: % of participants in the experimental and active comparator groups with PFS, OS, DOR, DCR, TTF, ORR, Cmax, AUClast, and AUC0-21

https://clinicaltrials.gov/ct2/show/NCT03329690

PeerView.com

DESTINY Gastric01



Shitara NEJM 2020

PeerView.com

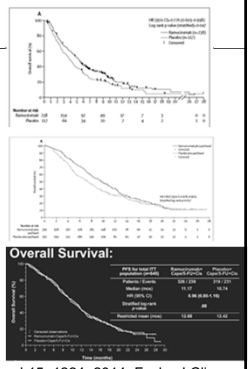
Phase III Trials: EGFr

- **Trials conducted with no biomarker selection of patients**
- **REAL 3: ECX + / - Panitumumab (U.K.)**
  - Negative: Panitumumab had inferior outcomes
- **EXPAND: Cape-Cis + / Cetuximab (E.U.)**
  - Negative: Cetuximab trended inferior
- **Nimotuzumab: Phase II Irinotecan + / - N second line**
  - PFS 75 vs 83 days, OS 250 vs 232 days
- **COG: BSC vs Gefitinib (U.K.): Negative**
  - EGFR amplification or copy number a predictive biomarker

Waddell T Lance Oncol 14: 481; 2013 Lordick F et al Lancet 14:490; 2013, Stoh Gastric Cancer 18: 824; 2015, Sutton JCO 30: 2012 (suppl 34 abstr 6)

Angiogenesis Agents

- **Ramucirumab: VEGFR2**
- **Second line: RAM vs BSC: Improved OS, PFS**
  - REGARD
- **Second Line: Pac/RAM vs Pac: Improved OS, PFS, RR**
  - RAINBOW
- **First line: Cape/Cis/RAM vs Cape/Cis: failed to improve OS, RR, despite improvement in PFS**
  - **RAINFALL**



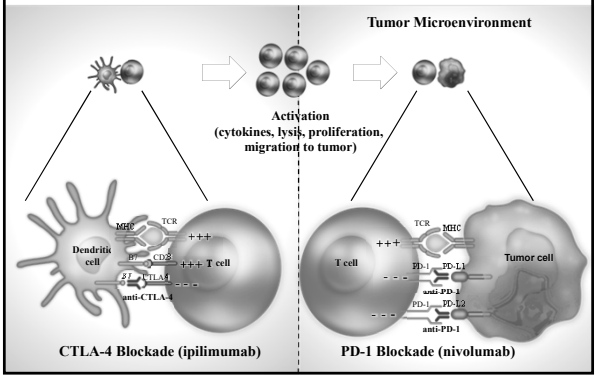
Fuchs Lancet 383: 31; 2013, Wilke Lancet Oncol 15: 1224; 2014, Fuchs J Clin Oncol 36: 2018

Angiogenesis: TKI + Immunotherapy

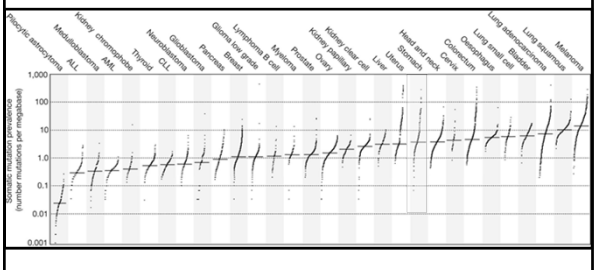
- **Regorafenib + Nivolumab: 40% RR in gastric in 25 pts**
- **Lenvatinib + Pembro (first/second line): 69% RR in 29 pts**

Fukuoka J Clin Oncol 38: 2053; 2020 Shitara Lance Oncol 21: 1057; 2020

Blocking CTLA-4 and PD-1



Somatic Mutation Prevalence



LB Alexandrov *et al. Nature* **000**, 1-7 (2013) doi:10.1038/nature12477

Immunotherapy in Esophagogastric Cancer: Anti PD-1, PDL-1 Antibodies

- **Single agent activity in refractory disease**
  - KEYNOTE 59: Pembrolizumab
  - Attraction 2: Nivolumab vs BSC
  - Javelin 300: Avelumab vs Physician choice
- **Comparison with second line chemotherapy**
  - KEYNOTE 61: Pembro vs Paclitaxel, adenocarcinoma
  - KEYNOTE 181: Pembro vs MD choice, SCC
  - Attraction 3: Nivolumab vs MD choice, SCC
- **First line use with or without chemotherapy**
  - KEYNOTE 62: Pembro, GEJ and gastric adeno
  - JAVELIN 100: Avelumab maintenance therapy after FP

Immunotherapy in Esophagogastric Cancer

- **Single agent activity in refractory disease**
  - KEYNOTE 59: Pembrolizumab, + MSI high and PDL-1+
  - Attraction 2/ONO: Nivolumab vs BSC
  - Javelin 300: Avelumab vs Physician choice
- **Comparison with second line chemotherapy**
  - KEYNOTE 61: Pembro vs Paclitaxel, adenocarcinoma
  - KEYNOTE 181: Pembro vs MD choice, SCC
- **First line use with or without chemotherapy**
  - KEYNOTE 62: GEJ and gastric adeno
  - JAVELIN 100: Avelumab maintenance therapy after FP
  - KEYNOTE 811: HER2+, chemo/tras + / - Pembro Ongoing
  - CHECKMATE 649: FOLFOX + / - Nivo
    - + for OS in PDL-1 5% or higher (press release)

Nivolumab (ONO-4538/BMS-936558) as Salvage Treatment After Second- or Later-Line Chemotherapy for Advanced Gastric or Gastroesophageal Junction Cancer (AGC): A Double-Blinded, Randomized, Phase 3 Trial

Yoon-Koo Kang,[1] Taroh Satoh,[2] Min-Hee Ryu,[1] Yee Chao,[3] Ken Kato,[4] Hyun Cheol Chung,[5] Jen-Shi Chen,[6] Kei Muro,[7] Won Ki Kang,[8] Takaki Yoshikawa,[9] Sang Cheul Oh,[10] Takao Tamura,[11] Keun-Wook Lee,[12] Narikazu Boku,[4] Li-Tzong Chen[13]

[1]Department of Oncology, University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea; [2]Frontier Science for Cancer and Chemotherapy, Osaka University Graduate School of Medicine, Suita, Japan; [3]Department of Oncology, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan; [5]Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Song Dang Institute for Cancer Research, Yonsei University College of Medicine, Yonsei University Health System, Seoul, Korea; [6]Division of Hematology/Oncology, Department of Internal Medicine, Linkou Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan; [7]Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [8]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [9]Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; [10]Division of Hematology/Oncology, Internal Medicine Department, College of Medicine, Korea University, Seoul, Korea; [11]Medical Oncology, Kindai University, Faculty of Medicine, Osakasayama, Japan; [12]Division of Hematology/Oncology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea; [13]National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan

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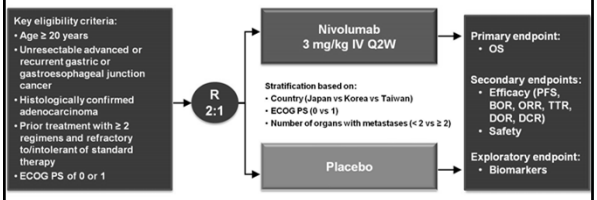
Presented By Yoon-Koo Kang at 2017 Gastrointestinal Cancers Symposium

Study Design and Endpoints



- Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Q2W, every 2 weeks; R, randomization; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response.

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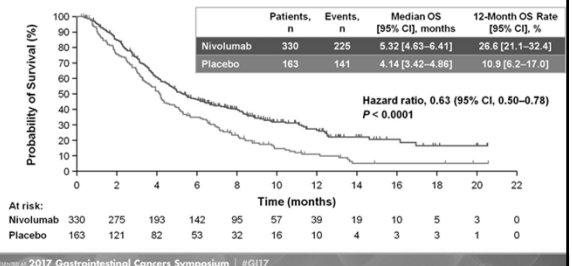
Overall Survival



	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]

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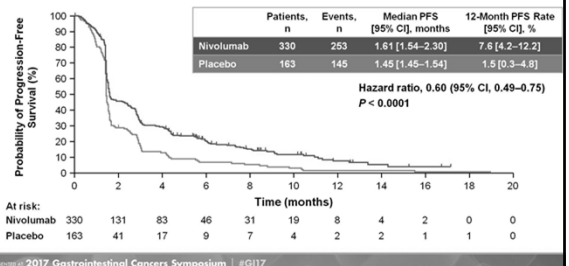
Progression-Free Survival



	Patients, n	Events, n	Median PFS [95% CI], months	12-Month PFS Rate [95% CI], %
Nivolumab	330	253	1.61 [1.54–2.30]	7.6 [4.2–12.2]
Placebo	163	145	1.45 [1.45–1.54]	1.5 [0.3–4.8]

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RECIST Response and Disease Control

	Nivolumab 3 mg/kg (n = 268)	Placebo (n = 131)
ORR, n (%) [95% CI] *P* value	30 (11.2) [7.7–15.6] < 0.0001	0 [0–2.8] —
BOR, n (%)		
Complete response	0	0
Partial response	30 (11.2)	0
Stable disease	78 (29.1)	33 (25.2)
Progressive disease	124 (46.3)	79 (60.3)
DCR, n (%) [95% CI] *P* value	108 (40.3) [34.4–46.4] 0.0036	33 (25.2) [18.0–33.5] —
Median TTR (range), months	1.61 (1.4–7.0)	—
Median DOR, months [95% CI]	9.53 [6.14–9.82]	—

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KEYNOTE-059 Cohort 1: Efficacy and Safety of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric Cancer

Charles S. Fuchs,[1] Toshihiko Doi,[2] Raymond WJ Jang,[3] Kei Muro,[4] Taroh Satoh,[5] Manuela Machado,[6] Weijing Sun,[7] Shadia I. Jalal,[8] Manish Shah,[9] Jean-Phillipe Metges,[10] Marcelo Garrido,[11] Talia Golan,[12] Mario Mandala,[13] Zev A. Wainberg,[14] Daniel V.T. Catenacci,[15] Yung-Jue Bang,[16] Jared Lunceford,[17] Mary Savage,[17] Jiangdian Wang,[17] Minori Koshiji,[17] Rita P. Dalal,[17] Harry H. Yoon[18]

[1]Yale Cancer Center, New Haven, CT, USA; [2]National Cancer Center East, Chiba, Kashiwa, Japan; [3]Princess Margaret Cancer Center, Toronto, ON, Canada; [4]Aichi Cancer Center Hospital, Nagoya, Aichi, Japan; [5]Graduate School of Medicine, Osaka University, Suita, Osaka, Japan; [6]Portuguese Institute of Oncology, Porto, Portugal; [7]University of Pittsburgh, Pittsburgh, PA, USA; [8]Indiana University School of Medicine, Indianapolis, IN, USA; [9]Weill Cornell Medical College; New York Presbyterian Hospital, New York, NY, USA; [10]Centre Hospitalier Regional Universitaire (CHRU) de Brest - Hopital Morvan, Brest, CEDEX, France; [11]Pontificia Universidad Católica de Chile, Santiago, Chile; [12]Sheba Medical Center at Tel Hashomer, Ramat Gan, Israel; [13]ASST Papa Giovanni XXIII, Bergamo, Italy; [14]Ronald Reagan UCLA Medical Center, Los Angeles, CA, USA; [15]University of Chicago Medicine, Chicago, IL, USA; [16]Seoul National University Hospital, Seoul, South Korea; [17]Merck & Co., Inc., Kenilworth, NJ, [18]Mayo Clinic, Rochester, MN, USA

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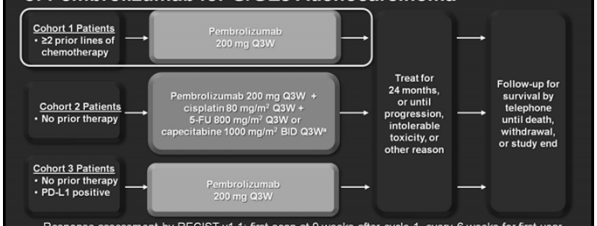
KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma



Response assessment by RECIST v1.1: first scan at 9 weeks after cycle 1, every 6 weeks for first year, followed by every 9 weeks

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[a]Capecitabine was administered only in Japan

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Baseline Disease Characteristics

Characteristic, n (%)	N = 259
Previous surgery for gastric cancer	
Yes (gastrectomy, other)	66 (25.5)
No	193 (74.5)
HER2 positive	63 (24.3)
PD-L1 expression	
Positive	148 (57.1)
Negative	109 (42.1)

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Response in All Patients

Response[a]	N = 259	
	%	95% CI
ORR (CR + PR)	11.6	8.0-16.1
CR	2.3	0.9-5.0
PR	9.3	6.0-13.5
SD	16.2	11.9-21.3
PD	56.0	49.7-62.1
DCR[b]	27.0	21.7-32.9

- Median (range) follow-up: 5.8 months (0.5-21.6)

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[a]Only confirmed responses were included [b]CR + PR + SD≥2 months

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Response by PD-L1 Expression

Response[a]	PD-L1 Positive (n = 148)		PD-L1 Negative (n = 109)	
	%	95% CI	%	95% CI
ORR	15.5	10.1-22.4	6.4	2.6-12.8
CR	2.0	0.4-5.8	2.8	0.6-7.8
PR	13.5	8.5-20.1	3.7	1.0-9.1
DCR[b]	33.1	25.6-41.3	19.3	12.3-27.9

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[a]Only confirmed responses were included [b]CR + PR + SD≥2 months

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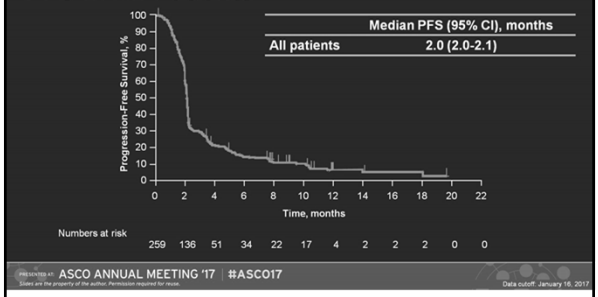
PFS in All Patients



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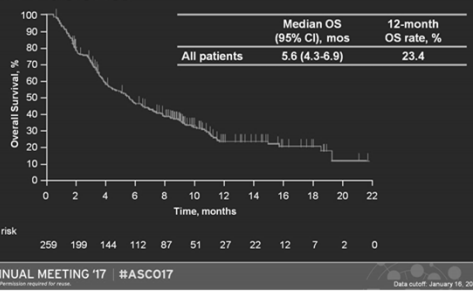
OS in All Patients



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Response by MSI Status (n = 174)

4.0% of patients were MSI-High

Response[a]	MSI-High (n = 7)		Non–MSI-High (n = 167)	
	%	95% CI	%	95% CI
ORR	57.1	18.4-90.1	9.0	5.1-14.4
CR	14.3	0.4-57.9	2.4	0.7-6.0
PR	42.9	9.9-81.6	6.6	3.3-11.5
DCR[b]	71.4	29.0-96.3	22.2	16.1-29.2

[a]Only confirmed responses were included (CR + PR = SD≥2 months). Data cutoff: January 16, 2017.

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Pembrolizumab vs Paclitaxel for Previously Treated Advanced Gastric or Gastroesophageal Junction Cancer: Phase 3 KEYNOTE-061 Trial

Charles S. Fuchs,[1] Mustafa Özgüroğlu,[2] Yung-Jue Bang,[3] Maria Di Bartolomeo,[4] Mario Mandalà,[5] Min-Hee Ryu,[6] Lorenzo Fornaro,[7] Tomasz Olesiński,[8] Christian Caglevic,[9] Hyun Cheol Chung,[10] Kei Muro,[11] Eray Goekkurt,[12] Wasat Mansoor,[13] Raymond S. McDermott,[14] Einat Schacham-Shmueli,[15] Xinqun Chen,[16] S. Peter Kang,[16] Carlos Mayo,[16] Atsushi Ohtsu,[17] Kohei Shitara[17]

[1]Yale Cancer Center, New Haven, CT, USA; [2]Istanbul University, Cerrahpaşa School of Medicine, Istanbul, Turkey; [3]Seoul National University College of Medicine, Seoul, South Korea; [4]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [5]Papa Giovanni XXIII Hospital, Bergamo, Italy; [6]Asan Medical Center, Seoul, South Korea; [7]Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy; [8]Maria Skłodowska-Curie Memorial Cancer Center, Warsaw, Poland; [9]Instituto Oncológico Fundación Arturo López Pérez, Santiago, Chile; [10]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea; [11]Aichi Cancer Center Hospital, Nagoya, Japan; [12]Hematology Oncology Practice Eppendorf (HOPE), Hamburg, Germany; [13]Christie Hospital NHS Foundation Trust, Manchester, UK; [14]Adelaide and Meath Hospital, Dublin, Ireland; [15]Rebba Medical Center, Ramat Gan, Israel; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]National Cancer Center Hospital East, Kashiwa, Japan

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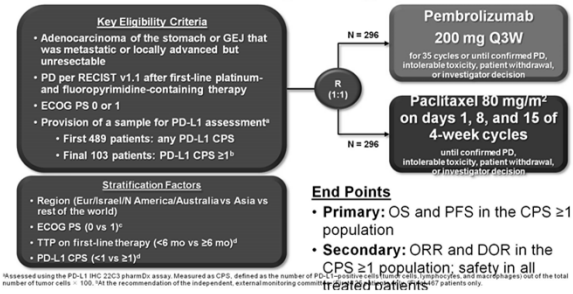
KEYNOTE-061 Study Design (NCT02370498)



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay. Measured as CPS, defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, and macrophages) out of the total number of tumor cells × 100. [b]At the recommendation of the independent, external monitoring committee, data were analyzed for the first 407 patients only.

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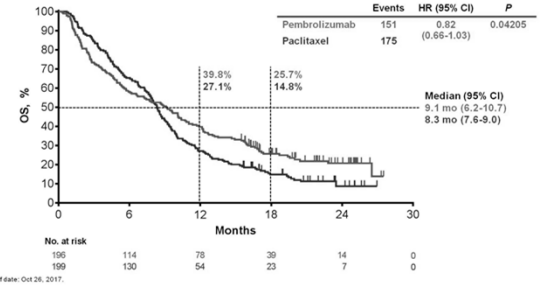
Overall Survival, CPS ≥1



Data cutoff date: Oct 26, 2017.

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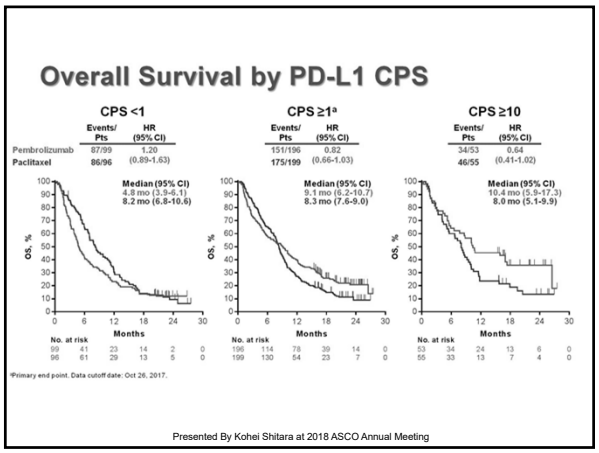

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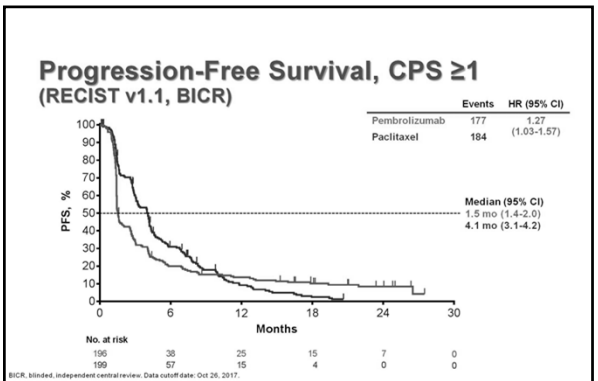

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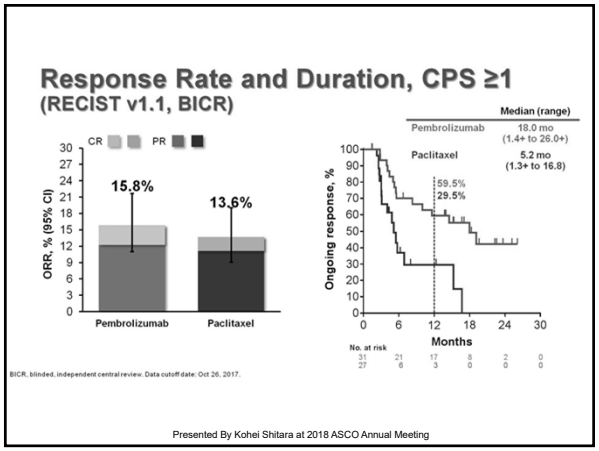

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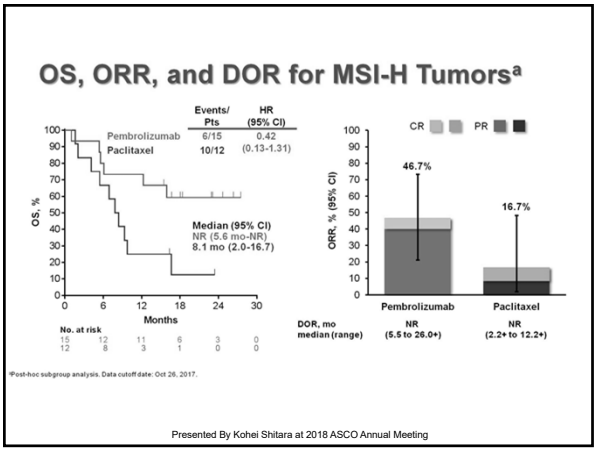

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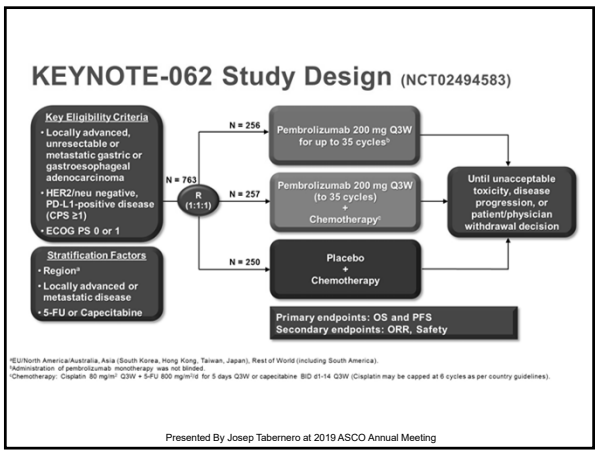

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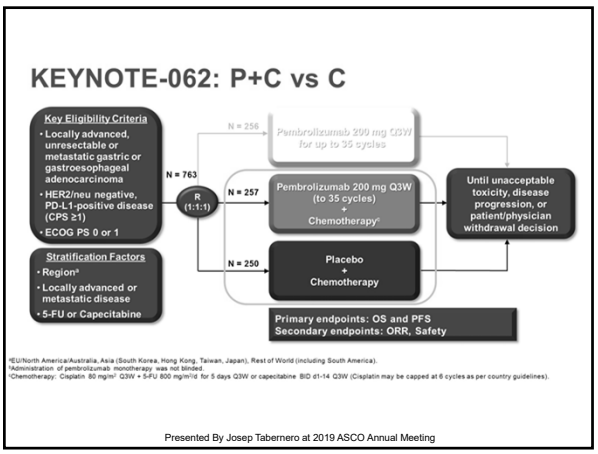

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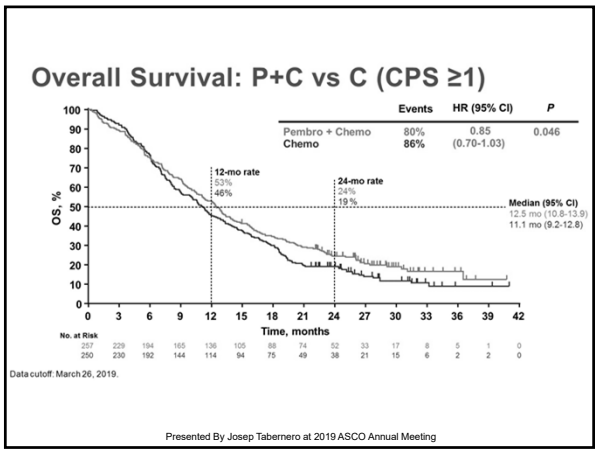

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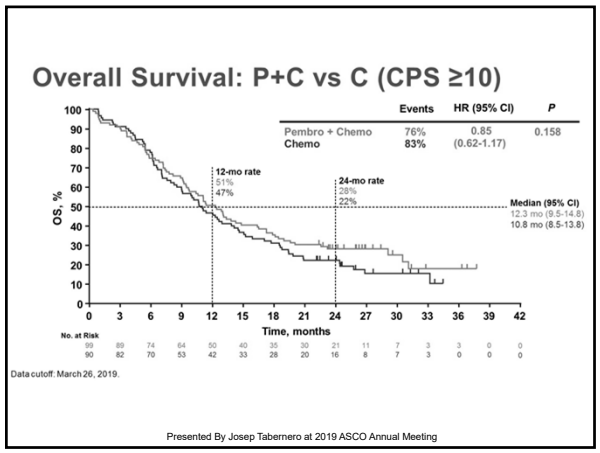

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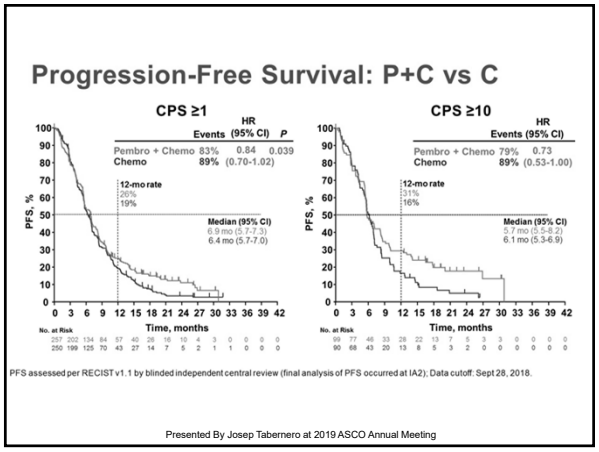

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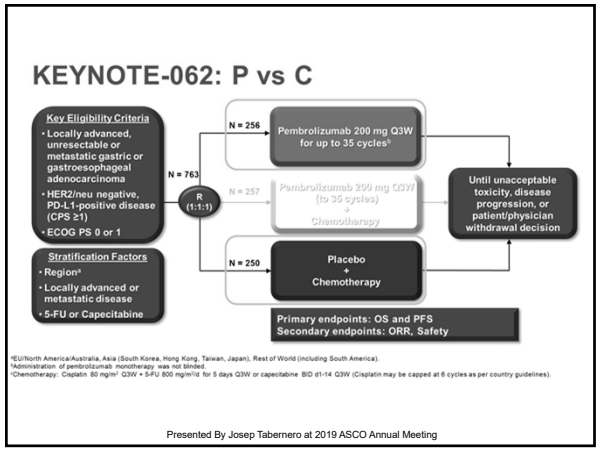

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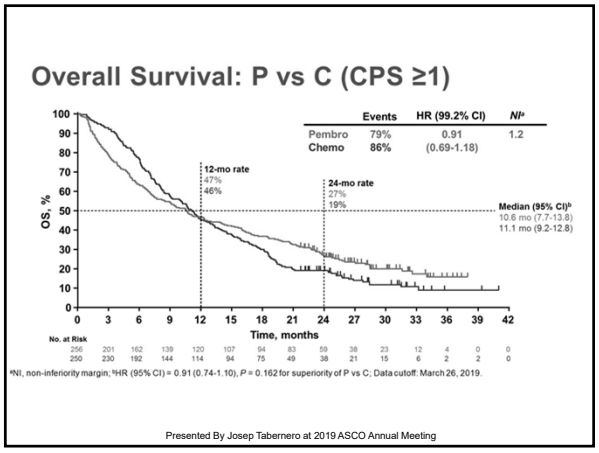

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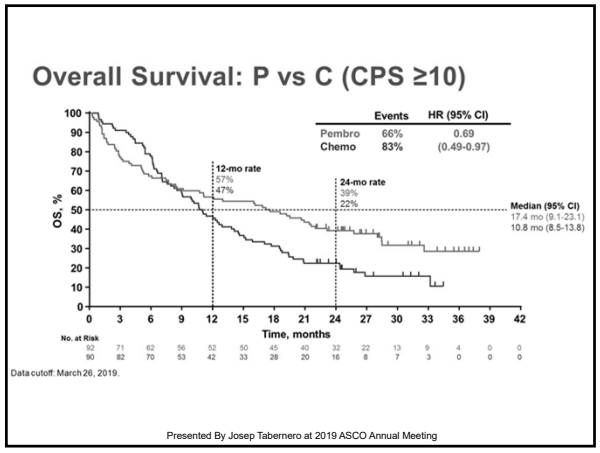

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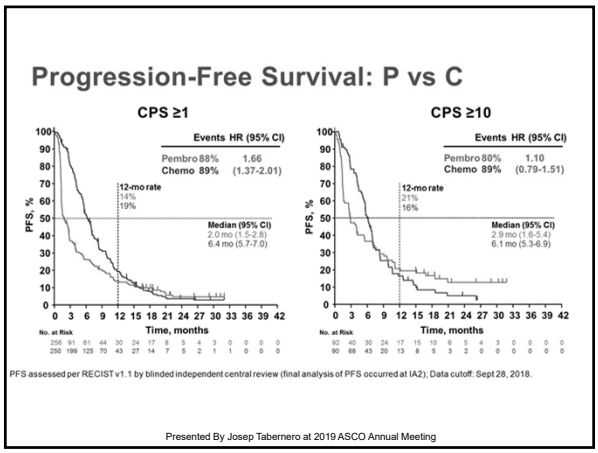

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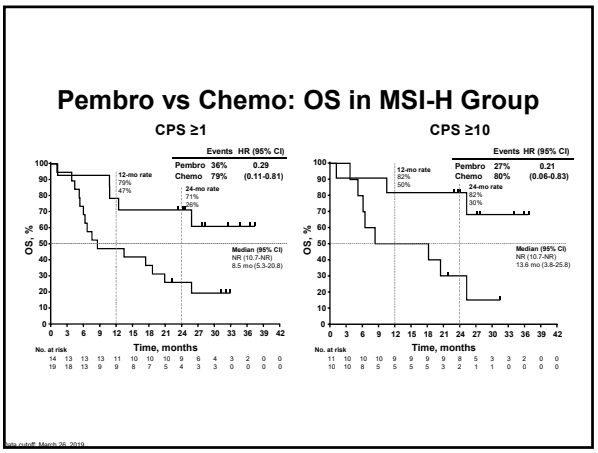

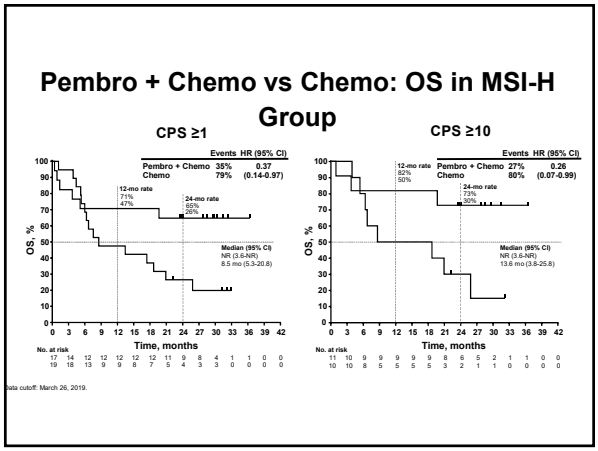

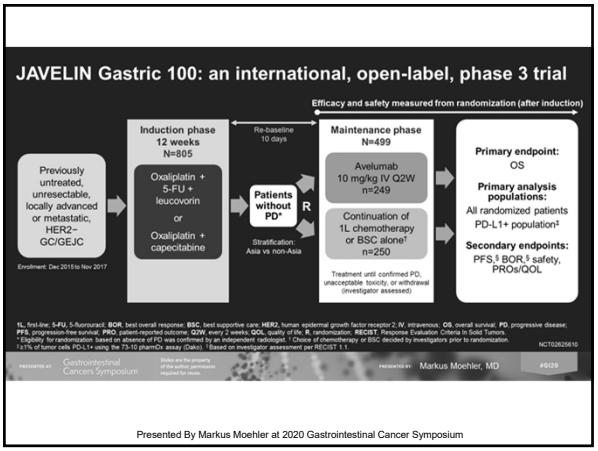

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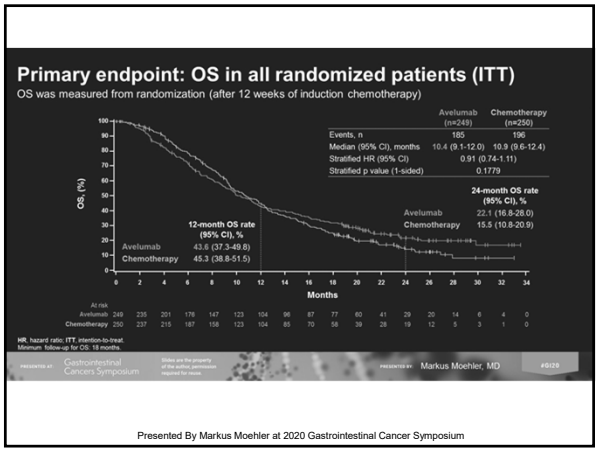

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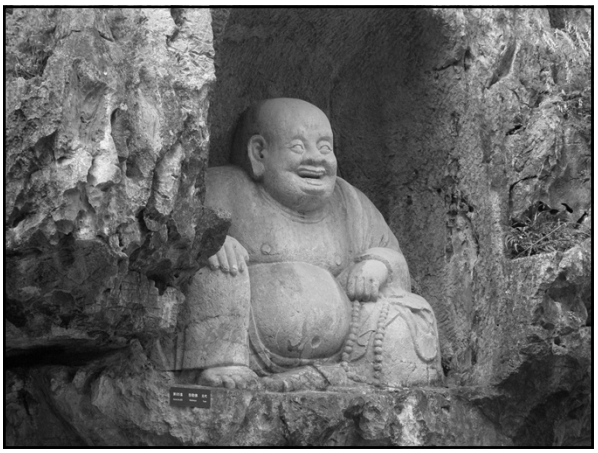
Gastric Cancer: Summary

- **Poor survival with Surgery Alone (20-30%)**
- **Adjuvant Therapy for Gastric Cancer:**
  - Surgery followed by 5-FU + RT (less than a D1-2 resection)
  - Pre and Post Op Chemo with ECF
    - Post op RT added no benefit
    - FLOT superior to ECF
  - Adjuvant chemo alone after D2 resection
    - RT adds no benefit

Gastric Cancer: Summary

- **Metastatic Disease**
  - Platinum + FU +/ - third drug
    - ECF, DCF, FLOT standard
    - Epirubicin may not add benefit
  - Two drugs (FOLFOX, FOLFIRI, Cape-Cis or Oxali) less toxic
  - Oxaliplatin, capecitabine = Cis, 5-FU
  - Second Line: taxane or irinotecan
- **Targeted therapies**
  - Trastuzumab improves outcome in HER2+ esophagogastric ca first line
  - Ramucirumab alone or with Paclitaxel improves outcomes second line
  - Pembrolizumab: approved for MSI-H, PDL-1 + refractory disease
    - Does not add to chemo first line in PDL-1 +
    - (Nivo/FOLFOX)



69

Metastatic Colon and Rectal Cancer

John L. Marshall, MD

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

69 – Metastatic Therapy for Colon and Rectal Cancer

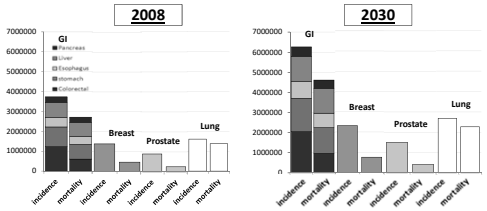
John L Marshall, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- Genentech, Amgen, Bayer, Taiho, Celgene, Merck, Caris, Indivumed

Worldwide Cancers Statistics



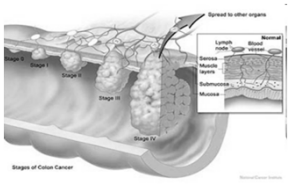
F. Bray et al, Lancet Oncol 2012; 13: 790–801 and *http://www.cancer.org/aboutus/globalhealth*. 2030 values are estimated using projected incidence and mortality rates from 2008 to 2030 and weighting for prevalence in developed compared to developing countries.

What do you see?

FU
FU
FU
FU
FU

5-FU!

Our Current Model of Colon Cancer



Colorectal Cancer: 20 Years Later
meta-analysis 1992 80405 results

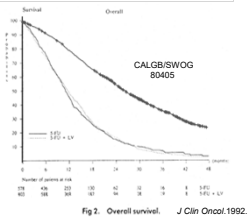
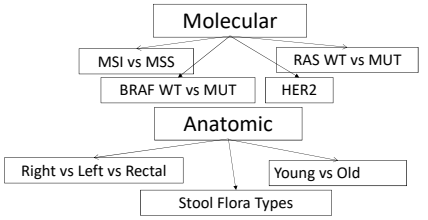


Fig 2. Overall survival. *J Clin Oncol*. 1992.

Reference for 1992 meta-analysis? J Clin Oncol. 1992 Jun;10(6):896-903.Really is venoon by permission

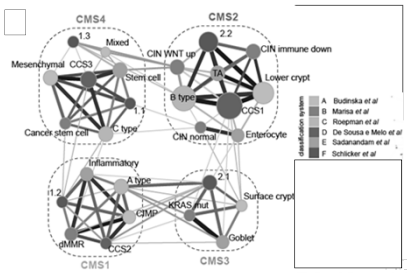
Colon Cancer: More than One Disease



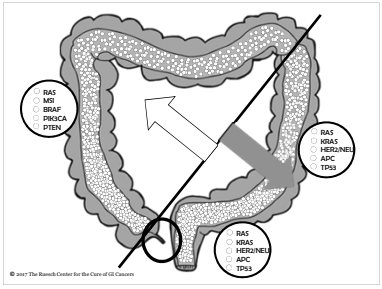
How and When to Test in CRC

- All stages, right away
  - MSI/MSS
- Metastatic disease, right away
  - RAS
  - BRAF
  - MSI
  - HER2
  - NTRK
- Tissue vs Liquid based
  - Similar TAT
  - Not the same
  - Tissue the standard

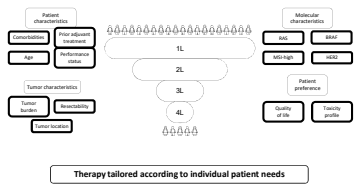
The Colorectal Cancer Consortium Consensus for Molecular Subtypes (n >4500)



Guinney J, et al. *Nat Med*. 2015;21(11):1350-1356.



What influences treatment choices in mCRC?

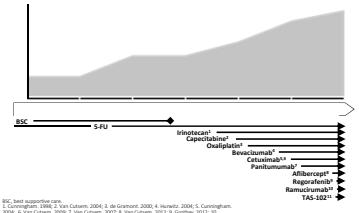


Therapy tailored according to individual patient needs

The Chess Board in Met CRC

- For all
  - 5FU/Cape
  - Oxali
  - Irinotecan
  - VEGF
  - TAS-102
  - Regorafanib
- For left, RAS WT, BRAF WT
  - Cetuximab
  - Panitumumab
- For BRAF v600e
  - Encorafanib, EGFR
- For rare tumors
  - HER2
    - Traztuzimab
  - NTRK
    - Larotrectinib
    - Entrectinib
  - MSI-H
    - Pembro
    - Nivo/ipi

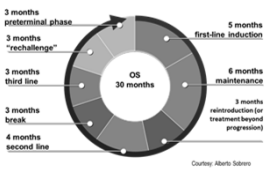
OS: Improvement Over Time



BSC, best supportive care.
1. Cunningham. 1998; 2. Van Cutsem. 2004; 3. de Gramont. 2000; 4. Hurwitz. 2004; 5. Cunningham. 2004; 6. Van Cutsem. 2009; 7. Van Cutsem. 2007; 8. Van Cutsem. 2012; 9. Grothey. 2012; 10. Tabernero. 2015; 11. Mayer. 2015; 12. Vaughn. 2011; 13. Sanoff. 2015.

Likely Never Resectable

- RT/LT
- RAS/BRAF/HER2/MSI
- Not how MUCH chemo but how LITTLE
- But always check back to see if a loco-regional approach might help
- Remove the primary?

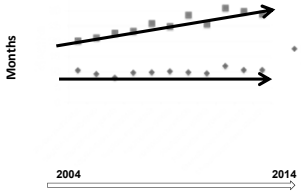


Courtesy: Alberto Sobrero

How to begin: 1st Line

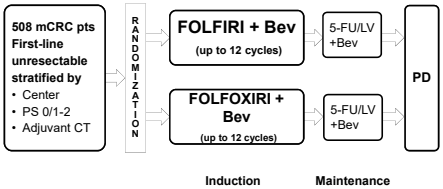
- 5FU/Cape alone?
- FU + Ox or Iri
- FU + Bev
- FU + Ox or Iri + Bev
- FU + Ox + Iri + Bev
- EGFR in front line

Although OS Continues to Improve, PFS has Been Mostly Stable With First-Line Therapy in the Chemobiologic Era



Hurwitz H, et al. *N Engl J Med*. 2004;350(23):2335-2342; Saltz LB, et al. *J Clin Oncol*. 2008;26(12):2013-2019; Bokemeyer C, et al. *Ann Oncol*. 2011;22(7):1535-1546; Van Cutsem E, et al. *J Clin Oncol*. 2011;29(15):2011-2019; Douillard JY, et al. *N Engl J Med*. 2013;369(11):1023-1034; Heinemann V, et al. *J Clin Oncol*. 2013;(suppl 31):abstract LBA3506; Falcone A, et al. *J Clin Oncol*. 2013;(suppl 31). Abstract 3505.

TRIBE Study Design

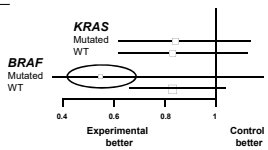


CT, chemotherapy; FU, fluorouracil; LV, leucovorin; Bev, bevacizumab; PD, progressive disease; FOLFOXIRI, fluorouracil, leucovorin, oxaliplatin, and irinotecan; FOLFIRI, fluorouracil, leucovorin, and irinotecan.

Loupakis F, et al. *N Engl J Med*. 2014;371:1609-1618.

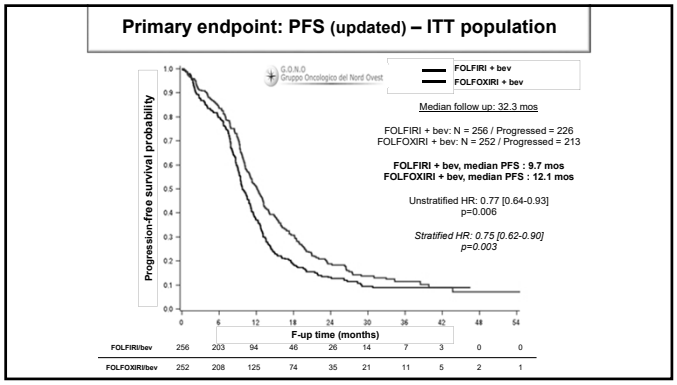
TRIBE Study Subgroup Analyses of PFS – Molecular Characteristics

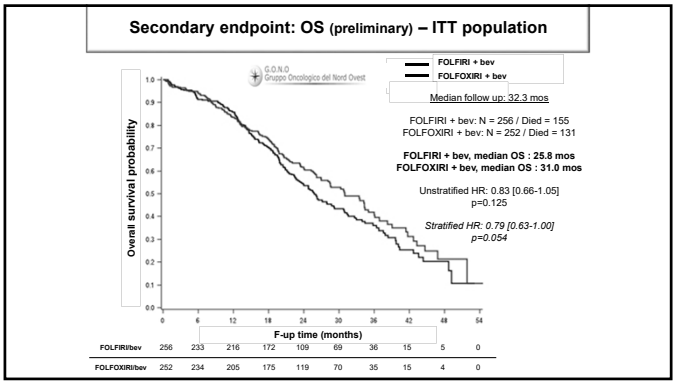
Factor	N	HR	*P* value
***KRAS* status**			
Mut	200	0.84	0.973
WT	193	0.83	
***BRAF* status**			
Mut	28	0.55	0.323
WT	365	0.83	

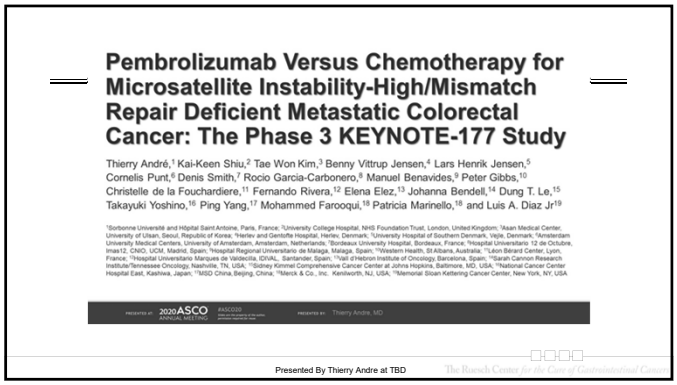


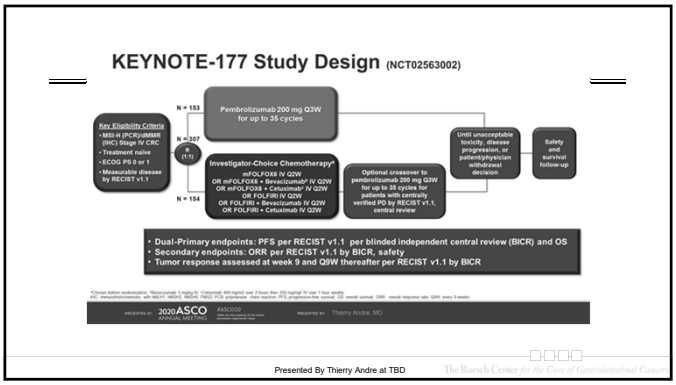
WT = wild-type.

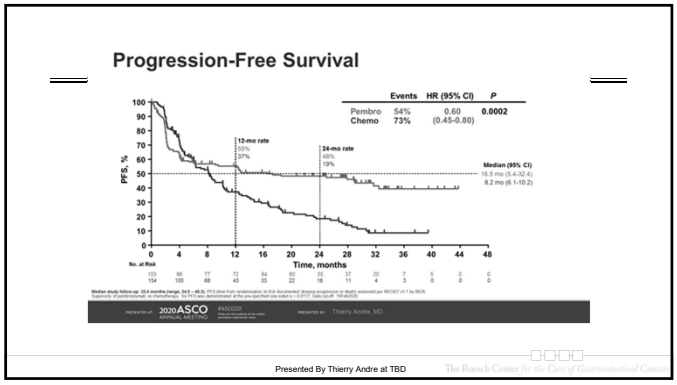
Loupakis F, et al. *N Engl J Med*. 2014;371:1609-1618.

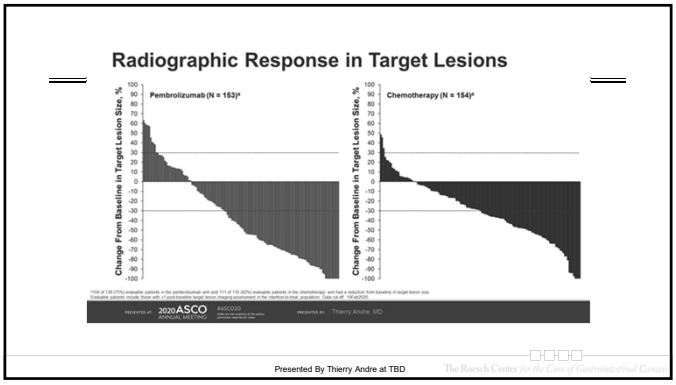




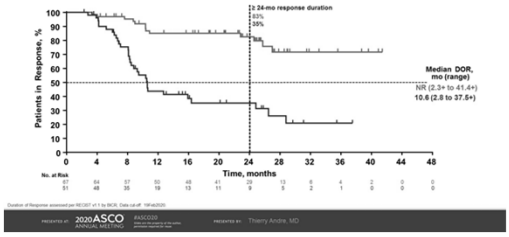








Duration of Response



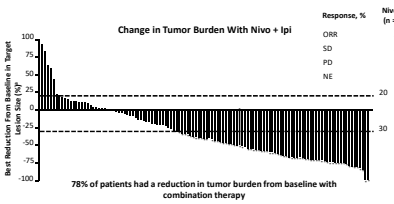
Presented By Thierry Andre at TBD

Adverse Events (AEs) in All Treated Patients

	Pembrolizumab N = 153		Chemotherapy N = 143	
All AEs	97%		99%	
Treatment-related	80%		99%	
Grade ≥3	22%		66%	
Death	0		1%[a]	
Discontinued	10%		6%	
Incidence ≥20%[b] in any group	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Diarrhea	25%	2%	52%	10%
Fatigue	21%	2%	44%	9%
Nausea	12%	0	55%	2%
Decreased appetite	8%	0	34%	2%
Stomatitis	5%	0	30%	4%
Alopecia	3%	0	20%	0
Vomiting	3%	0	28%	4%
Decreased neutrophil count	1%	0	23%	17%
Neutropenia	0	0	21%	15%
Peripheral sensory neuropathy	0	0	20%	2%

Presented By Thierry Andre at TBD

CheckMate-142: Response for Nivo + Ipi in dMMR/MSI-H Metastatic CRC



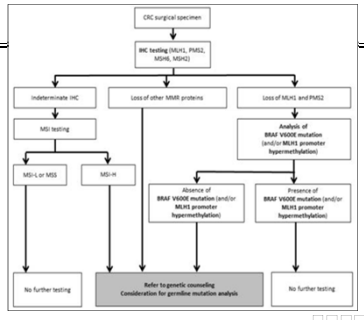
Response, %	Nivo + Ipi (n = 119)	Nivo (n = 74)
ORR	55	31
SD	31	38
PD	12	26
NE	3	5

Andre. ASCO GI. 2018. Abstr 553. Overman. J Clin Oncol. 2018;36:773.

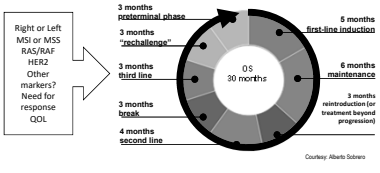
Measuring MSI is Confusing

- IHC test for the presence 4 proteins
  - MLH1, MLH6, PMS2, MSH2
  - Present = Normal
  - Missing- reflex to gene test
- Gene sequencing
  - Length of microsatellites compared to normal
  - Can be done by NexGen
  - Need normal tissue
- Germ Line vs Somatic

Useful Chart



2020: A classical case of mCRC

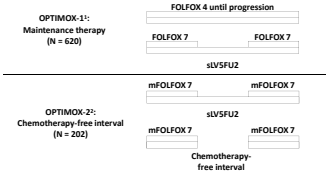


Maintenance

- Why we do it
  - Optimox, or should we optimiri?
- Timing of change
  - Switch or reduce
- What drugs
  - 5-FU or capecitabine?
  - Bevacizumab? Erlotinib[1]? Another agent?
- What if front-line is an EGFR regimen?
- Do we build resistance versus start and stop?
- Other diseases—lung, breast, heme, prostate…

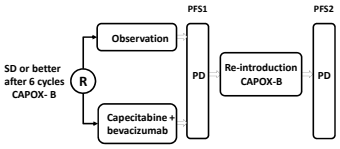
Optimox = optimization of oxaliplatin; Optimiri = irinotecan in front-line therapy.
1. Not FDA-approved for mCRC.

OPTIMOX Studies



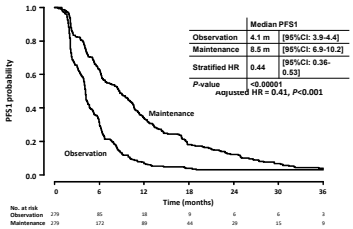
1. Tournigand C et al. *J Clin Oncol.* 2006;24:394-400. 2. Chibaudel B et al. *J Clin Oncol.* 2009;27:5727-5733.

CAIRO 3: Maintenance with Capecitabine + Bevacizumab vs. Observation
Study Design



Simkens LH, et al. *Lancet.* 2015 Apr 7. pii: S0140-6736(14)62004-3. doi: 10.1016/S0140-6736(14)62004-3. [Epub ahead of print]

PFS1

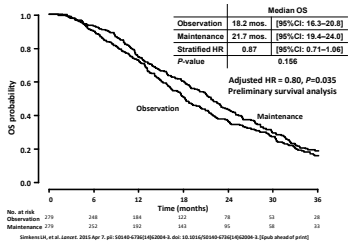


	Median PFS1	
Observation	4.1 m	[95%CI: 3.9-4.4]
Maintenance	8.5 m	[95%CI: 6.9-10.2]
Stratified HR	0.44	[95%CI: 0.36-0.53]
P-value	<0.00001	

Adjusted HR = 0.41, *P*<0.001

Simkens LH, et al. *Lancet.* 2015 Apr 7. pii: S0140-6736(14)62004-3. doi: 10.1016/S0140-6736(14)62004-3. [Epub ahead of print]

Overall Survival



	Median OS	
Observation	18.2 mos.	[95%CI: 16.3–20.8]
Maintenance	21.7 mos.	[95%CI: 19.4–24.0]
Stratified HR	0.87	[95%CI: 0.71–1.06]
P-value	0.156	

Adjusted HR = 0.80, *P*=0.035
Preliminary survival analysis

Simkens LH, et al. *Lancet.* 2015 Apr 7. pii: S0140-6736(14)62004-3. doi: 10.1016/S0140-6736(14)62004-3. [Epub ahead of print]

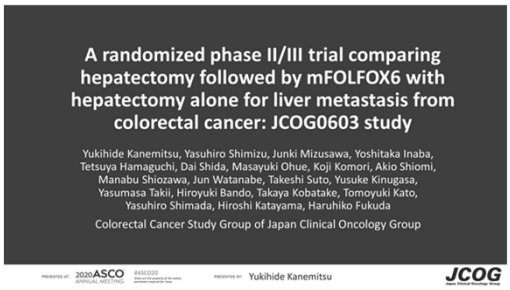
Stage 4 NED

- Anyone know what to do?
- Role of neo-adjuvant
- After surgery, do you?
  - Watch and wait
  - "12" cycles
  - Maintenance therapy

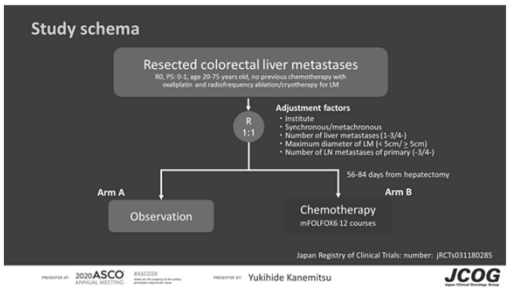
Rationale for Neoadjuvant Therapy

- Assess biology / chemo-responsiveness of disease
- Treat micro-metastatic disease (which chemotherapy can cure) as soon as possible
- *Potentially decrease surgical complications by making surgery more feasible*

- Potential downsides: hepatotoxicity; complications; complete response can hide metastatic sites; fear of "lost opportunity" if progression; etc



Presented By Yukihide Kanemitsu at TBD



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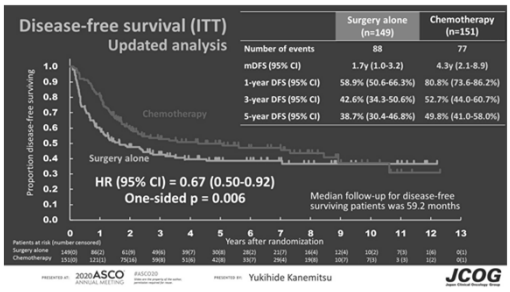

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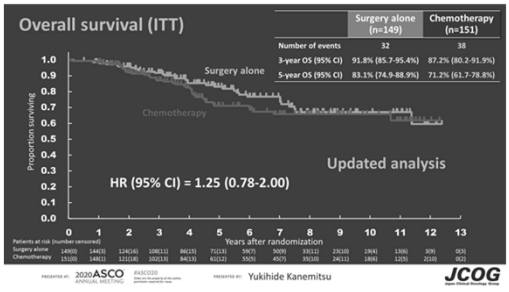

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Rational Combination Therapy

EGFR Biomarker Evolution
Retrospective Biomarker Discovery

Enrichment	% Patients	Response Rate
EGFR Receptors	100%	8-11%
KRAS	60%	15-20%
Extended RAS/BRAF	40%	> 20%
Left Sided CRC	20%	++
HER2 negative	15%	+++

Encorafenib plus Cetuximab With or Without Binimetinib for *BRAF* V600E Metastatic Colorectal Cancer: Updated Survival Results from a Randomized, 3-Arm, Phase 3 Study vs Choice of Either Irinotecan or FOLFIRI plus Cetuximab (BEACON CRC)

Scott Kopetz, Axel Grothey, Eric Van Cutsem, Rona Yaeger, Harpreet Wasan, Takayuki Yoshino, Jayesh Desai, Fortunato Ciardiello, Fotios Loupakis, Yong Sang Hong, Neeltje Steeghs, Tormod Kyrre Guren, Hendrik-Tobias Arkenau, Pilar García-Alfonso, Ashwin Gollerkeri, Kati Maharry, Janna Christy-Bittel, and Josep Tabernero

BEACON CRC: Binimetinib, Encorafenib, And Cetuximab COmbined to Treat *BRAF*-mutant ColoRectal Cancer

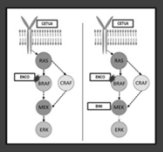
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Scott Kopetz, MD, PhD

MAPK Pathway Inhibition in *BRAF V600E*-mutant CRC

- *BRAF* V600E mutation occurs in 10%–15% of patients and confers a poor prognosis[1-3]
- BRAF inhibitors alone are ineffective due to the feedback activation of EGFR, leading to continued cell proliferation[4-6]
  - Feedback may be overcome by targeting multiple pathway nodes, ie BRAF/MEK/EGFR
  - Preclinically, addition of MEK inhibitor improved outcomes
- In the primary analysis of the BEACON CRC study, the regimens of Encorafenib (ENCO) + Cetuximab (CETUX) ± Binimetinib (BINI) had manageable safety profile and encouraging activity in patients with *BRAF* V600E mCRC[7]

MAPK Signaling in Colorectal Cancer[8]



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Study Design

Patients with *BRAF* V600E-mutant mCRC with disease progression after 1 or 2 prior regimens; ECOG PS of 0 or 1; and no prior treatment with any RAF inhibitor, MEK inhibitor, or EGFR inhibitor

Phase 3

R 1:1:1

- ENCORAFENIB + BINIMETINIB + CETUXIMAB (ENCO/BINI/CETUX) n = 205
- ENCORAFENIB + CETUXIMAB (ENCO/CETUX) n = 205
- FOLFIRI + CETUXIMAB, or irinotecan + CETUXIMAB (Control) n = 205

Primary Endpoints:
- ENCO/BINI/CETUX vs Control
- OS (All randomized Pts)
- ORR – Blinded Central Review (1st 331 randomized Pts)

Randomization was stratified by ECOG PS (0 vs. 1), prior use of irinotecan (yes vs. no), and cetuximab source (US-licensed vs. EU-approved)

Secondary Endpoints: ENCO/CETUX vs Control and ENCO/BINI/CETUX vs ENCO/CETUX - OS & ORR, PFS, Safety, QOL

Post hoc Updated Analysis: includes 6 months of additional follow-up since cut off for primary analysis

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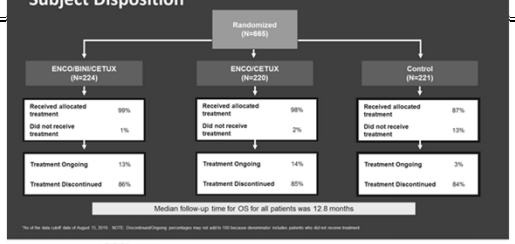
PRESENTED BY: Scott Kopetz, MD, PhD

Subject Disposition



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PRESENTED BY: Scott Kopetz, MD, PhD

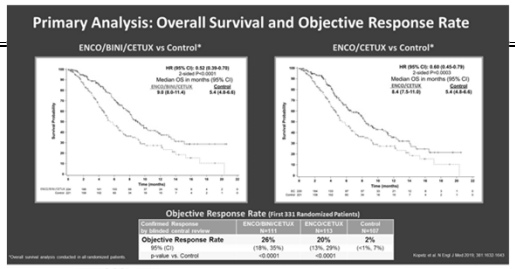
Baseline Patient Characteristics

CHARACTERISTIC	ENCO/BINI/CETUX N=224	ENCO/CETUX N=220	Control N=221
Female	53%	48%	57%
Age, median (range), years	62 (26, 85)	61 (30, 91)	60 (27, 91)
ECOG PS 0	52%	51%	49%
Location of primary tumor*			
Left colon (includes rectum)	35%	38%	31%
Right colon	56%	50%	54%
≥3 organs involved	49%	47%	44%
Presence of liver metastases	64%	61%	58%
Prior lines of therapy			
1	65%	66%	66%
>1	35%	34%	34%
MSI-H†	10%	9%	5%
CEA Baseline Value > 5 ug/L	80%	70%	81%
CRP Baseline Value > 10mg/L	42%	36%	41%

Abbreviations: CEA, carcinoembryonic antigen; CRP, C-reactive protein; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MSI-H, microsatellite instability high (abnormal high); Baseline characteristics are summarized for all RO randomized patients. †Based on assessment by polymerase chain reaction. MSI status is missing or not available in 2.7% of patients. *Remaining patients had primary tumor in both left and right sides of colon and those with unknown location of primary tumor

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

PRESENTED BY: Scott Kopetz, MD, PhD



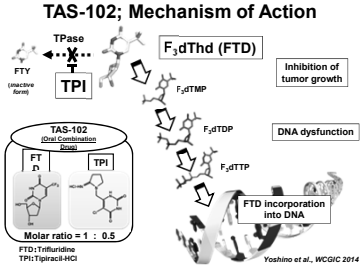
Presented By Scott Kopetz at TBD

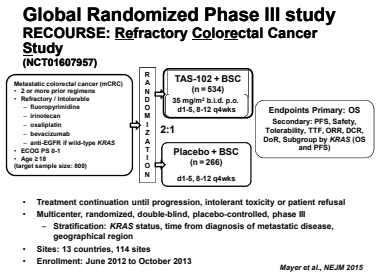
The Roesch Center for the Care of Gastrointestinal Cancers

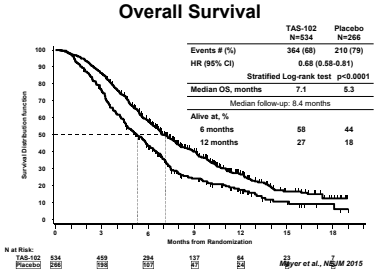
Refractory Colon Cancer: Many options, new data

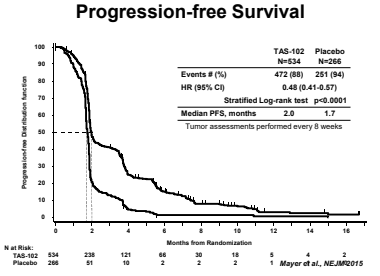
- TAS 102
- Regorafanib
- HER 2 as a target
- Immune Therapy
- Precision Medicine
- Recycled chemotherapy
- Biologics beyond progression
- Maintenance therapy 1 and sometimes 2 and 3!

The Roesch Center for the Care of Gastrointestinal Cancers



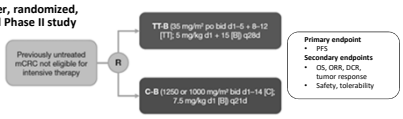






Refractory mCRC: TASCO-1

Multicenter, randomized, open-label Phase II study



Primary endpoint
- PFS

Secondary endpoints
- OS, ORR, DCR, tumor response
- Safety, tolerability

- Median PFS was 9.2 months TT/B vs 7.8 months
  - (HR) of 0.71 (95% confidence interval [CI] 0.48-1.06)
- Preliminary median OS was 18 months TT/B vs 16.2 months C-B
  - HR of 0.56 (95% CI, 0.32-0.98)

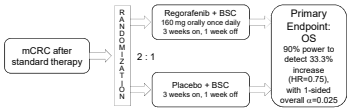
What comes next if this is 1L?

BID, twice daily; C-B, capecitabine + bevacizumab; CI, confidence interval; DCR, disease control rate; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; TT/B, trifluridine/tipiracil + bevacizumab.

Lesniewski-Kmak K, et al. *Ann Oncol.* 2018;29 (suppl 5; abstr O-022).

The Ruesch Center for the Care of Gastrointestinal Cancers

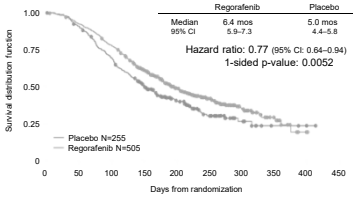
CORRECT study design



- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - 2:1 randomization
  - Strat. factors: prior anti-VEGF therapy, time from diagnosis of mCRC, geographical region
- Global trial: 16 countries, 114 active centers
  - 1,052 patients screened, 760 patients randomized within 10 months
- Secondary endpoints: PFS, ORR, DCR
- Tertiary endpoints: duration of response / stable disease, QOL, pharmacokinetics, biomarkers

Grothey et al., Lancet 2012

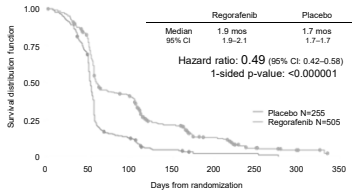
Overall survival (primary endpoint)



Primary endpoint met prespecified stopping criteria at interim analysis (1-sided p<0.009279 at approximately 74% of events required for final analysis)

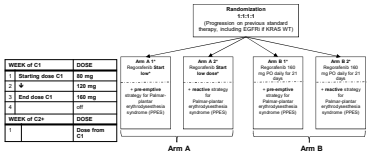
Grothey et al. Lancet 2012

Progression-free survival (secondary endpoint)



Grothey, Van Custem et al., Lancet 2012

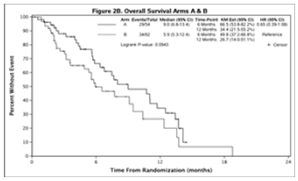
ReDOS design



WEEK of C1	DOSE
1 Starting dose C1	80 mg
2 ↓	120 mg
3 End dose C1	160 mg
4	off
WEEK of C2+	DOSE
↑	Dose from C1

1ary endpoint: proportion of patients who complete 2 cycles of protocol treatment and initiate cycle 3 in arm A and arm B
2ary endpoints: OS, PFS, TTP

Phase II ReDOS Study: *OS (secondary endpoint)*



HR, hazard ratio; KM est, Kaplan-Meier estimate; OS, overall survival.
Data on File, ACCRU.

Toxicity Management

- Must maintain close focus on:
  - Oxaliplatin neurotoxicity
  - Capecitabine HFS
  - Bevacizumab vascular toxicity (eg, HTN, bleeding)
  - EGFR rash management
- Use the drugs wisely, optimizing QOL
- Remember, chemotherapy is not curative in this setting; dose intensity is not critical
- Management of MCRC is like a marathon, not a sprint

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Basic Rules

- Possible advantage to "induction" chemo but don't go too long
- Use EGFR therapy when you need a response
  - Only RAS and maybe BRAF WT
  - Only left sided?
- Maintenance therapy helps
- Unclear on stage IV NED
- Don't leave known survival on the table

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CRC Practice Changes 2020

- Neo-Adjuvant Therapy
- MSI testing for all CRC patients (arguably all solid tumors)
- RAS/BRAF, HER2 for all stage 4 CRC
- Sidedness matters-
  - Prognostic and predictive
- Increased need for multi-disciplinary teams
  - Loco-regional therapies (surgery, liver-directed therapies) can play a large role in selected patients
- Treatment pathways will vary according to
  - Molecular biology
  - Anatomy
  - Met distribution
  - Age and PS of patient

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Adjuvant Therapy for Colon and Rectal Cancer

Daniel G. Haller, MD, FACP,FRCP

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

70 – Adjuvant Therapy of Colon and Rectal Cancer

Daniel G. Haller, MD

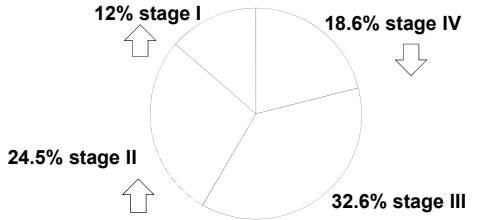
Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- N/A

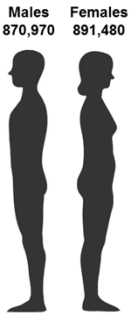
CRC: Demographics and Presentation

- **Estimated 2020 U.S. incidence (new cases): 145,420**
  - **104,610 colon; 43,340 rectal**
- **Estimated 2020 U.S. mortality: 53,200**



In patients age 35 and younger, by 2030, colon cancer cases are expected to increase by 90% and rectal cancer cases are expected to increase by 124%

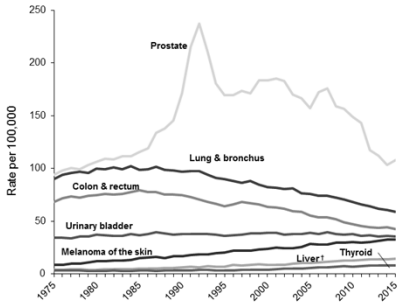
Estimated New Cancer Cases* in the US in 2019



Males		Females	
Prostate	20%	Breast	30%
Lung & bronchus	13%	Lung & bronchus	13%
Colon & rectum	9%	Colon & rectum	7%
Urinary bladder	7%	Uterine corpus	7%
Melanoma of skin	7%	Melanoma of skin	5%
Kidney & renal pelvis	5%	Thyroid	4%
Non-Hodgkin lymphoma	5%	Non-Hodgkin lymphoma	4%
Oral cavity & pharynx	4%	Kidney & renal pelvis	3%
Leukemia	4%	Pancreas	3%
Pancreas	3%	Leukemia	3%
All other sites	22%	All other sites	21%

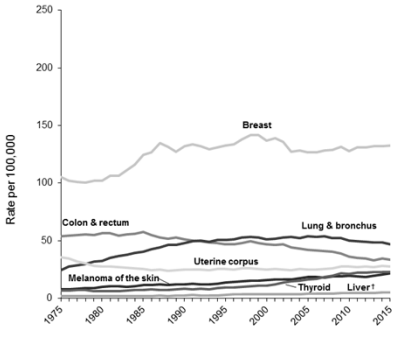
*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

Trends in Cancer Incidence Rates* Among Males, US, 1975-2015



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting. †Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2018.

Trends in Cancer Incidence Rates* Among Females, US, 1975-2015



*Age-adjusted to the 2000 US standard population and adjusted for delays in reporting. †Includes the intrahepatic bile duct.
Source: Surveillance, Epidemiology, and End Results (SEER) Program, National Cancer Institute, 2018.

COLORECTAL CANCER
Dietary risk factors

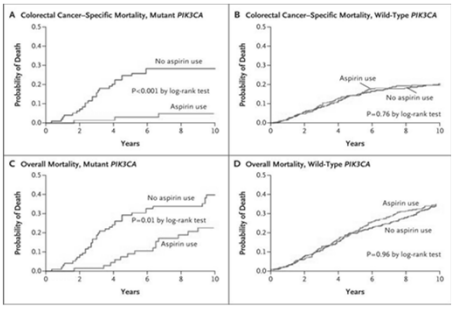
INCREASED RISK	*DECREASED RISK*
• Excess fat	• High intake of fiber
• Excess calories	• Vitamin D
• Low intake of fiber	• Calcium
• Alcohol	• Aspirin
• Smoking	

Wynder EL, Reddy BS, Weisburger JH. *Cancer.*1992;70:1222-1228.
Howe GR et al. *JNCI.* 1992;84:1887-1896.

Data from Observational Studies for Stage I-III Disease

- Decrease risk of recurrence (secondary prevention)
  - Physical activity (The co.21 Colon Health and Life-Long Exercise Change (CHaLLEnge) trial (accrual 2/3 complete)
  - Avoidance of Western pattern diet
  - Avoidance of class II/ III obesity (BMI > 35 kg/m2)
    - Metabolic syndrome
  - Aspirin or COX-2 inhibitor (ASCO 2015, Bains, #3504)(KRAS WT JCO 2017)
  - Higher vitamin D levels (also true in mCRC from C80405; ASCO 2015,Ng, #3503; SUNSHINE supplemental D3 trial; Ng, 2017)
- No association with recurrence to date
  - Weight change (gain or loss)
  - Obesity BMI < 35 kg/m2
  - Smoking status or history
  - Multivitamins

Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival: Nurses and Health Professionals Study



N Engl J Med. 2012 Oct 25; 367(17): 1596–1606.

Add-Aspirin trial: A phase III, double blind, placebo-controlled, randomized trial assessing the effects of aspirin on disease recurrence and survival after primary therapy

- Eligible participants (n=9,920) from the UK and India will have had potentially curative treatment for non-metastatic cancer. 4 separate tumour cohorts – breast (BC), colorectal (CRC), gastro-oesophageal (GOC) and prostate cancer
- participants are randomised to aspirin 100mg, 300mg or placebo daily for > 5 years
- Each tumour-specific cohort is individually powered and has a separate disease-specific primary outcome measure: BC (n = 3,100) invasive disease-free survival (DFS**); CRC (n = 2,600) DFS**; GOC (n = 2,100) overall survival (OS); and PC (n = 2,120) biochemical recurrence-free survival
- Blood/tissue specimens collected at enrolment will allow tumour-specific mutations to be used as stratification factors

J Clin Oncol 32:5s, 2014 (suppl; abstr TPS1617)

Adjuvant ASA Trials

- ASPIRIN: patients over 70
  - Leiden University
  - Started 2014; expected completion 2022
  - Est. accrual 1558; 80 mg/d x5 years
  - OS primary endpoint; DFS secondary
- ASCOLT: SE Asia
  - Stages II and III; 200 mg/d x3 years
  - Activated 2007; est. closure 2022

  - Neither prospectively targets PIK3CA-mutated populations!

Surveillance after surgery
Summary of the recent studies

Study	Type of study	Years	Number of Patients	Stages	Time to Detection of Recurrence	Resection of Recurrences	Overall Survival	CRC-Specific Survival
FACS	Pragmatic RCT	2003-2009	1202	Dukes A-C (I-III)	No sig diff	4.3-5.7% higher (p=0.02)	No sig diff	No sig diff
GILDA	Pragmatic RCT	1998-2006	1228	Dukes B2-C (II-III)	5.9 months earlier (95% CI 2.71-9.11)	No sig diff	No sig diff	Not reported
COLOFOL	Pragmatic RCT	2006-2010	2509	II-III	Not reported	Not reported	No sig diff	No sig diff
Alliance	Retrospective cohort	2006-2007	8529	I-III	No sig diff	No sig diff	No sig diff	Not reported

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PRESENTED BY: Christine M. Veenstra, MD, MSHP

Presented By Christine Veenstra at 2019 ASCO Annual Meeting

Current guidelines for surveillance: US

Surveillance Strategy	ASCO (2013)	NCCN (2018)	ASCRS (2015)
Stage	II-III	I-III	I-III
Clinical exam	Q 3-6 mths x 5 yrs	Q 3-6 mths x 2 yrs, then Q 6 mths until 5 yrs (stages II/III)	Q 3-6 mths x 2 yrs, then Q 6 mths until 5 yrs
CEA	Q 3-6 mths x 5 yrs	Q 3-6 mths x 2 yrs, then Q 6 mths until 5 yrs (stages II/III)	Q 3-6 mths x 2 yrs, then Q 6 mths until 5 yrs
CT chest/abdomen	Annually x 3 yrs; high risk consider Q 6-12 mths x 3 yrs	Q 6-12 mths x 5 yrs (stages II/III)	Annually x 5 yrs
CT pelvis	For rectal cancer, frequency per MD judgment	Q 6-12 mths x 5 yrs (stages II/III)	Annually x 5 yrs
Colonoscopy	1 yr after surgery, then Q 5 yrs	1 yr after surgery, repeat in 3 yrs, then Q 5 yrs	1 yr after pre-op colonoscopy (3-6 mths after surgery if concerning pre-op colonoscopy
Rectosigmoidoscopy	For rectal cancer w/o radiation, Q 6mths x 2-5 yrs	N/A	For rectal cancer, Q6-12 mths x 3-5 yrs

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Risk-adapted strategies for surveillance

- Clinical & Pathology markers
  - Poor tumor differentiation
  - Lymphovascular invasion
  - Microsatellite instability
  - Tumor mutational status
  - Positive surgical margins
- Circulating tumor cells/DNA
- Biomarkers in tumor cells
  - VEGF
  - IL-8
  - CD3+ & cytotoxic CD8+ T cells
- Tumor gene expression panels
  - 12-gene recurrence score

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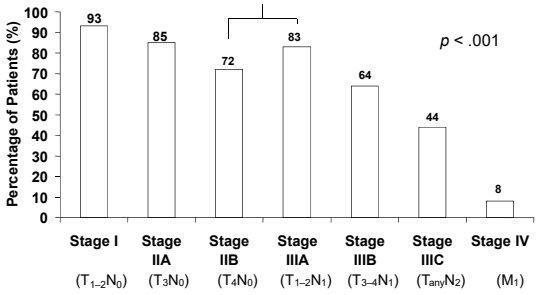
AJCC 8th Edition: 2018

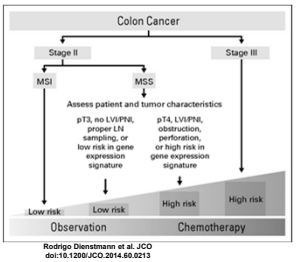
Stage IIIA:	**T1 - T2**	**N1 / N1c**	**M0**
	T1	**N2a**	**M0**
Stage IIIB:	**T3 - T4a**	**N1 / N1c**	**M0**
	T2 - T3	**N2a**	**M0**
	T1 - T2	**N2b**	**M0**
Stage IIIC:	**T4a**	**N2a**	**M0**
	T3 - T4a	**N2b**	**M0**
	T4b	**N1 - N2**	**M0**

5-Year Relative Survival By AJCC 6th Edition Stage



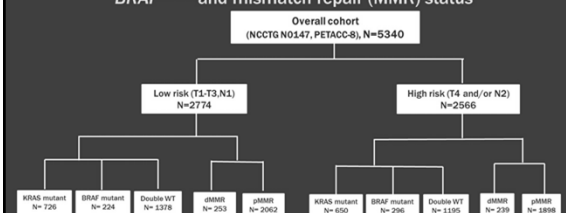
O'Connell et al., 2004.

Decision-making flow chart for adjuvant therapy in early-stage colon cancer



Rodrigo Dienstmann et al. JCO doi:10.1200/JCO.2014.60.0213

Low and high risk T, N stage III colon cancers subgrouped by *KRAS*, *BRAF*^{V600E} and mismatch repair (MMR) status



NB - KRAS exon 2 mutational status and not exon 2-4 KRAS/NRAS testing used

Presented By Richard Wilson at 2019 ASCO Annual Meeting

What have we learnt?

- N and T stage were the top 2 contributors to prediction of TTR - validating use of low and high risk grouping in stage III CC
- Utility of dMMR status as a prognostic feature found in low not high risk groups, which fits with changes in its impact from stage II through to stage IV CRC
- *KRAS* exon 2 mutations had largest relative contribution to TTR in both risk groups
- Contribution of $BRAF^{V600E}$ mutations to TTR was significantly increased in high vs low risk patients
- $BRAF^{V600E}$ mutations were the primary driver of SAR, especially in high risk patients - consistent with data in stage IV disease

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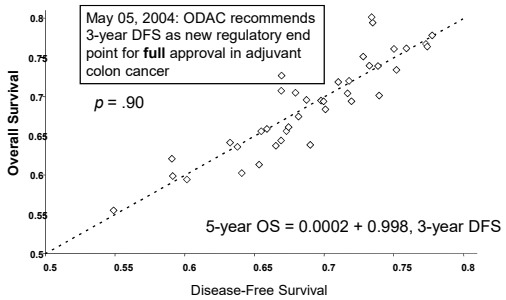
3-Year Disease-Free Survival vs. 5-Year Overall Survival



ODAC = FDA Oncology Drugs Advisory Committee; DFS = disease-free survival; OS = overall survival.
Sargent et al., 2005.

ACCENT
Adjuvant Colon Cancer Endpoints Group

Re-evaluating Disease-Free Survival as an Endpoint versus Overall Survival in Stage III Adjuvant Colon Cancer Trials with Chemotherapy +/- Biologics: An Updated Surrogacy Analysis Based on 15,719 Patients from the ACCENT Database

Qian Shi, Aimery De Gramont, Jesse G. Dixon, Jun Yin, Eric Van Cutsem, Julien Taieb, Steven R. Alberts, Norman Wolmark, Hans-Joachim Schmoll, Leonard B. Saltz, Richard M. Goldberg, Rachel Kerr, Sara Lonardi, Takayuki Yoshino, Greg Yothers, Axel Grothey, Thierry Andre, and Mohamed E. Salem
on behalf of Adjuvant Colon Cancer ENdpoinTs (ACCENT) Group

Presented By Qian Shi at 2019 ASCO Annual Meeting

Background

- Long clinical trial timelines are required when overall survival (OS) is considered as the primary endpoint in **stage III colon cancer** trials
- Disease-free survival with 3 years median follow-up (3y DFS) was validated as a surrogate for overall survival with 5 years median follow-up (5y OS)[1,2,3]
- Patients treated with fluorouracil, leucovorin and oxaliplatin showed improved survival after recurrence (SAR) and OS over years [4]
  - Changes in treatment options for salvage treatment at relapse, better patient care, etc.
- Extended SAR and OS reduce the reliability of 3y DFS as a surrogate of 5y OS in a simulation study [5]

[1]Sargent et al. JCO 2005; [2]Sargent et al. JCO 2007; [3]Sargent et al. EJC 2011; [4]Salem et al. ASCO GI 2018; [5]de Gramont et al. JCO 2010

Presented By Qian Shi at 2019 ASCO Annual Meeting

Results: Trial- and Individual Patient-Level Surrogacy (3y DFS vs. 5-8y OS)

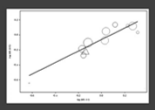
X-year OS	N Comparisons (N pts)	R^2_{WLS} (95% CI)
5y OS	11 (15,719)	0.81 (0.65, 0.96)
6y OS	11 (15,719)	0.88 (0.77, 1.00)
6.5y OS	10 (13,455)	0.93 (0.84, 1.00)
7y OS	9 (11,494)	0.92 (0.77, 1.00)
8y OS	5 (6,843)	0.88 (0.63, 1.00)

R^2 = 0.90

Stage III, 5FU
(Sargent JCO 2007)

Presented By Qian Shi at 2019 ASCO Annual Meeting

An Updated Surrogacy Analysis Based on 18,886 Patients from the ACCENT Database. Shi et al



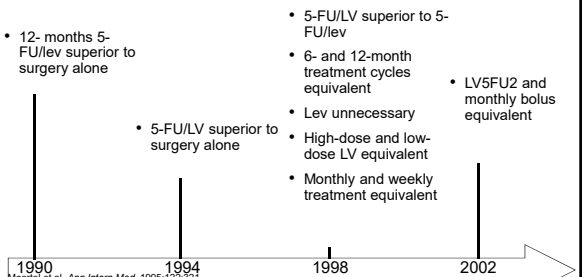
R^2_{WLS} (95% CI)	R^2_{Copula} (95% CI)
0.74 (0.54, 0.94)	0.89 (0.77, 1.00)

3y DFS remains the valid surrogate endpoint for 5y OS

- 3y DFS is a valid endpoint for this specific combination of colon cancer patients
- Will specific subsets, e.g. BRAF mutant, or HER2 amplified, or Left sided RAS WT, have the same results?
- If we pull those subsets out of a standard dataset, will 3yr DFS have as robust an R^2?

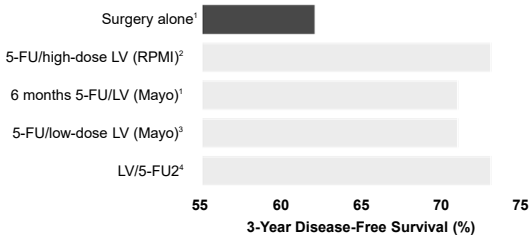
Presented By David Ryan at 2019 ASCO Annual Meeting

History of adjuvant therapy of colon cancer before oxaliplatin



Moertel et al. *Ann Intern Med.* 1995;122:321.
Francini et al. *Gastroenterol.* 1994;106:899.
Wolmark et al. *Proc Am Soc Clin Oncol.* 1996;15:205. Abstract
O'Connell et al. *J Clin Oncol.* 1998;16:295.
Haller et al. *Proc Am Soc Clin Oncol.* 1998;17:256a. Abstract 982.
Andre et al. *Proc Am Soc Clin Oncol.* 2002. Abstract 529.

5-FU: Historical Standard in the Adjuvant Setting



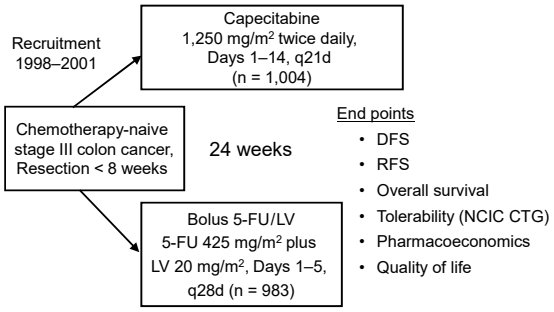
- Patients with stage II and III colon cancer

(1) IMPACT Investigators, 1995; (2) Wolmark et al., 1993; (3) QUASAR Group, 2000; (4) André et al., 2003.

Extending Benefit beyond FU/LV in High-risk Stage II/III Colon Cancer

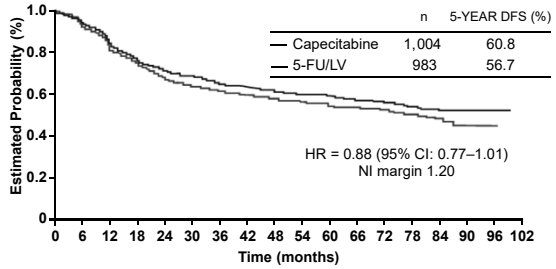
- **Can convenience of administration be improved?**
  - **replace 5-FU with capecitabine**
- **Do combination therapies offer advantages over 5-FU alone?**
  - **oxaliplatin-based regimens: MOSAIC (infusion), NSABP C0-7 (bolus)**
  - **irinotecan-based regimens: CALGB (bolus), PETACC-3 (infusion), ACCORD-2**
- **Can we further improve results? The role of biologics:**
  - **anti-EGFR (cetuximab): N0147,PETACC8**
  - **anti-VEGF (bevacizumab): C-08, AVANT**
- **Duration of therapy: 3 vs. 6 months (IDEA)**
  - **ASCO PLENARY 2017; NEJM**
- **More is better?: FOLFOXIRI in high-risk T4, N2**

X-ACT Trial Design



RFS = recurrence-free survival; NCIC CTG = National Cancer Institute of Canada Clinical Trials Group.
Twelves et al., 2005.

X-ACT: 5-Year Disease-Free Survival

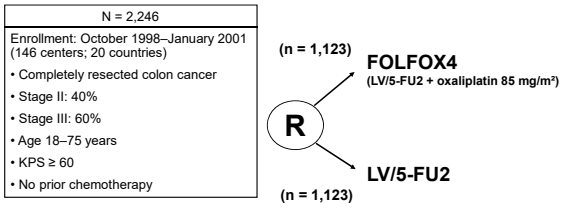


Test of noninferiority, $p < .0001$.
Test of superiority, $p = .0682$.

NI = noninferiority.
Twelves et al., 2007.

- Median follow-up: 6.8 years

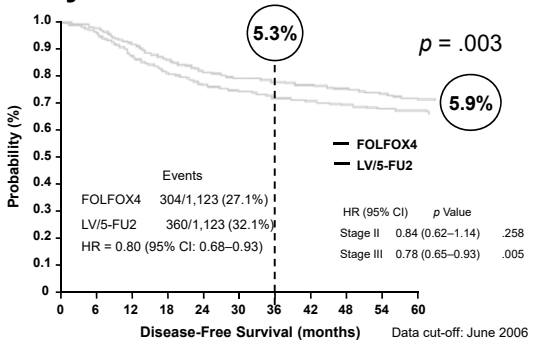
MOSAIC: Study Design



Primary end point: 3-yr Disease-free survival
Secondary end points: Safety and overall survival

R = randomize; LV/5-FU2 = leucovorin 200 mg/m² IV over 2 hours followed by 5-FU 400 mg/m² bolus and 5-FU 600 mg/m² IV over 22 hours on Days 1 and 2, every 14 days; FOLFOX4 = LV/5-FU2 + oxaliplatin 85 mg/m² IV over 2 hours on Day 1; KPS = Karnofsky performance status.
de Gramont et al., 2007, JCO 2009

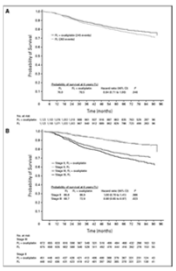
3-yr Disease-Free Survival



ITT = intent to treat; HR = hazard ratio; CI = confidence interval.
de Gramont et al., 2007.JCO 2009

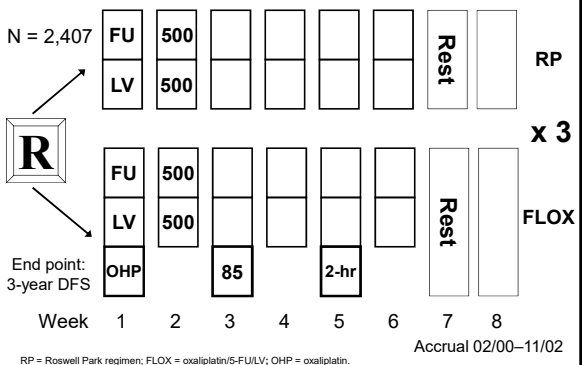
MOSAIC: 6 yr OS results

Kaplan-Meier estimates of overall survival (A) by treatment arm and (B) by treatment arm and by stage (intent-to-treat population).



André T et al. JCO 2009;27:3109-3116

NSABP C-07



RP = Roswell Park regimen; FLOX = oxaliplatin/5-FU/LV; OHP = oxaliplatin.
Wolmark et al., 2005.

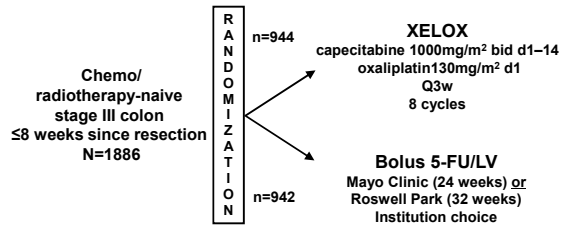
Oxaliplatin Benefit: C-07 and MOSAIC

	3-year DFS(%)	Δ (%)	HR
C-07	**76.5**	**4.9**	**0.79**
MOSAIC	**77.9**	**5.1**	**0.77**

Wolmark et al., 2005.

5-yr OS demonstrated in MOSAIC, not C-07

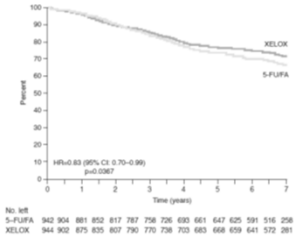
Adjuvant XELOX vs. 5-FU/LV:XELOXA Phase III trial (NO16968)



- Primary endpoint: superior 3-yr DFS with XELOX vs. 5-FU
- Secondary endpoints: overall survival, tolerability, convenience, medical care use biomarkers, pharmacogenetic information (optional)

Haller et al, JCO April 10, 2011 vol. 29 no. 11 1465-1471

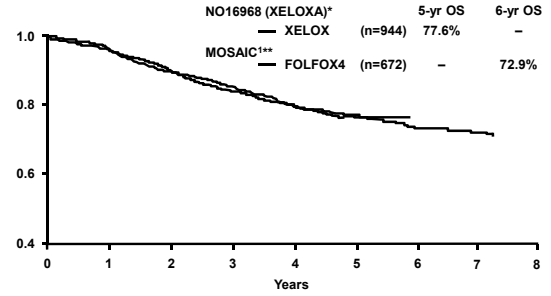
Adjuvant XELOX vs. 5-FU/LV:XELOXA Phase III trial (NO16968): 7-yr OS f/u



Δ 4.8%

JCO June 2015

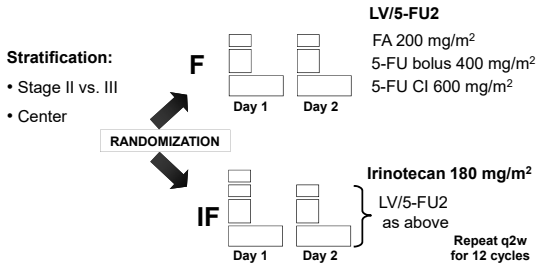
Cross-trial comparison of MOSAIC and XELOXA: OS in stage III disease



*Median observation time: 57.0 months
**Median follow-up: 81.9 months
ITT population

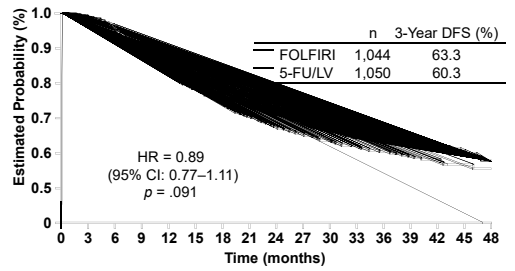
1. André et al. JCO 2009

PETACC-3: Study Design



CI = continuous infusion.
Van Cutsem et al., 2005.; JCO 2009

PETACC-3: DFS Not Significantly Improved With FOLFIRI in Stage III

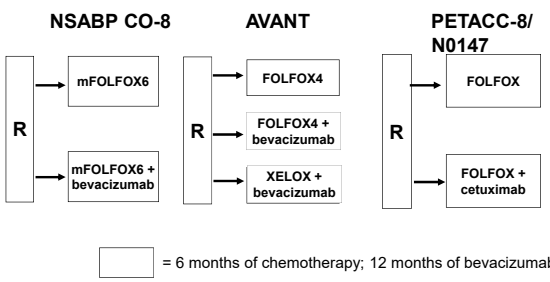


Van Cutsem et al., 2005; JCO 2009

3-year DFS (Stage III): cross-trial comparison

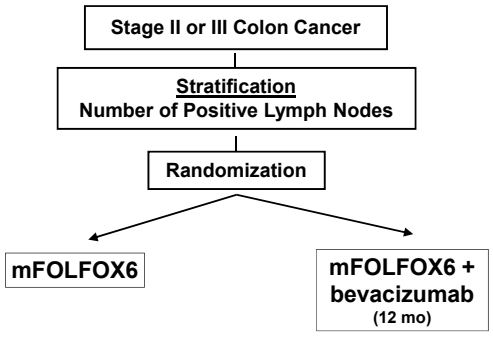
	Trial	Therapy	3-year DFS
No therapy	Moertel	Observation	52%
	IMPACT	Observation	44%
Monotherapy	IMPACT	5-FU/LV	62%
	Punt	5-FU/LV	65%
	Fields	5-FU/LV	67%
	André	LV5FU2	61%
	MOSAIC	5-FU/LV	65%
	X-ACT	Capecitabine	64%
Combination therapy	PETACC-3	LV5FU2+IRI	63%
	MOSAIC	FOLFOX4	73%
	NSABP	FLOX	72%
	XELOXA	XELOX	71%

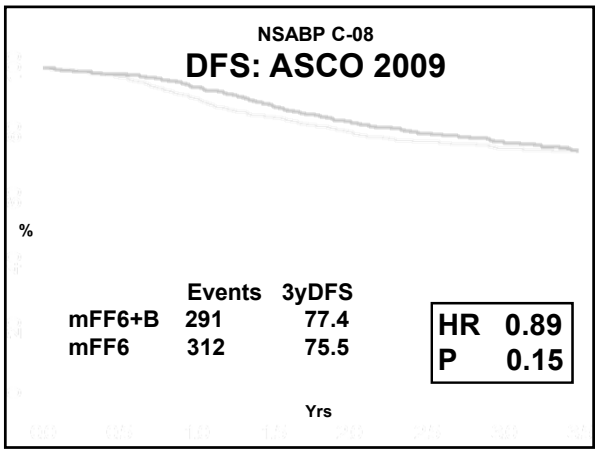
FOLFOX as standard treatment arm: biologics

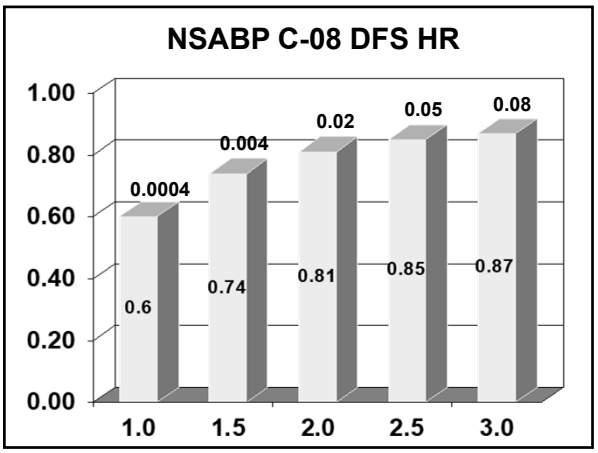


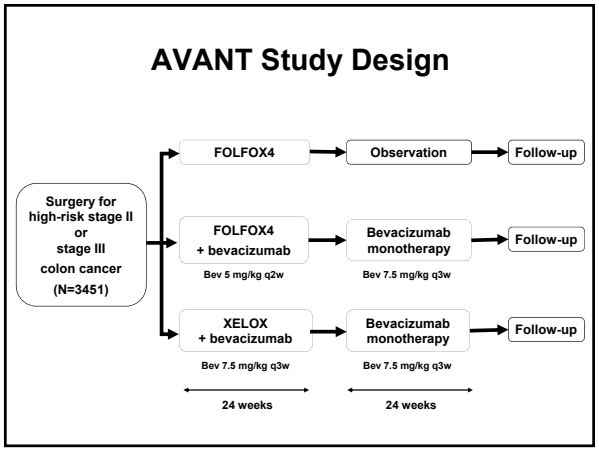
= 6 months of chemotherapy; 12 months of bevacizumab

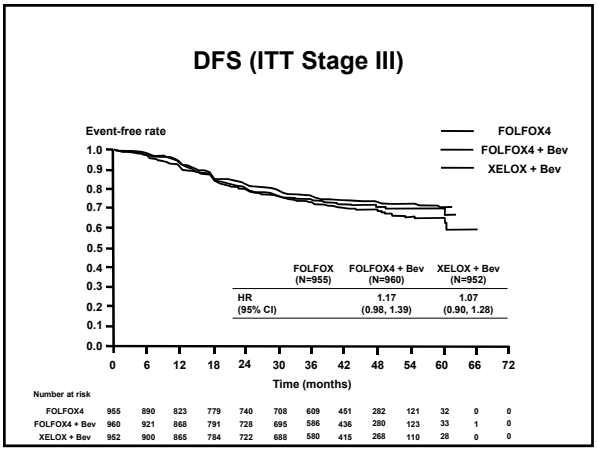
NSABP C-08 Schema

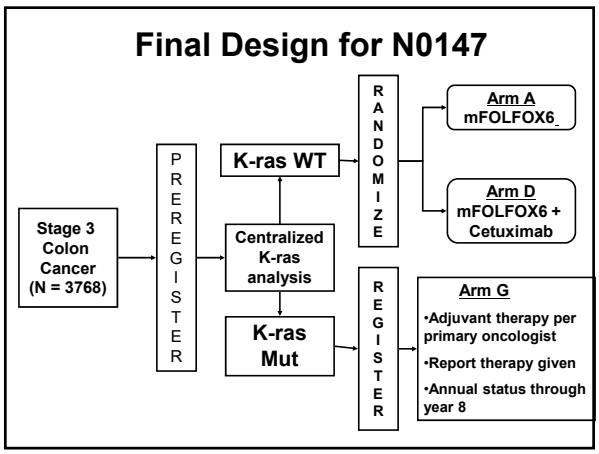


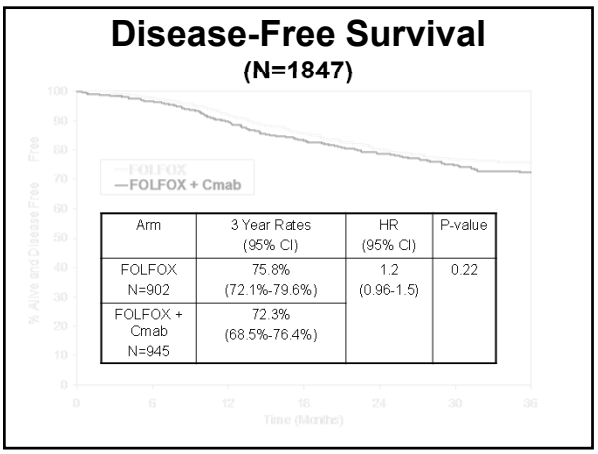












Possible Explanations and Implications of N0147

1. Antibody Dependent Cellular Cytotoxicity (ADCC): not relevant with cetuximab
2. EGFR Signaling is complicated
   – Robust EGFR resistance networks
3. EGFR is not a relevant target in colon cancer micro metastasis (how to select biologics for future adjuvant trials?)
4. Increased toxicity with antibody, especially in >70 yrs, led to early discontinuations and reduced toxicity

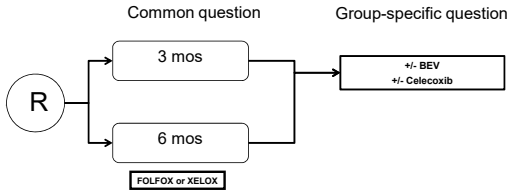
NB: PETACC-8 …also negative

Prospective Pooled Analysis of Six Phase III Trials Investigating Duration of Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) for Patients with Stage III Colon Cancer: The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration

Qian Shi, Alberto F. Sobrero, Anthony F. Shields, Takayuki Yoshino, James Paul, Julien Taieb, Ioannis Souglakos, Rachel Kerr, Roberto Labianca, Jeffrey A. Meyerhardt, Franck Bonnetain, Toshiaki Watanabe, Ioannis Boukovinas, Lindsay A. Renfro, Axel Grothey, Donna Niedzwiecki, Valter Torri, Thierry Andre, Daniel J. Sargent, Timothy Iveson

IDEA (International Duration Evaluation in Adjuvant) colon cancer, a prospective pooled analysis

- Worldwide effort to address duration question of oxaliplatin (3 vs 6 mos): NEUROPATHY

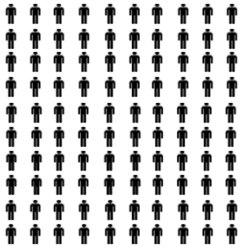


MOSAIC Peripheral Neuropathy

	LV5FU2 Grade 3	FOLFOX4 Grade 3
During Treatment	0.2%	12.5%
18 months post treatment	n/a	0.7% (24.1% all grade)

At 48 months, grade 1, 2, and 3 PSN was observed in 11.9%, 2.8%, and 0.7% of the patients examined, respectively

Stage III Colon Cancer



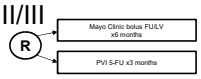
Cured because they got adjuvant therapy after surgery

Only ones that benefit from chemo (as measured by cure)

Presented by: Jeffrey Meyerhardt, MD, MPH

3 vs. 6 months of Fluoropyrimidines

- 801 pts stage II/III

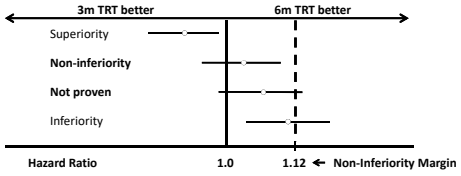


5-yr	Mayo x6 mos	PVI x3 mos
RFS	66.7%	73.3%
OS	71.5%	75.7%

Chau, Ann Oncology 2005 Apr;16(4):549-57

IDEA Non-inferiority Hypothesis Testing

Statistical Conclusions Under Different Scenarios



TRT: treatment

Piaggio et al. JAMA 2012;308(24):2594-2604

Presented by: Jeffrey Meyerhardt, MD, MPH

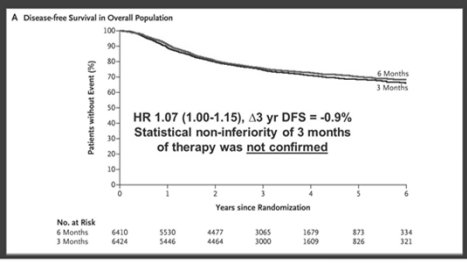
IDEA Trials Summary (NEJM 3/29/18)

Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy (JCO 4/5/18)
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia, Sweden, New Zealand (Lancet 2018)
IDEA France	CAPOX or mFOLFOX6	2010	France (JCO 4/5/18))
C80702	mFOLFOX6	2440	US, Canada (ASCO 2020)
HORG	CAPOX or FOLFOX4	708	Greece (Annals of Oncology 2019)
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan (JAMA Oncology 2019)

*4 studies included high-risk stage II patients; only stage III colon cancer patients were included in the pooled primary analysis

Presented by: Qian Shi, PhD on behalf of IDEA collaborators

IDEA collaboration: 6 trials, 12 countries, 12,834 patients!

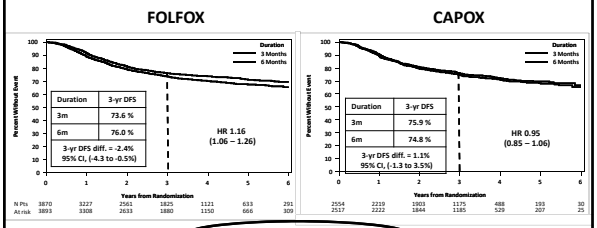


PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Christopher Lieu, MD

Grothey A et al. N Engl J Med 2018;378:1177-1188

Presented By Christopher Lieu at TBD

DFS Comparison by Regimen



Interaction p-value = 0.0051

Shi et al ASCO 2017

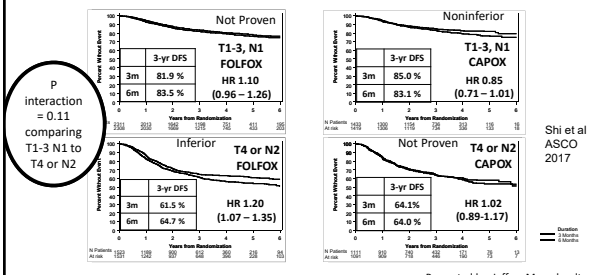
Presented by: Jeffrey Meyerhardt, MD, MPH

Could the Choice of Chemo Matter

- Arguments for Yes…
  - In the first 4 weeks of CAPOX, the dose of oxaliplatin received is 260 mg/m^2. However, with FOLFOX it is 170 mg/m^2
  - Compliance and overall dose intensity better
  - More continuous 5-FU is better

Presented by: Jeffrey Meyerhardt, MD, MPH

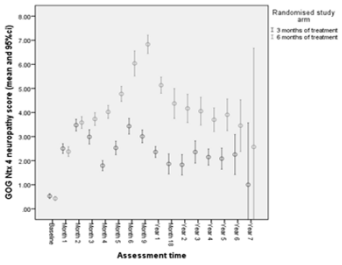
DFS Comparison by Risk Group and Regimen in IDEA



Shi et al ASCO 2017

Presented by: Jeffrey Meyerhardt, MD, MPH

Results:
Neuropathy measured by patient questionnaire over time by treatment duration



Iveson et al ASCO 2017

Presented by: Jeffrey Meyerhardt, MD, MPH

IDEA Clinical Consensus: Risk-based approach to adjuvant chemotherapy in stage III colon cancer

Risk group	Recommended duration of adjuvant therapy	
	3 months	6 months
T1-3 N1 (~60% of stage III)	———	
T4 and/or N2 (Or other high-risk factors)	———	- - -

Duration of therapy determined by
- tolerability of therapy
- patient preference
- assessment of risk of recurrence
- Regimen (CAPOX vs FOLFOX)

Presented by: Qian Shi, PhD on behalf of IDEA collaborators

"Hybrid" 3 vs. 6 months

CAPOX/FOLFOX x3 mos ⇨ Capecitabine/FU x3 mos

Mimics clinical practice in which oxaliplatin is deleted from regimen for neuropathy and fluoropyrimidine is continued

Adjuvant therapy for stage III colon cancer: state of the art

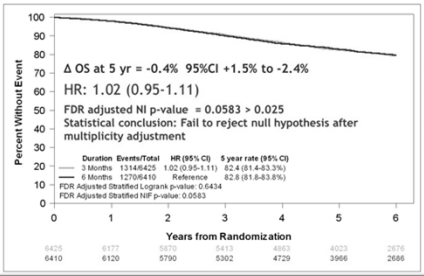
NCCN National Comprehensive Cancer Network®

T1–3, N1 (low-risk stage III)	Preferred: • CAPEOX (3 mo)[q,t] or • FOLFOX (3–6 mo)[q,t] (category 1 for 6 mo) or Other options include: Capecitabine (6 mo)[q] or 5-FU (6 mo)[q]
T4, N1–2; T Any, N2 (high-risk stage III)	Preferred: • CAPEOX (3–6 mo)[q,r,t] (category 1 for 6 mo) or • FOLFOX (6 mo)[q,r,t] (category 1) or Other options include: Capecitabine (6 mo)[q,r] or 5-FU (6 mo)[q,r]

https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf

Presented By Christopher Lieu at TBD

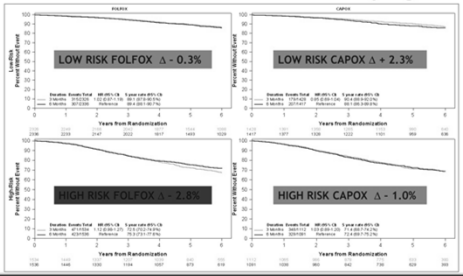
IDEA overall population – Overall Survival



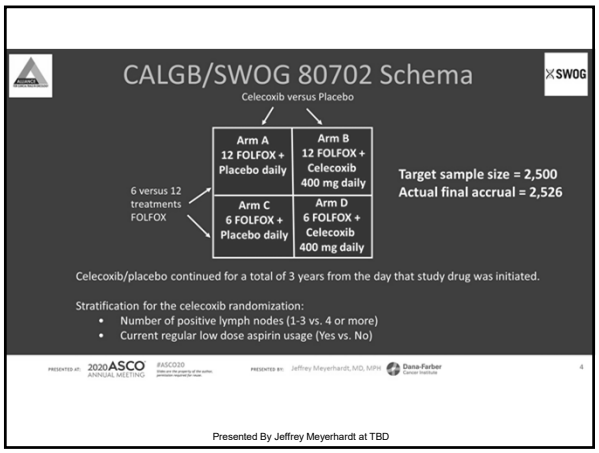
Study did not meet the secondary endpoint of non-inferiority for overall survival

Presented By Christopher Lieu at TBD

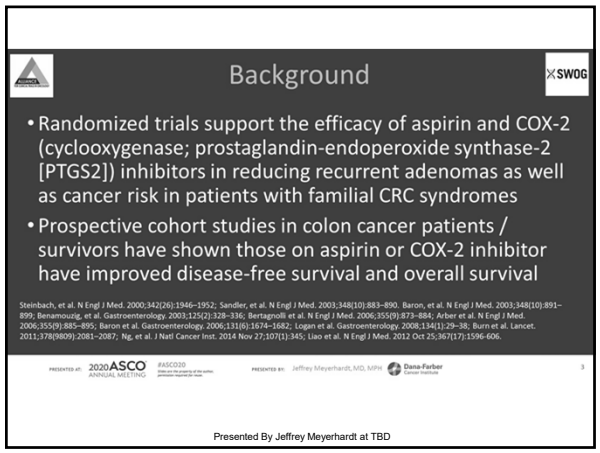
Overall survival data mimics DFS data by regimen



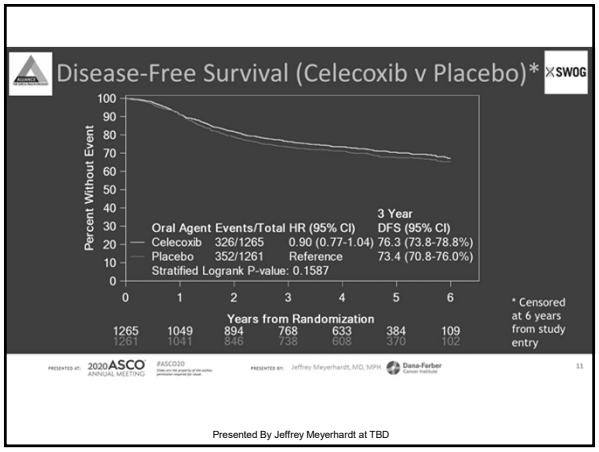
Presented By Christopher Lieu at TBD



Presented By Jeffrey Meyerhardt at TBD



Presented By Jeffrey Meyerhardt at TBD



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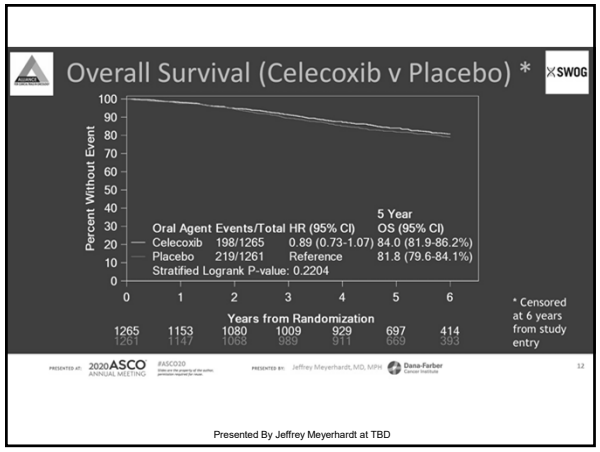

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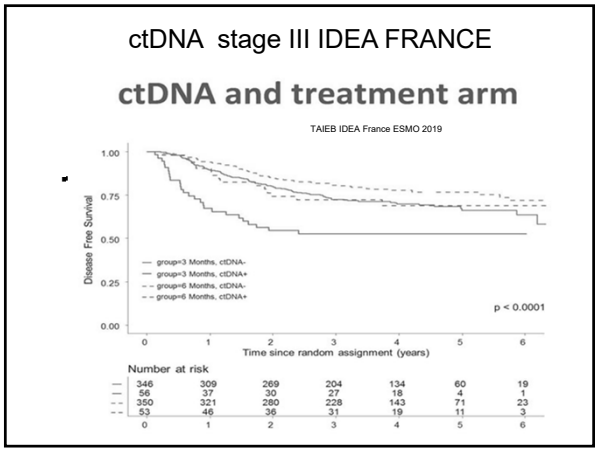
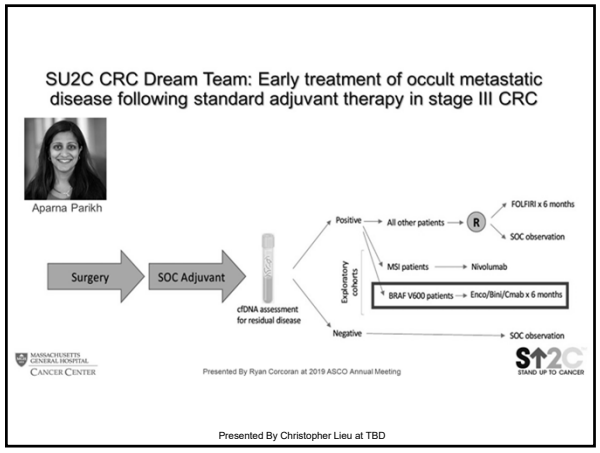
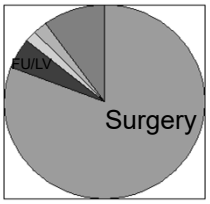




Presented By Christopher Lieu at TBD

Adjuvant Therapy for Stage II Colon Cancer



Existing Tools for Selecting Stage II Patients for Treatment Are Inadequately Validated

Recurrence Risk
- **Bowel obstruction or perforation**
- **T-Stage**
- **# of nodes assessed**
- **Tumor grade**
- **Lymphatic/vascular invasion**
- **Margin status**
- **Perineural invasion**
- **Mismatch repair status (MMR)**

According to Current Guidelines
- **No molecular markers (except dMMR) have been routinely established in clinical practice for stage II colon cancer**
- **Treatment decisions are based on the expectation that higher risk stage II patients derive larger absolute benefit with adjuvant chemotherapy**

Potential Risk Factors in stage II Colon Cancer

- Sidedness
  - 1,437,846 patients, showed that primary colon tumors occurring on the left side were associated with an absolute 19% reduced risk of death (hazard ratio [HR], 0.82; *P* < .001). This result was independent of tumor stage, race, use of adjuvant chemotherapy, the year of study, or number of study participants (Petrelli, JAMA Oncology 2016)
- ctDNA: prognostic
  - 230 patients with resected stage II colon cancer. In patients not treated with adjuvant chemotherapy, ctDNA was detected postoperatively in 14 of 178 (7.9%) patients, 11 (79%) of whom had recurred at a median follow-up of 27 months; recurrence occurred in only 16 (9.8 %) of 164 patients with negative ctDNA [P < 0.001]. In patients treated with chemotherapy, the presence of ctDNA after completion of chemotherapy was also associated with an inferior recurrence-free survival (HR, 11; 95% CI, 1.8 to 68; P = 0.001) (Tie, Sci Transl Med 2016)

IDEA Trials Summary (High Risk Stage II)

Trial	Regimen(s)	HR stage II Colorectal Cancer Patients	Enrolling Country
TOSCA	CAPOX or FOLFOX4	1268	Italy
SCOT	CAPOX or mFOLFOX6	1078*	UK, Denmark, Spain, Australia, Sweden
HORG	CAPOX or FOLFOX4	413	Greece
ACHIEVE2	CAPOX or mFOLFOX6	514	Japan

*Included 130 rectal patients

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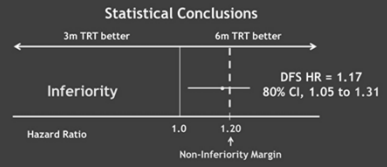
Results: Primary DFS Analysis (mITT), cont.



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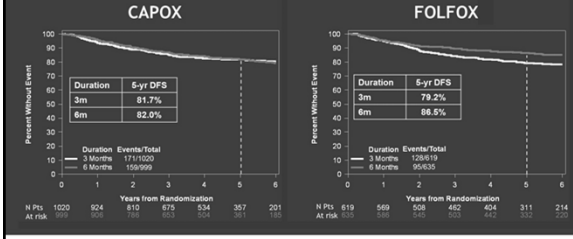
Results: DFS Comparison by Regimen



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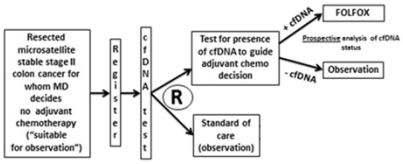
Stage II Adjuvant Study: NRG-GI005 (COBRA)

Evaluating early intervention for Minimal Residual Dz

Van Morris



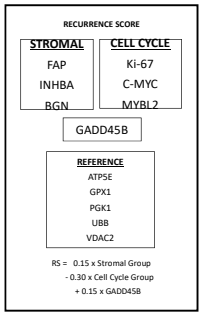
Primary objective: Clearance of cfDNA (to undetectable levels) for patients cfDNA+ at randomization

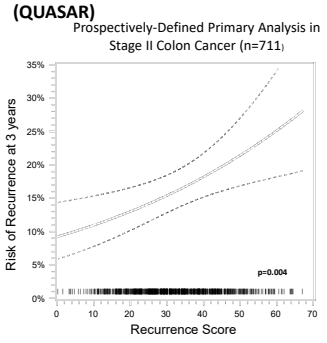
cfDNA: cell-free DNA
Abstract #TPS4121 – NCT04068103

Morris, Kopetz

Presented By Christopher Lieu at TBD

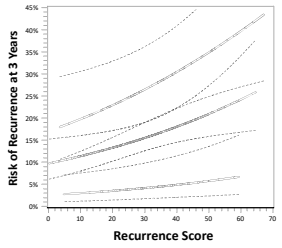
The 12-Gene Colon Cancer Recurrence Score (RS) Predicts Recurrence Following Surgery in Stage II Colon Cancer (QUASAR)





Kerr et al., ASCO 2009, #4000

QUASAR Results: Recurrence Score® Result, T Stage, and MMR Deficiency Are Key Independent Predictors of Recurrence in Stage II Colon Cancer



T4 and MMR proficient (13%)

T3 and MMR proficient (74%)

T3 and MMR deficient (11%)

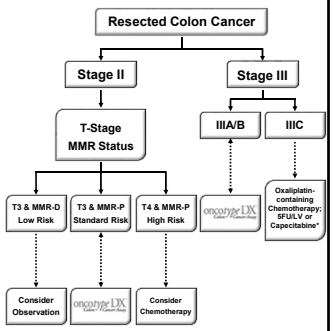
Rare patients (2% of all patients) with T4, MMR-D tumors had estimated recurrence risks that approximated (with large confidence intervals) those for patients with T3 stage, MMR-P tumors and were not included in this figure.

Kerr D, et al. *J Clin Oncol*. 2009;27: abstract 4000.
Gray R, et al. *J Clin Oncol*. 2011;29(35):4611-9.

Oncotype DX® Colon Cancer Assay

Incorporating the Recurrence Score® Result into Treatment Decision Making

- The Recurrence Score predicts recurrence risk in stage II and III colon cancer
- The Recurrence Score enables better discrimination of absolute treatment benefit as a function of risk
- Oncotype DX for colon cancer leads to a change in treatment recommendations in 45% of patients (ASCO GI 2013)
- Incorporating the Recurrence Score result with traditional factors may better inform adjuvant therapy decisions



MMR-D, mismatch repair deficient; MMR-P, mismatch repair proficient
*Patients not considered candidates for oxaliplatin

What is the (Standard) Adjuvant Therapy in Colon Cancer ?

- FOLFOX (or XELOX) is standard adjuvant therapy in
  - most stage III
  - can be considered in high-risk stage II colon cancer
  - very consistent results for oxaliplatin across trials
- Capecitabine (or 5FU/LV) for
  - patients who are not considered candidates for oxaliplatin (elderly, IIIA?)
  - selected stage II, pMMR
- Irinotecan, bevacizumab, and cetuximab have failed!
- Less is more: IDEA
- More is better: FOLFIRINOX for high-risk stage III (T4, N2)
- New Biologics: atezolimumab (PDL-1) MSI-H

ATOMIC; Alliance A021502

Stage III colon cancer

- **FOLFOX x6 mos**
- **FOLFOX x 6 mos Atezolizumub x 12 mos**

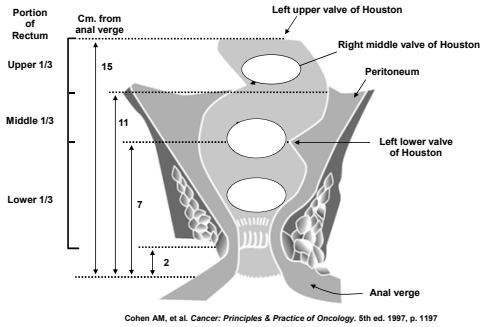
- Started 9/17; 700 pts planned
- Stratified by T, N stage and tumor sidedness
- 90% power to detect an effect size expressed as hazard ratio of 0.6 for the primary endpoint DFS at two-sided alpha of 0.05

IROCA Trial (Canada+France)

- Colon Cancer (High-risk Stage III; pT4N1 or pT1-4 N2)
- 640 pts; started 3/17
- Stratification
  - T1-T3N2 vs T4aN1 versus T4bN1 versus T4N2
  - Right colon (right of splenic flexure) vs left colon
  - Country (France vs Canada)

R → **mFOLFOX6 x6 mos**
R → **mFOLFIRINOX x6 mos**

Rectal Cancer



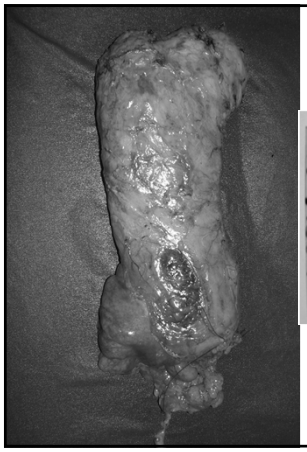
Cohen AM, et al. *Cancer: Principles & Practice of Oncology.* 5th ed. 1997, p. 1197

Endpoints in Clinical Trials in Rectal Cancer

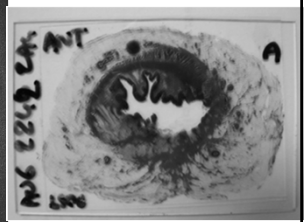
- **Overall Survival**
- **Disease-free survival**
- Distant failure
- **Local failure**
- **R0 margin**
- **Circumferential margin**
- **pCR rate**
- **Downstaging (T,N)**
- **Toxicity/morbidity (acute/late)**
- **Sphincter preservation (late function)**

Issues in Surgery

- Who and where?
  - Surgeon-specific volume was associated with 2-year mortality and remained an important predictor even after adjustment for hospital volume. Surgeon volume was also better than hospital procedure volume at predicting long-term survival
- TME
- Laparoscopic vs open procedures
- Local excision
  - ASCO U Tumor Board 12/15 local excision for cT2N0 or cT3N0 distal rectal adenocarcinoma



TME



ypT0 N0 – R0

Quirke - Dworak

89

Z6051: Laparoscopic Rectal Cancer Trial

Eligible pt with stage II-III primary rectal adenocarcinoma by ERUS or MRI staging

⇩

Randomization

⇩ Open rectal resection

⇩ Laparoscopic rectal resection

242 patients with laparoscopic resection and 222 with open resection were evaluable.

Z6051: Laparoscopic Rectal Cancer Trial

- **Primary outcome assessing efficacy: composite of circumferential radial margin greater than 1 mm, distal margin without tumor, and completeness of TME. A 6% noninferiority margin was chosen according to clinical relevance estimation.**
- **Successful resection occurred in 81.7% of laparoscopic resection cases (95% CI, 76.8%-86.6%) and 86.9% of open resection cases (95% CI, 82.5%-91.4%) and did not support noninferiority.**
- **Patients underwent low anterior resection (76.7%) or abdominoperineal resection (23.3%). Conversion to open resection occurred in 11.3% of patients.**
- **Operative time was significantly longer for laparoscopic resection (mean, 266.2 vs 220.6 minutes; mean difference, 45.5 minutes; 95% CI, 27.7-63.4; *P* < .001).**
- **ALaCaRT Randomized Clinical Trial: noninferiority of laparoscopic surgery compared with open surgery for successful resection was not established. Although the overall quality of surgery was high, these findings do not provide sufficient evidence for the routine use of laparoscopic surgery. Longer follow-up of recurrence and survival is currently being acquired.**

JAMA. 2015;314(13):1346-1355.; *JAMA*. 2015;314(13):1356-1363

ADJUVANT RECTAL CANCER POOLED ANALYSIS

Gunderson et al J Clin Oncol. 2010

- **Intermediate risk patients** (T1-2N1, T3N0)
  - Tri-modality adjuvant therapy for all patients may be excessive treatment, based on OS of >80% with surgery + chemotherapy
- **Moderately-high risk patients** (T1-2N2, T3N1, T4N0)
  - 5-yr OS ranges from 20-80%
  - Improvement in OS should be feasible since some treatment arms had DFS of only 20-50%
- **High-risk patients** (T3N2, T4N1, T4N2)
  - 5-yr OS was <50% in most groups of patients
  - More aggressive postoperative, preoperative or targeted therapy is indicated

NCCTG 79-47-51: CTX/XRT vs: XRT Alone

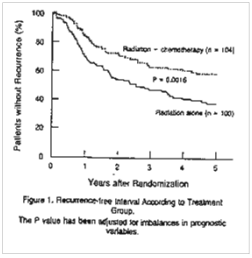


Figure 1. Recurrence-free Interval According to Treatment Group. The P value has been adjusted for imbalances in prognostic variables.

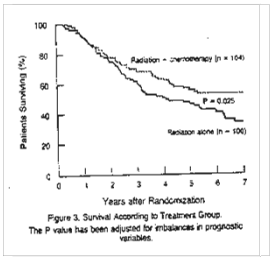


Figure 3. Survival According to Treatment Group. The P value has been adjusted for imbalances in prognostic variables.

Recurrence-free Survival Overall Survival

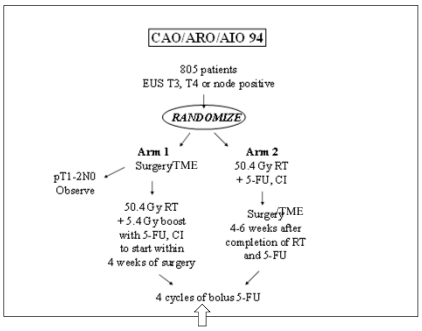
NEJM, 324(11):712-715, 1991

Pre-operative therapy in rectal cancer

- Emphasis on curative resection in addition to sphincter preservation
  - Requires accurate pre-operative staging
  - pre-operative tumor down-staging (CRM)
  - surgical technique (TME)
  - accurate pathological staging (R0)
  - reduce acute and late toxicities

CRM = circumferential resection margin; TME = total mesorectal excision

German CAO/ARO/AIO-94 Study



Pathohistologic Tumor Stage

	Postoperative RCT n= 394	Preoperative RCT n = 405
No tumor	0.7%	7.7 %
UICC- I	18 %	25 %
UICC-II	28 %	29 %
UICC-III	39 %	26 %
UICC-IV	7 %	6 %
Missing	6 %	6 %

DOWNSTAGING

P < 0.0001

Preoperative vs Postoperative Therapy of Rectal Cancer

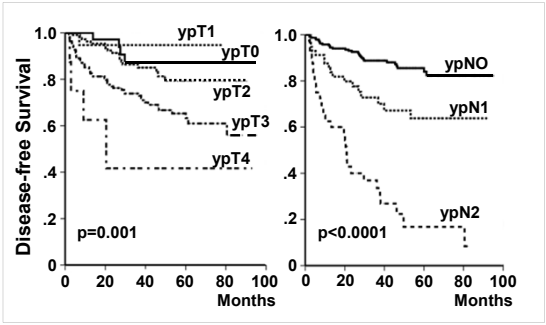
German Rectal Cancer Study

CAO/ARO/AIO-94, NEJM 2004

- **Decreased acute and delayed toxicities with preoperative therapy**
- **Sphincter preservation in 43 (39%) vs 17 (20%) in those declared to require APR at randomization**
- **Locoregional failure: 6% vs 12%**
- **No difference in distant metastases, DFS or OS**

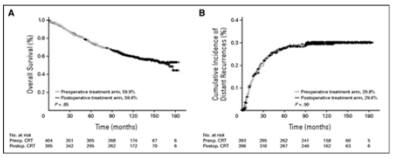
Early Prognostic factors – ypT/ypN

Disease-free survival after R0-resection (n=344)



CAO/ARO/AIO-94: 11-yr results

(A) Overall survival and (B) cumulative incidence of distant recurrences in the intention-to-treat population.



Sauer R et al. JCO 2012;30:1926-1933

©2012 by American Society of Clinical Oncology

Phase III: CAO/ARO/AIO-04

Best arm of CAO/ARO/AIO-94:

RT 50.4 Gy + 5-FU
1000 mg/m² days 1-5 + 29-33

→ **5-FU**
500 mg/m² d 1-5, q29
4 cycles (4 months)

Based on phase I/II trials:

RT 50.4 Gy + 5-FU/OX
Oxaliplatin: 50 mg/m² d 1, 8, 22, 29
5-FU: 250 mg/m² d 1-14 + 22-35
Note: Chemo gap during 3rd week of RT

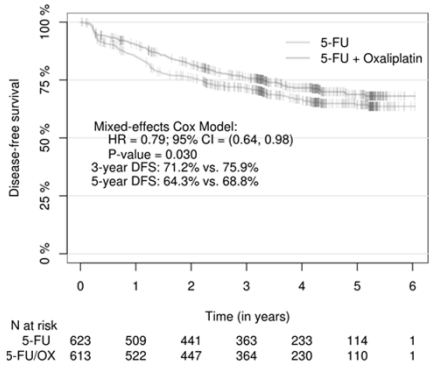
→ **mFOLFOX6**
Oxaliplatin: 100 mg/m² d1,q15
Folinic acid: 400 mg/m² d1
5-FU: 2400 mg/m² d1-2
8 cycles (4 months)

T M E

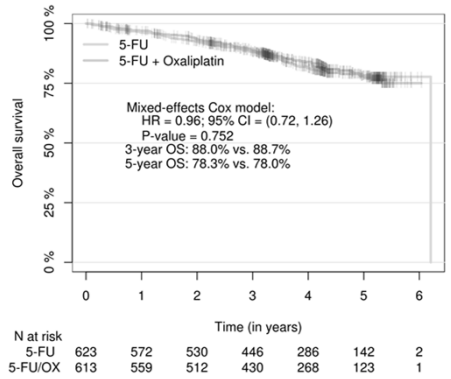
NB: different 5-FU regimens in both pre- and post-operative Rx arms

Primary Endpoint DFS **Median Follow-up: 50 months (range, 0.3 – 73)** **Intention-to-treat** **Time between randomisation and the first of the following events:**	**5-FU Arm n=623**	**5-FU/Ox Arm n=613**
Incomplete local resection (R2)	**10**	**5**
Locoregional recurrence after R0/R1 resection (+/- distant metastases)	**23**	**12**
Distant metastases/Progression	**149**	**115**
Death **Overall** **Cancer-/treatment related/surgical mortality** **Unrelated** **Unknown**	 **106** **69/4/6** **26** **1**	 **96** **54/7/4** **31** **0**
First events for DFS (total)	**198**	**159**

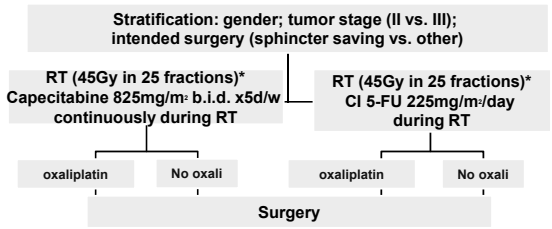
Disease-free Survival: Intention-to-treat analysis



Overall Survival: Intention-to-treat analysis



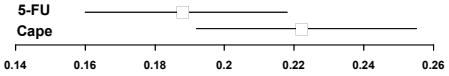
NSABP R-04



O'Connell, et al; JCO Jun 20, 2014:1927-1934

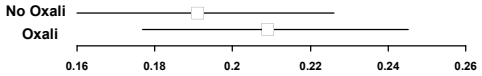
Pathologic Complete Response by Treatment 5-FU vs Capecitabine

pCR Status	5-FU	Cape	Total
without pCR	584	550	1134
with pCR	135	157	292
Total Patients	719	707	1426
pCR Rate (%) 95% CI	18.8 16.0-21.8	22.2 19.2-25.5	P-value .12



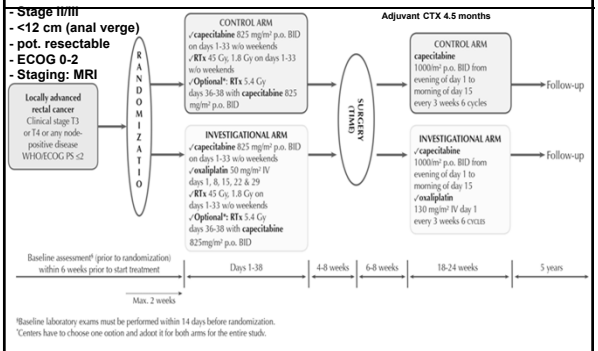
Pathologic Complete Response by Treatment Oxaliplatin vs None

pCR Status	No Oxali	Oxali	Total
without pCR	469	457	926
with pCR	111	121	232
Total Patients	580	578	1158
pCR Rate (%) 95% CI	19.1 16.0-22.6	20.9 17.7-24.5	P-value 0.46



Design: PETACC6, ASCO 2018

- Stage II/III
- <12 cm (anal verge)
- pot. resectable
- ECOG 0-2
- Staging: MRI



Hans-Joachim Schmoll http://clicktoeditURL.com 10

Relapse rate @ 5 years

Loco-regional Relapse

Cape 8.7 %
CapeOx 6.0 %

Gray test: p=0.238

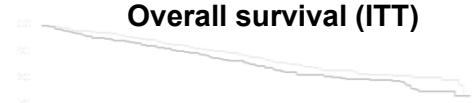
Distant Relapse

Cape 21.4 %
CapeOx 19.2 %

Gray test: p=0.261

Hans-Joachim Schmoll 10

Overall survival (ITT)

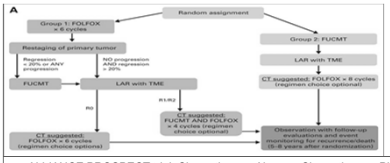


HR 1.17 p = 0.252
95% CI (0.89-1.54)
Cox model adjusted for strat. factors (except center)

	Cape	CapeOx
5-year	83.1%	80.1%
6-year	81.2%	77.7%
7-year	73.5%	73.7%

Hans-Joachim Schmoll

The administration of radiation therapy: Do all patients need radiation?



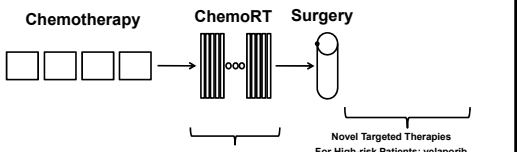
ALLIANCE PROSPECT trial: Chemotherapy Alone or Chemotherapy Plus Radiation Therapy in Treating Patients With Locally Advanced Rectal Cancer Undergoing Surgery

Clinical Stage: T2N1, T3N0, T3N1; no APR
Primary Outcome Measures: Pelvic R0 resection rate (Ph II), DFS (Phase III),TLR
Secondary: pCR, OS, AEs, rates of receiving pre- or post-operative 5FUCMT

Estimated Enrollment:	**1060**
Study Start Date:	January 2012
Completion Date:	July 2017 (Final data collection date for primary outcome measure)

Surgery: when?

Total Neoadjuvant Therapy
Distal, or bulky T4, or N2



Novel Targeted Therapies
For High-risk Patients: velaporib
Inactive as maintenance in NRG study: ASCO 2019

Novel Radiosensitization Strategies

Courtesy of Thom George, PI

Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) in locally advanced rectal cancer – the randomized RAPIDO-trial

Renu R Bahadoer[1], Esmée A Dijkstra[2], Boudewijn van Etten[2], Corrie AM Marijnen[1,3], Hein Putter[1], Elma Meershoek-Klein Kranenbarg[1], Annet GH Roodvoets[1], Iris D Nagtegaal[4], Regina GH Beets-Tan[3], Lennart K Blomqvist[5], Tone Fokstuen[5], Albert J ten Tije[6], Jaume Capdevila[7], Mathijs P Hendriks[8], Ibrahim Edhemovic[9], Andrés Cervantes[10], Per J Nilsson[5], Bengt Glimelius[11], Cornelis JH van de Velde[1], Geke AP Hospers[2] and collaborative investigators.

[1]Leiden University Medical Center, Leiden, the Netherlands, [2]University Medical Center Groningen, Groningen, the Netherlands, [3]Netherlands Cancer Institute, Amsterdam, the Netherlands, [4]Radboud University Medical Center, Nijmegen, the Netherlands, [5]Karolinska University Hospital, Stockholm, Sweden, [6]Amphia Hospital, Breda, the Netherlands, [7]Vall d'Hebron University Hospital, Barcelona, Spain, [8]Northwest Clinics, Alkmaar, the Netherlands, [9]Institute of Oncology Ljubljana, Ljubljana, Slovenia, [10]Biomedical Research Institute Incliva, Valencia, Spain, [11]Uppsala University, Uppsala, Sweden.

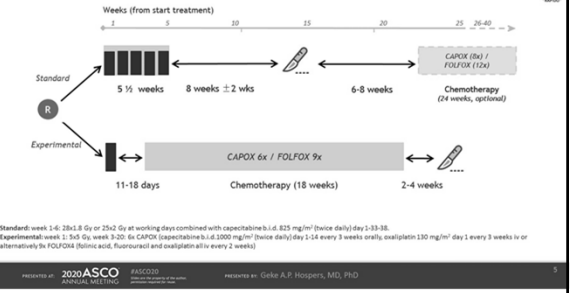
Principal investigators

umcg · Leiden University Medical Center · Karolinska Institutet · Uppsala Universitet

PRESENTED AT: 2020ASCO ANNUAL MEETING #ASCO20 PRESENTED BY: Geke A.P. Hospers, MD, PhD

Presented By Geke Hospers at TBD

Study design



Standard: week 1-6: 28x1.8 Gy or 25x2 Gy at working days combined with capecitabine b.i.d. 825 mg/m² (twice daily) day 1-33-38.
Experimental: week 1: 5x5 Gy, week 3-20: 6x CAPOX (capecitabine b.i.d.1000 mg/m² (twice daily) day 1-14 every 3 weeks orally, oxaliplatin 130 mg/m² day 1 every 3 weeks iv or alternatively 9x FOLFOX4 (folinic acid, fluorouracil and oxaliplatin all iv every 2 weeks)

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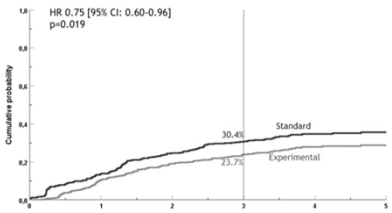
Presented By Geke Hospers at TBD

Disease-related Treatment Failure



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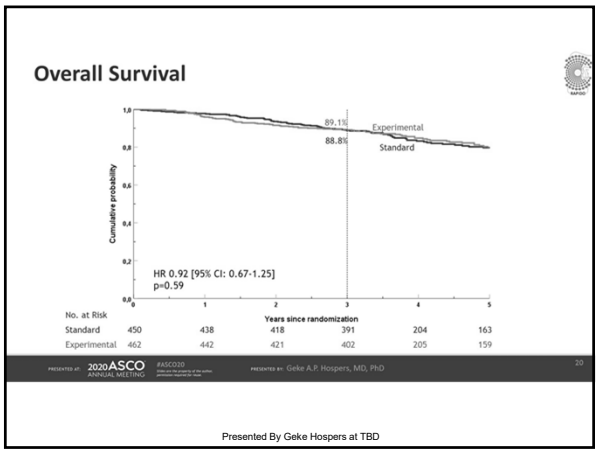
Presented By Geke Hospers at TBD



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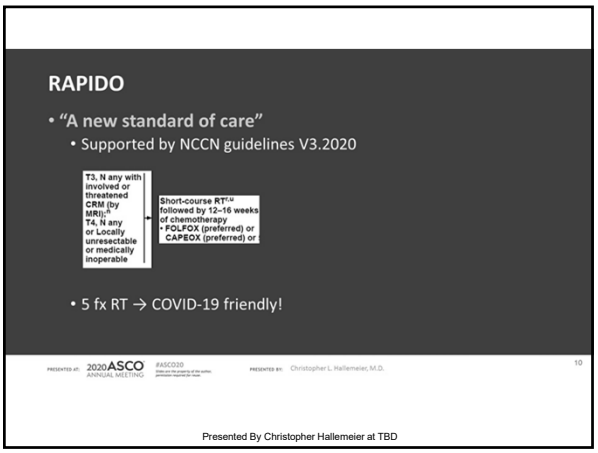
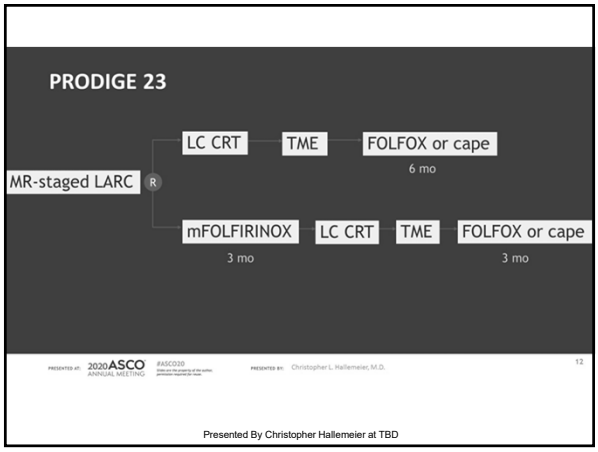
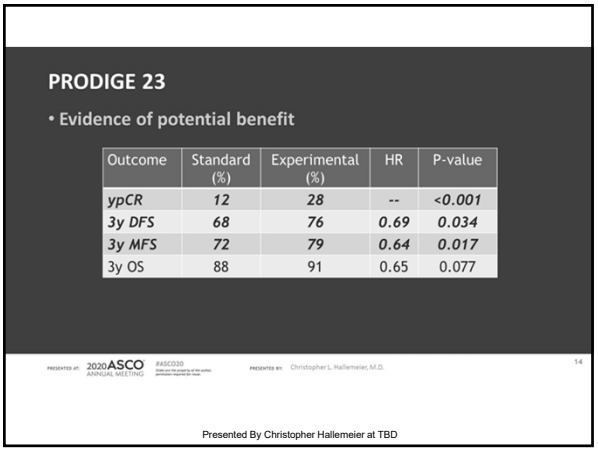


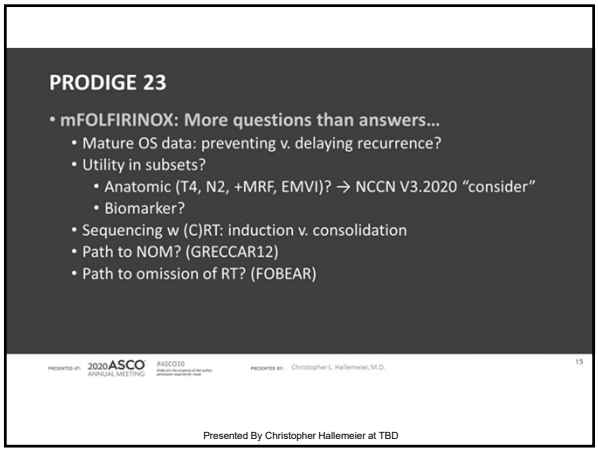
Presented By Christopher Hallemeier at TBD



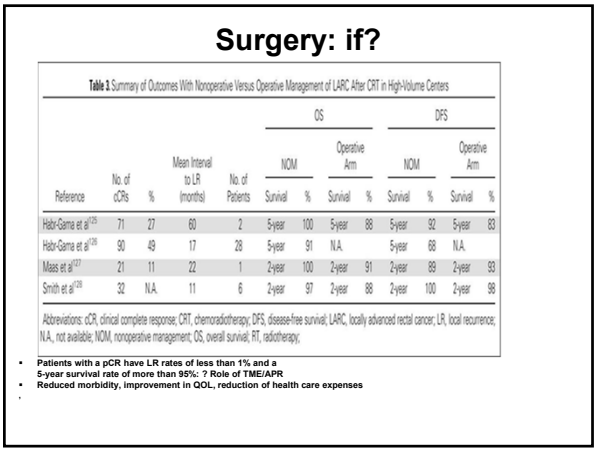
Presented By Christopher Hallemeier at TBD



Presented By Christopher Hallemeier at TBD



Presented By Christopher Hallemeier at TBD



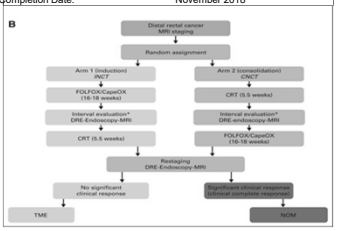
Surgery: if?

- **cCR rates: vary depending on approach**
  - – Traditional NAT, 21%
  - – Possibly higher with TNT approach
- **With NOM: approximate 25% local recurrence**
- **95% can be salvaged with TME**
- **Short-term survival does not appear to be compromised**
- – More data on long-term survival needed

Surgery: if?

- **cCR does not always correlate with pCR, and current imaging modalities cannot distinguish tumor remnants from tissue fibrosis with certainty**
- **Studies to date have been small, single-arm**
- **Short follow-up, lost to follow-up, optimal surveillance, compliance**

Estimated Enrollment: 300
Actual Study Start Date: November 2013
Estimated Study Completion Date: November 2018

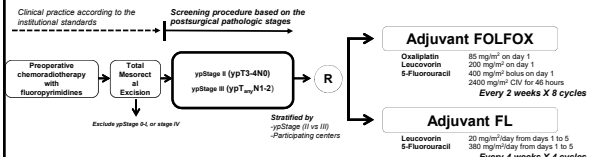


Memorial Sloan Kettering Cancer Center phase II trial

Establishing the role of adjuvant chemotherapy

- Staging for neoadjuvant therapy
  - In the original CAO/ARO/AIO trial, in patients who were assigned to initial surgery: UICC pathologic stage was stage I in 18%, stage II in 28%, stage III in 39%, stage IV in 7%
  - Therefore, only ~50% of patients could have benefitted from adjuvant treatment, and many likely needed neither CT or XRT; in many studies, half or less of patients actually received postoperative therapy
- Improved preoperative staging would likely reduce this problem, but are there available techniques for selecting at-risk patients after neoadjuvant therapy?
  - Initial cTN stage or ypTNM stage
  - pCR
  - TRG
  - ONCOTYPE DX® (Dutch TME surgery alone st II and III): Recurrence Score predicted recurrence risk (p=0.011), with particularly strong results in stage II.
  - ctDNA

ADORE TRIAL; ASCO 2018



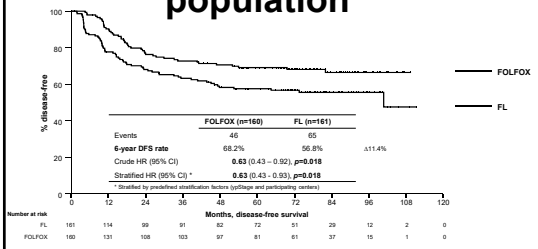
Key inclusion criteria

- Preoperative chemoradiotherapy with fluoropyrimidines alone; *oxaliplatin or other combined regimens were not allowed.*
- Total mesorectal excision (TME) was mandatory.
- Curative surgery (no microscopic residual tumor), ≤ 8 weeks prior to randomization.

KIM, TAE WON

1
2
4

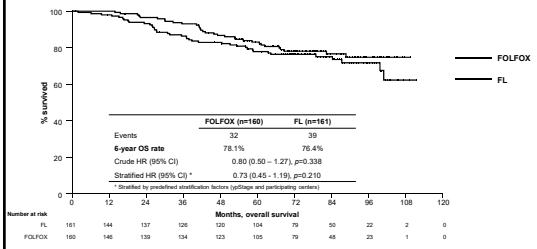
Disease-free survival, ITT population



KIM, TAE WON

1
2
5

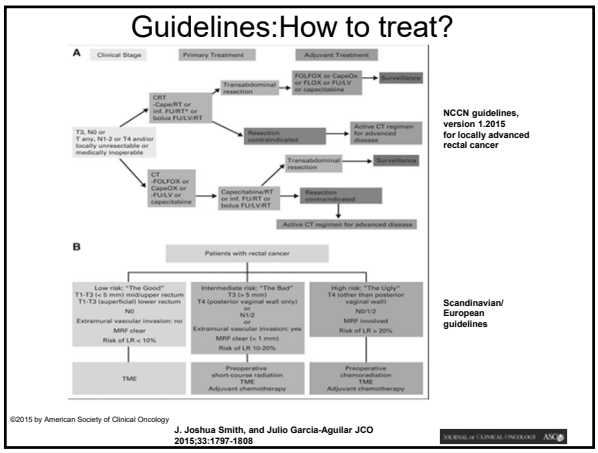
Overall survival, ITT population



6-yr followup: In the subgroup analysis for OS, those with ypN2 (HR 0.42 [0.18-0.96], p= 0.04) and minimally regressed tumor (HR 0.42 [0.19-0.97], p= 0.043) benefited from FOLFOX

JCO 2018

Guidelines:How to treat?



NCCN guidelines, version 1.2015 for locally advanced rectal cancer

Scandinavian/ European guidelines

J. Joshua Smith, and Julio Garcia-Aguilar JCO 2015;33:1797-1808

71

Anal Cancer

John S. Macdonald, MD, FACP

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

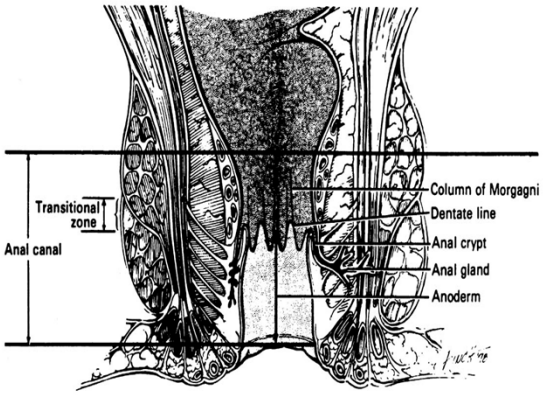
71 – Anal Cancer

Daniel G. Haller, MD, FACP, FRCP, FASCO

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

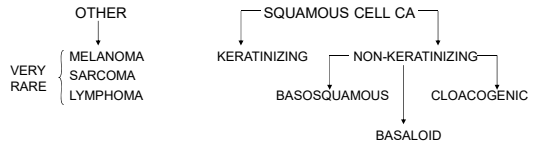
- **Interests- Speakers Bureau: Amgen, TAIHO, Lilly, Exilixis**



ANAL CANCER EPIDEMIOLOGY

- 8590 new cases (2960 men and 5900 women) of anal cancer involving the anus, anal canal, or anorectum will occur in the United States in 2020, accounting for approximately 2.7% of digestive system cancers.
- It has been estimated that 1350 deaths due to anal cancer will occur in the United States in 2020.
- the incidence rate of invasive anal carcinoma in the United States increased by approximately 1.9-fold for men and 1.5-fold for women from the period of 1973 through 1979 to 1994 through 2000 and has continued to increase since that time.

ANAL CANCER CELL TYPES



AJCC Anatomic Stage

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T1-2	N1	M0
Stage IIIB	T4	N0	M0
Stage IIIC	T3-4	N1	M0
Stage IV	Tany	Nany	M1

T1 2 cm or less; T2 2-<5 cm; T3 5 or greater

Prognosis

- The prognosis of anal carcinoma is related to the size of the primary tumor and the presence of lymph node metastases
- According to the SEER database ~50% of anal carcinomas were localized at initial diagnosis (Stage I-IIB); these patients had an 80% 5-year survival rate.
- Approximately 29% of patients had anal carcinoma that had already spread to regional lymph nodes at diagnosis (Stage III); these patients had a 60% 5-year survival rate.
- The 12% of patients presenting with distant metastasis demonstrated a 30.5% 5-year survival rate.

ANAL CANCER
ETIOLOGY
non-HPV ASSOCIATIONS

- Herpes Virus Type 2
- Immunosuppression (Transplant)
- Smoking (RR 9.4)
- HIV alone not associated

ANAL CANCER
Anal Ca/AIN are STDs

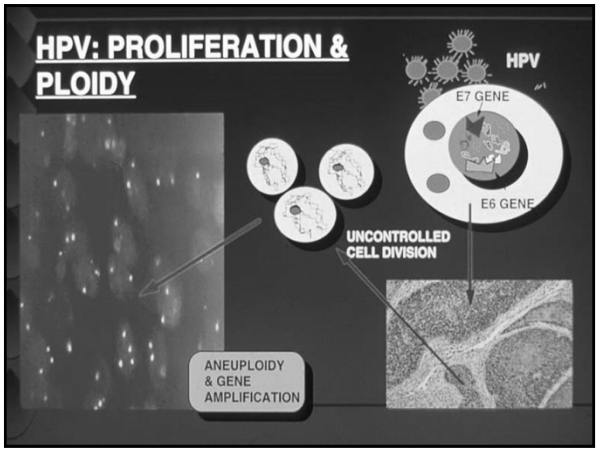
Population	Multiple partners	Anal receptive intercourse	V.D. in partner
324 patients 554 controls	P < .001	3.4 (O.R.)	2.4 (O.R.)

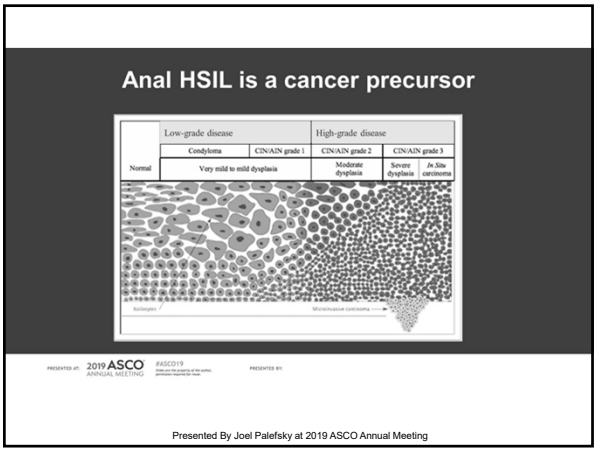
Frisch, et al., NEJM 337:1350, 1997

ANAL CANCER
STD
Anal Ca. or AIN

Population	Tumor⊕HPV-16
324 ♀ 93 ♂	84%

Frisch, et al., NEJM 337:1350, 1997





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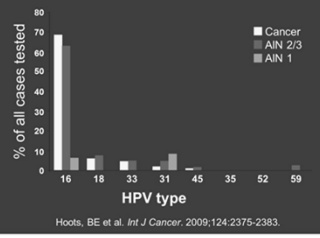
HPV types in anal LSIL, HSIL and cancer



Hoots, BE et al. *Int J Cancer*. 2009;124:2375-2383.

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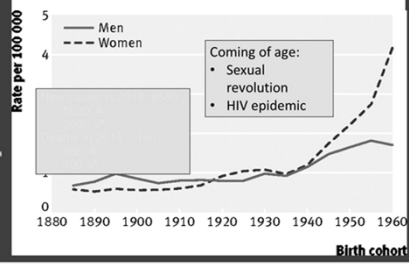
Anal Cancer Rates by Birth Cohort



Simpson J A D , Scholefield J H
BMJ 2011;343:bmj.d6818

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Recent trends in anal cancer incidence AIDS and cancer registry match study

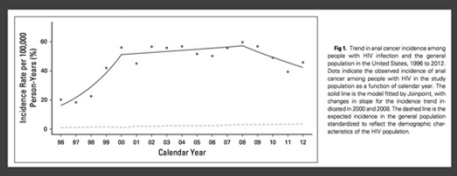

Fig 1. Trend in anal cancer incidence among people with HIV infection and the general population in the United States, 1996 to 2012. Dots indicate the observed incidence of anal cancer among people with HIV in the study population as a function of calendar year. The solid line is the model fitted by Joinpoint, with changes in slope for the incidence trend indicated in 2000 and 2008. The dashed line is the expected incidence in the general population standardized to reflect the demographic characteristics of the HIV population.

Colon-Lopez V. et al J Clon Oncol 2018; 36:68-75

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High prevalence of anal HPV infection and HSIL in HIV+ men and women

	Anal HPV prevalence	Anal HSIL prevalence	Anal cancer incidence
HIV-infected MSM	96%	43%	131/100,000
HIV-infected MSW	59%	?	46/100,000
HIV-infected women	90%	28%	30/100,000

Chin-Hong et al. *Ann Int Med*. 2008;149:300-6; Silverberg M et al. CID 2012; 54:1026-34
Conley et al. JID 2010; 202:1567-76'Stier EA et al. Presented at International Anal Neoplasia Society (IANS) Scientific Meeting, San Francisco, CA. November 11-13, 2016

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The nonavalent HPV vaccine

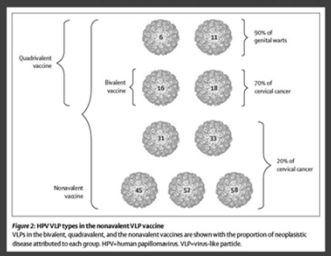


Figure 2: HPV VLP types in the nonavalent VLP vaccine
VLPs in the bivalent, quadrivalent, and the nonavalent vaccines are shown with the proportion of neoplastic disease attributed to each group. HPV=human papillomavirus. VLP=virus-like particle.

Schiller J. Lancet Oncol 2015;16(5):e217-25

Presented By Joel Palefsky at 2019 ASCO Annual Meeting

The NEW ENGLAND JOURNAL of MEDICINE

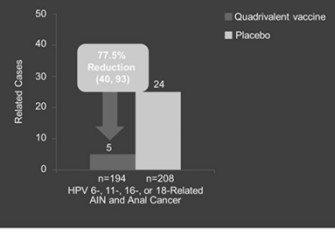
ORIGINAL ARTICLE

HPV Vaccine against Anal HPV Infection and Anal Intraepithelial Neoplasia

Joel M. Palefsky, M.D., Anna R. Giuliano, Ph.D., Stephen Goldstone, M.D., Edson D. Moreira, Jr., M.D., Carlos Aranda, M.D., Heiko Jessen, M.D., Richard Hillman, M.D., Daron Ferris, M.D., Francois Coutlee, M.D., Mark H. Stoler, M.D., J. Brooke Marshall, Ph.D., David Radley, M.S., Scott Vuocolo, Ph.D., Richard M. Haupt, M.D., M.P.H., Dalya Guris, M.D., and Elizabeth I.O. Garner, M.D., M.P.H.

Presented By Joel Palefsky at 2019 ASCO Annual Meeting

Quadrivalent vaccine in males: efficacy against HPV 6/11/16/18-related AIN and anal cancer in MSM



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Recommendations for HPV vaccine

- FDA recently approved vaccination up to age 45 years
- ACIP recommendation [redacted] (CDC) Age 9-26
- Decision to vaccinate above age 26 is individualized
  - Number of prior sexual partners
  - Likelihood of future sexual exposure
  - Vaccine is safe
  - Vaccine may or may not be costly

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Who should be screened?

- All HIV-positive men regardless of sexual orientation
- All HIV-negative MSM
- Women with high-grade cervical or vulvar lesions or cancer
- All HIV+ women
- All men and women with perianal condyloma
- Solid organ transplant recipients
- Over 25 years if immunosuppressed, inc. HIV
- Over 40 years if immunocompetent

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ANAL CANCER
CURRENT THERAPIES

Local resection (early lesions with sphincter sparing)

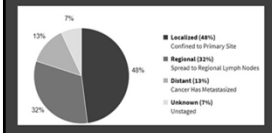
T_1-T_2 N_0

Combined modality therapy

1) 5-FU/Mitomycin-C/XRT
2) Any Rx better than FU-Mito-C?

Salient Facts of Surgically Unresectable/ Metastatic Anal Cancer

- The majority of patients will present with locally advanced disease and will be treated with concurrent chemoXRT with curative intent.
  - Risk factors for residual or recurrent disease include T>4 cm and N+



- Metastatic disease will develop in < 20% of patients
- **Historically, no** well established chemotherapy regimen for metastatic pts
  - 5-yr OS = 30%

C. Eng: MD Anderson Manual of Clinical Oncology, 2006; Frisch et al: J Natl Cancer Inst 92:1500-10, 2000; Frisch M, et al: J Natl Cancer Inst 91:708-15, 1999; Eng et al: OncoTarget 2014; www.seer.gov; Gunderson et al, JCO, 2012.

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ANAL CANCER
RESULTS OF ABDOMINAL PERINEAL RESECTION

No. Pts.*	Operative Mortality (%)	5-yr Survival (%)	Local-Regional Failure (%)
460	5.5 (2.5-8)	55 (45-66)	30 (27-35)

* 5 Series

Harter & Ahlgren, GI Oncology, 1992

ANAL CANCER
RADIOTHERAPY ALONE AS TREATMENT FOR ANAL CANCER

Series	No. of Pts.	Dose (cGy)	Complications Requiring Surgery (%)	Local Control (%)	5-Yr Survival (%)	Retention of Functional Anus (%)
Inst. Curie	158	6500-7500	8	67	59	73
Inst. Gustave Roussy	64	6000-6500	14	91 ($T_{1,2}$) 76 (T_1)	46	74
Princess Margaret	51	4500-6000	12	57	59	76
Centre Léon Bérard	222	3000-4200 (Ext) 1500-2000 (Implt) 4500-6200	3	79	65	--

Squamous cell carcinoma of the Anus

- Usually localized with a low risk of metastases at presentation
- Metastases rare unless primary uncontrolled
- So local control ? more important than distant metastases.

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Site of relapse after CRT with 50.4Gy from ACT II (940 patients)

Primary Inguinal/pelvic nodes Metastases/oligometastases	Number	% total relapses
Pelvic - no metastases	133	64%
Pelvic - with metastases	30	14%
Distant metastases only	46	22%
Total crude pelvic failure (with or without metastases)	163	78%
Total relapses	209/940	

Data from ACT II Sebag-Montefiore D et al ASCO 2012

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Early Summary

- Early and late toxicities induced by CRT substantial
- 10–20% of patients are not sensitive to CRT or relapse early after treatment.
- Once relapsed, only 30-40% of patients can be salvaged by abdominoperineal resection

16

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ANAL CANCER
5-FU + MITO-C + XRT

5-FU: 1000 mg/m^2 x 4 days CI
MMC: 10-15 mg/m^2 day 1 i.v.
XRT: 3000-4000 R

- 11 pts all bx-proved NED (median f/u 1 yr)
- 1 pt dead p.e. NED at autopsy

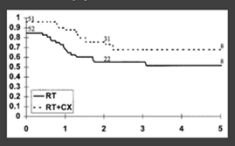
Flam, et al., ASCO 1:97, 1982

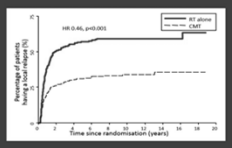
ANAL CANCER
5-FU + MITO-C + XRT

Institution	Regimen	No. Pts	CR (%)
Wayne State	5-FU + Mitomycin-C + 30 GY XRT (Simul)	122	113/122 (93%)
Memorial	5-FU + Mitomycin-C + 30 GY (Sequential)	37	19/37 (52%)
Princess Margaret	5-FU + Mitomycin-C + 50 GY vs. 60 GY only	30 25	27/30 (93%) 15/25 (60%)

Squamous cell carcinoma of the Anus

- Chemoradiation more effective in achieving local control than radiotherapy alone.





EORTC 22861 Bartelink H et al J Clin Oncol 1997 ACT I Trial UKCCR Lancet 1996

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Squamous cell carcinoma of the Anus

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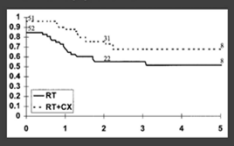

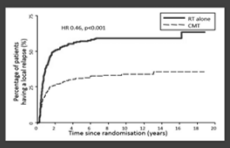

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Squamous cell carcinoma of the Anus

- Chemoradiation more effective in achieving local control than radiotherapy alone.
- Addition of MMC to 5FU CRT essential component
- No benefit from addition of induction chemotherapy (5FU/cisplatin prior to CRT
- No benefit from consolidation chemotherapy after CRT
- No benefit for 5FU/cisplatin vs 5FU/MMC
- No benefits and excessive toxicity from cetuximab

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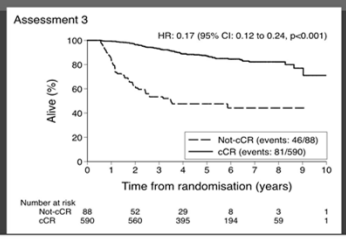
Outcomes if in CCR at 26 weeks (ACT II)



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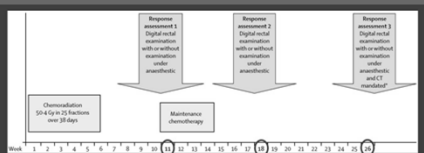
Best time to assess complete clinical response (cCR) after CRT : ACT II data



- n=691 attended all three assessments
- cCR: 64%, 80% and 85% at assessments 1, 2 and 3, respectively
- 72%: no cCR at assessment 1; cCR by assessment 3
- 5-year OS (at assessment 3): cCR=87%; non-cCR=48%

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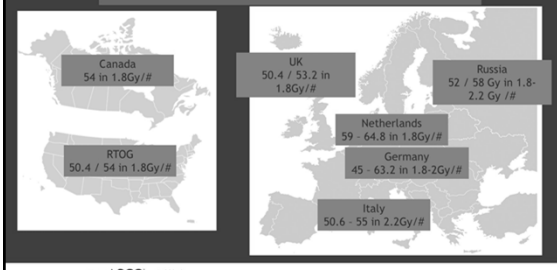
To biopsy or not?

- Needle biopsy may have false negative
- Biopsy before 26 weeks may be too soon: false positive
- Excisional biopsy may increase risk of sphincter incompetence

Radiotherapy Doses to primary tumour



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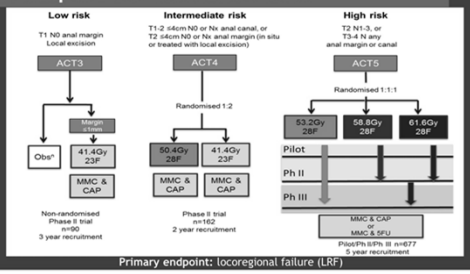
Risk-adapted RT: the PLATO trial



Primary endpoint: locoregional failure (LRF)

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Nivolumab After Combined Modality Therapy in Patients With High Risk Stage II-IIIB Anal Cancer NCT03233711

ECOG-ACRIN Cancer Research Group

- Nivolumab IV over 30 minutes on day 1. Treatment repeats every 14 days for up to 12 courses in the absence of disease progression or unacceptable toxicity.
- Primary endpoint 5 years DFS
- Started April 2018 - Estimated enrolment -200 by
- 2020

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Survivorship –late toxicity

- Grade 3 and above (classified as severe) up to 33.3%.
- The most commonly reported late toxicities were faecal incontinence (up to 44%), diarrhea (up to 26.7%), and ulceration (up to 22.6%)
- Intensity-modulated radiation therapy appears to reduce late toxicity.

Pan YB, Maeda Y, Wilson A, Glynne-Jones R, Vaizey CJ. **Late gastrointestinal toxicity after radiotherapy for anal cancer: a systematic literature review.** Acta Oncol. 2018 Nov;57(11):1427-1437

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Prior Published Regimens for Metastatic Anal SCCA

Author	N	Agents	ORR	Med PFS (months)	Med OS (months)
Wilking 1985	15	Vincristine, bleomycin & High-dose methotrexate	3/12 (25%)	2M	NR
Ajani 1989	3	5-FU/CDDP	NA	17M (2 of 3)	NA
Faivre 1999	18	5-FU/CDDP	65% (CR=15%)	4M	NA
Hainsworth 2001	60 (4 with anal cancer)	TPF (max = 4 cycles)	65% (CR = 25%)	26M	NR
Jhawer 2006	20	Mitomycin C, adriamycin, cisplatin, bleomycin-CCNU	12/20 (60%)	8M	15
Alcindor 2008	5	Taxol (1st and 2nd line)	60%	Range: 3-8M	Range: 4-20M
Abbas 2011	7	Taxol (2nd line)	57%	Range: 2-8M	Range: 5-14M
Kim 2013	8	DCF	CR: 50% (3/4 resected)	19-88M	1 yr: 62.53M%
Eng, 2014	77	Carbo/Taxol and 5-FU/CDDP	33% - 57%	7M (5M vs. 16M)	22M (17M vs. 53M)
Kim, 2018	69	Docetaxel, cisplatin, and 5-FU (DCF)	89%	11M	NR

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International Rare Cancer Initiative (IRCI)/ECOG EA#2133
InterAACT: 1st line Met SCCA of the Anal Canal

NCT02560298

R

Arm A → Cisplatin 75 mg/m2 day 1 + 5FU 1000mg/m2 infusion/24 hours/4 days q28 days

- Treatment for 6M and cont at the discretion of the investigator
- Substratification: **HIV+/HIV-**, HPV status, and prior XRT
- CT scans: q3M
- **N=90**

Arm B → Carboplatin (AUC = 5) + Taxol (weekly) q 21 days

Study PI's – S Rao, US PI: C Eng

Objective: Feasibility and to identify best chemotherapy backbone to build for biologic development
1) Primary endpoint: RR
2) Secondary endpoints: PFS, OS, correlatives, and QOL, etc.

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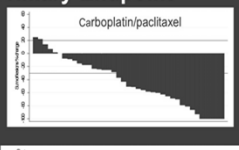
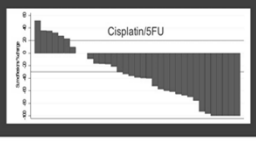
InterAACT/EA#2133 Primary Endpoint

Response (RECIST)	Carboplatin-Paclitaxel N=39		Cisplatin-5FU N=35	
	N	(%) CI	N	(%)
CR	5	12.8	5	14.3
PR	18	46.2	15	42.9
SD	10	25.6	7	20.0
PD	6	15.4	8	22.9
CR/PR	23	59 *95% CI: [42.1-74.4]*	20	57 *95% CI: [39.4-73.7]*





Rao et al, ESMO 2018

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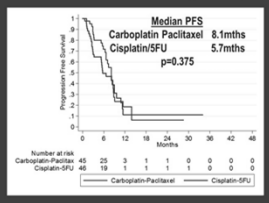
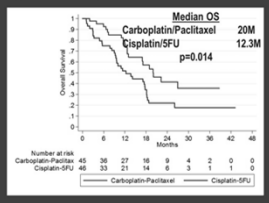
InterAACT/EA#2133: Secondary Endpoints of PFS and OS

Median follow-up of 25.3 M





Rao et al, ESMO 2018

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Presented By Cathy Eng at 2019 ASCO Annual Meeting

NCI9673 (Part A): Multi-Institutional Phase II ETCTN Study of Nivolumab in Previously Treated Metastatic SCCA

Patients with metastatic squamous cell carcinoma of the anal canal
- Treated with at least one prior therapy for metastatic disease
- No prior immune therapies received as part of cancer treatment

- Simon Optimal, two-stage phase II study, H_0: $p \leq 0.05$ and an alternative hypothesis H_a: $p \geq 0.20$,
- $\alpha = 0.10$ and a $\beta = 0.10$

12 patients treated initially with nivolumab 3 mg/kg IV every 2 weeks

Patients will be followed for best response using RECIST criteria 1.1

- Diagnostic imaging was completed every 6 wks
- Primary endpoint: RR
- ECOG PS = 0-1
- HIV+ (CD4 > 300) and Hepatitis patients were not excluded
- Exploratory correlatives were collected.

0 responses → Stop trial

≥1 response → Expand trial to include 25 additional patients with metastatic SCCA

Morris et al...Eng: Lanc Onc, 2017

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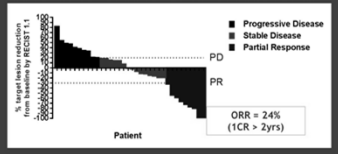
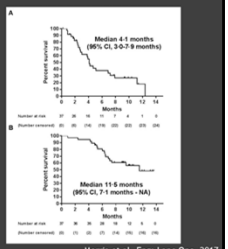
NCI9673 (Part A): Secondary Endpoints: PFS and OS





Morris et al...Eng: Lanc Onc, 2017

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Presented By Cathy Eng at 2019 ASCO Annual Meeting

NCI9673 (Part B): Randomized Phase II ETCTN Study of Nivolumab +/- Ipilimumab in Metastatic SCCA of the Anal Canal

Patients with metastatic squamous cell carcinoma of the anal canal
- Treated with at least one prior therapy for metastatic disease
- No prior immune therapies received as part of cancer treatment

N=36/100
Opened October 2018
PI: C. Eng

1:1

- Diagnostic imaging q8 wks
- ECOG PS = 0-1
- HIV+ (CD4 > 300) and Hepatitis patients were not excluded

Nivolumab (480 mg IV q4 weeks)

Nivo + Ipilimumab (480mg IV q4 weeks) + 1 mg/kg IV q8 weeks)

Primary endpoint: PFS, Secondary endpoints: OS, RR, and SAE's
Exploratory correlatives to be collected.

NCT02314169

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Pembrolizumab for Advanced Anal Squamous Cell Carcinoma: Results From the Phase 2 KEYNOTE-158 Study

Aurelien Marabelle,[1] Philippe Cassier,[2] Marwan Fakih,[3] Tormod Guren,[4] Antoine Italiano,[5] Steven Kao,[6] Dorte Nielsen,[7] Paolo Ascierto,[8] Giovanni Mendonca Bariani,[9] Armando Santoro,[10] Jamil Asselah,[11] Anthony El-Khoueiry,[12] Kristen Spencer,[13] Shunji Takahashi,[14] Arkendu Chatterjee,[15] Fan Jin,[15] Kevin Norwood,[15] Jean-Pierre Delord[16]

[1]Gustave Roussy, INSERM U1015, Villejuif, France; [2]Centre Léon Bérard, Lyon, France; [3]City of Hope National Medical Center, Duarte, CA, USA; [4]Oslo University Hospital, Oslo, Norway; [5]Institut Bergonie , Bordeaux, France; [6]Chris O'Brien Lifehouse, Camperdown, NSW, Australia; [7]Herley Hospital, University of Copenhagen, Copenhagen, Denmark ; [8]Istituto Nazionale Tumori IRCCS Fondazione Pascale, Naples, Italy; [9]Instituto do Câncer do Estado de São Paulo, Universidade de São Paulo, São Paulo, Brazil ; [10]Humanitas Clinical and Research Hospital, IRCCS, Humanitas University, Milan, Italy; [11]McGill University, Montreal, QC, Canada; [12]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [13]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [14]Cancer Institute Hospital of the Japanese Foundation for Cancer Research, Tokyo, Japan; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]Institut Claudius Regaud IUCT-Oncopole, Toulouse, France

Presented By Aurelien Marabelle at 2020 Gastrointestinal Cancer Symposium

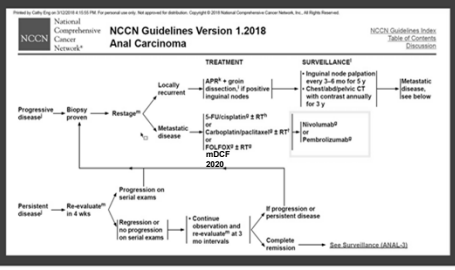
Antitumor Activity
(RECIST v1.1, Central Review)

	All Patients N = 112	PD-L1 Positive N = 75	PD-L1 Negative N = 30
ORR, % (95% CI)	10.7 (5.7–18.0)	14.7 (7.6–24.7)	3.3 (0.1–17.2)
Best overall response			
CR	6 (5.4)	6 (8.0)	0
PR	6 (5.4)	5 (6.7)	1 (3.3)
SD	17 (15.2)	11 (14.7)	4 (13.3)
PD	74 (66.1)	48 (64.0)	21 (70.0)
Nonevaluable[a]	1 (0.9)	0	1 (3.3)
No assessment[b]	8 (7.1)	5 (6.7)	3 (10.0)

Data are presented as n (%), unless otherwise noted.
[a]Patients for whom not all target lesions were captured on ≥1 postbaseline imaging assessment.
[b]Patients for whom no postbaseline tumor assessment was performed.
Data cutoff date: June 27, 2019 .

Presented By Aurelien Marabelle at 2020 Gastrointestinal Cancer Symposium

Change in 2018 NCCN Guidelines



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Presented By Cathy Eng at 2019 ASCO Annual Meeting

Phase 1 study of pembrolizumab in people with HIV and cancer

2019 American Society of Clinical Oncology Annual Meeting
June 2, 2019
Chicago, IL

Thomas S Uldrick MD, MS
Deputy Head, Global Oncology
PI, Cancer Immunotherapy Trials Network-12
Associate Member, Vaccine and Infectious Disease Division
Associate Member, Clinical Research Division
Fred Hutchinson Cancer Research Center

cancer immunotherapy trials network
FRED HUTCH CURES START HERE
NCI NATIONAL CANCER INSTITUTE Center for Cancer Research

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Presented By Thomas Uldrick at 2019 ASCO Annual Meeting

Conclusions

- Pembrolizumab has acceptable safety in cancer patients with HIV on ART and >100 CD4 cells/μL
- Clinical benefit noted in lung cancer, lymphoma, and KS
- Activity noted in liver cancer
- ***Anti-PD-1 therapy is appropriate for FDA-approved indications and cancer clinical trials in this population***
- Prospective evaluation of pembrolizumab as first systemic therapy in Kaposi sarcoma on-going
- Pembrolizumab may be associated with polyclonal KSHV-associated B-cell lymphoproliferation
- Patients with KSHV-associated Castleman disease should not be treated with pembrolizumab

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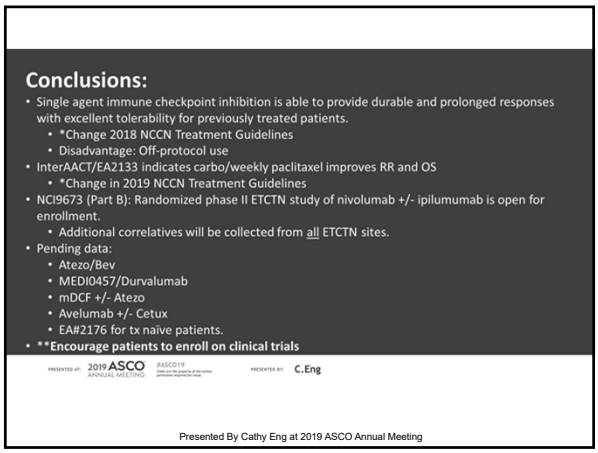


Presented By Cathy Eng at 2019 ASCO Annual Meeting

72

Hepatobiliary Cancer

Daniel G. Haller, MD, FACP,FRCP

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

72 – Hepatobiliary Cancer

Daniel G. Haller, MD, FACP, FRCP, FASCO

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Interests- Speakers Bureau: Amgen, TAIHO, Lilly, Exilixis**

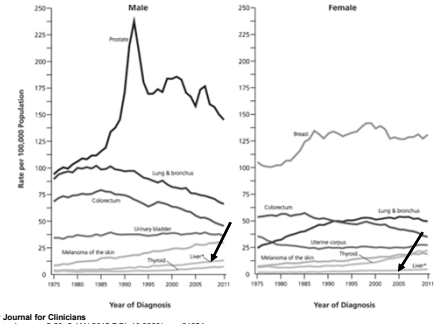
Hepatobiliary Carcinomas:

ACS 2020 Incidence and Mortality

	Incidence	Mortality
Liver/ Intrahepatic bile duct (~75% HCC)	42,810	30,160
GB/ extrahepatic bile duct	11,980	4,090

ACS Cancer Statistics

Trends in Incidence Rates for Selected Cancers by Sex, United States, 1975 to 2011



CA: A Cancer Journal for Clinicians
Volume 65, Issue 1, pages 5-29, 5 JAN 2015 DOI: 10.3322/caac.21254
http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full#caac21254-fig-0003

ACS Cancer Statistics, 2020

New cases: An estimated 42,810 new cases of liver cancer (including intrahepatic bile duct cancers) will be diagnosed in the US during 2020, approximately three-fourths of which will be hepatocellular carcinoma (HCC). Liver cancer is about 3 times more common in men than in women.

Incidence trends: Liver cancer incidence has more than tripled since 1980; from 2006 to 2015, the rate increased by about 3% per year. ~70% of HCCs could be prevented.

Deaths: An estimated 30,160 liver cancer deaths will occur in 2020.

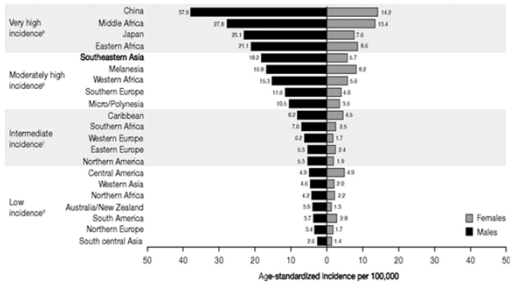
Mortality trends: Liver cancer death rates have increased by almost 3% per year since 2000.

CA: A Cancer Journal for Clinicians
Volume 66, Issue 1, pages 5-29, 5 JAN 2015 DOI: 10.3322/caac.21254
http://onlinelibrary.wiley.com/doi/10.3322/caac.21254/full#caac21254-fig-0003

Hepatocellular Carcinoma

- Incidence
  - among the most common tumors in the world:
    - Liver cancer in adult men is the fifth most frequently diagnosed cancer worldwide, and is the second leading cause of cancer-related death in the world
  - >800,000 deaths annually
  - wide regional variation
    - highest in Southeast Asia and sub-Saharan Africa
    - epidemiological links to environmental, occupational exposure, life style (NASH)
    - implications for reduction of risk and prevention

Global variation in liver cancer incidence rates



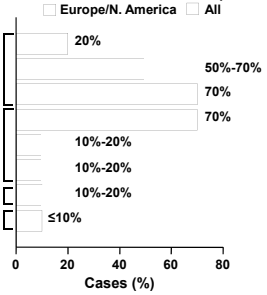
Venook A P et al. The Oncologist 2010;15:5-13

Hepatocellular Carcinoma

- Etiology
  - Cirrhosis
    - HBV
    - HCV
    - Alcoholic
    - NASH (Nonalcoholic steatohepatitis)
  - Metabolic diseases
    - hemochromatosis
    - hereditary tyrosinemia
    - alpha-1 antitrypsin deficiency

Risk Factors for HCC Worldwide

% of Patients With Risk Factor in SHARP trial			Asia/Africa*	Japan	Europe/N. America	All
Sorafenib (n=299)	Placebo (n=303)					
29	27	Hepatitis C	20%	50%-70%	70%	70%
19	19	Hepatitis B	10%-20%	10%-20%		
26	26	Alcohol	10%-20%			
9	10	Other	≤10%			



*Excluding Japan.

Llovet JM et al. *Lancet.* 2003;362:1907-1917. 2. Llovet J et al. *J Clin Oncol.* 2007;25(Suppl 18):LBA1.

Obesity and NASH in HCC

•Obesity is a risk factor for worse outcomes in HCC

•Metabolic syndrome and HCC: Non-alcoholic steatohepatitis (NASH)-increasing in West

Abdominal obesity
Atherogenic dyslipidemia
Elevated blood pressure
Insulin resistance or glucose intolerance
Prothrombotic state (e.g., high fibrinogen or plasminogen activator inhibitor–1 in the blood)
Proinflammatory state (e.g., elevated C-reactive protein in the blood)

A Siegel, S Wang, J Yu, E Lim, J Jacobson, R Brown, A Neugut.
College of Physicians and Surgeons

Hepatocellular Carcinoma

- Hepatitis and HCC: mechanisms
  - tumors arise in the context of chronic liver-cell injury, inflammation and increased turnover of hepatocytes
  - viral genome may be integrated in hepatocyte DNA, leading to mutations, deletions, etc.
  - viral gene products may increase the expression of growth-factor regulating genes involved in malignant transformation

Statins and HCC

- **Population-based cohort study of 260,864 HCV-infected patients enrolled in the Taiwan National Health Insurance Research Database**
- **Among the 35,023 patients using statins, 1,378 had HCC. Among the 225,841 patients not using statins 26,505 were diagnosed with HCC. A dose-response relationship between statin use and HCC risk was observed.**
- **Possible mechanisms:**
  - **statins may exert anti-HCV activity via the inhibition of cholesterol synthesis and HCV replication.**
  - **statins may limit the development of HCC through the inhibition of products downstream of the mevalonate pathway and disrupt the growth of malignant cells, eventually leading to apoptosis.**
  - **recent studies have associated statin use with higher sustained virologic response rates after treatment with peginterferon and ribavirin.**
  - **Observational studies in Taiwan of patents with viral HCC have shown palliative benefits with lower HCC-specific deaths in all stages**

Tsan et al, JCO 2013; Shao et al, Medicine 2015 Oct;94(42):e1801
Simon TG, Duberg AS, Aleman S, et al.
Lipophilic statins and risk for hepatocellular carcinoma and death in patients with chronic viral hepatitis: results from a nationwide Swedish population.
Ann Intern Med. doi: 10.7326/M18-2753.

Hepatocellular Carcinoma

- Pathology
  - Gross
    - nodular
      - most common pattern
    - massive
      - solitary component, occupying one lobe
    - diffusely infiltrating
      - usually associated with cirrhosis

Hepatocellular Carcinoma

- Pathology:
  - Uncommon, favorable forms of hepatocellular carcinoma
    - fibrolamellar
      - younger females
    - pedunculated HCC (subcapsular)
    - "minute" HCC
      - found by accident or by screening
  - differential diagnosis
    - focal nodular hyperplasia and adenomatous hyperplasia
    - cholangiocarcinoma
    - metastatic tumors

Hepatocellular Carcinoma

- Diagnosis
  - Radiographic techniques
    - ultrasound
      - cheap, reliable, useful for screening
    - CT/MRI
      - useful to determine extent of disease for staging and resectability
  - Biopsy
    - FNA *vs* core biopsy
    - rare seeding of biopsy track (<1%)
      - May avoid if OLT is being considered

Hepatocellular Carcinoma

- AFP
  - increased in 80-90% of patients from Far East with HCC
  - increased in 50-70% of patients from North America and Europe
  - elevations of greater than 400 are generally considered diagnostic for HCC
  - AFP >400 have poorer prognosis
    - Usual level for stratification in RCTs

Hepatocellular Carcinoma

- General Principles of Screening
  - identification of high-risk groups
  - reliable diagnostic tools
    - Ultrasound
    - AFP
  - cost
  - compliance
  - availability of treatment that alters natural history of the disease

Hepatocellular Carcinoma

- **Screening: generally recommended, but**
  - few large-scale screening trials have been completed to demonstrate efficacy
  - small studies show anecdotal cases of early HCC resected with curative intent
  - ? Whether all patients with HBV, HCV, hemochromatosis should undergo AFP and US screening, and at what intervals
  - ? Whether early detection prolongs survival in patients who have developed cirrhosis
- **Potential Harms**
  - Up to one-third of patients with cirrhosis may experience physical harms related to false-positive and indeterminate screening results
  - Most harms consist of additional diagnostic exams
  - Severe physical harm (e.g. invasive procedures or procedure-related complications) is rare

RCT in HCC Screening

- 18,816 people, aged 35-59 years with hepatitis B virus infection or a history of chronic hepatitis in urban Shanghai, China. Participants were randomly allocated to a screening (9,373) or control (9,443) group
- Screening group participants were invited to have an AFP test and ultrasonography examination every 6 months.
- HCC mortality rate was significantly lower in the screened group than in controls, being 83.2/100,000 and 131.5/100,000, respectively, with a mortality rate ratio of 0.63 (95%CI 0.41-0.98)

Zhang, et al. J Cancer Res Clin Oncol. 2004 Jul;130(7):417-22.

Screening for HCC

Guideline	EASL[1]	AASLD[2]	JSH[3]	APASL[4]
Definition of high-risk population	• Pts with cirrhosis, Child-Pugh stage A and B • Pts with cirrhosis, Child-Pugh stage C awaiting liver transplantation • Pts without cirrhosis with HBV and an intermediate or high risk of HCC (PAGE-B score ≥ 10a) • Pts without cirrhosis with chronic HCV and bridging fibrosis	• Pts with cirrhosis, Child- Pugh stage A and B • Pts with cirrhosis, Child- Pugh stage C awaiting liver transplantation • Pts without cirrhosis with HBV	• Extremely high-risk pts: o Pts with cirrhosis and HBV •or HCV • High-risk pts: •o Non-viral cirrhosis o Pts without cirrhosis with •HBV or HCV	• Pts with cirrhosis • Pts without cirrhosis with •HBV: o Asian females > 50 yrs o Asian males > 40 yrs o Africans > 20 yrs o Family history of HCC
Screening interval	Every 6 months	Every 4-8 months	• Every 3-4 months in extremely high-risk pts • Every 6 months in high-risk pts	Every 6 months
Imaging modality	US (performed by experienced personnel)	US	US CT/MRI optional every 6–12 months in extremely high-risk pts	US
Biomarkers	Not recommended	At discretion of provider	AFP AFP-L3 fractions DCP	AFP (+ US)

Hepatitis B Vaccine to Prevent Hepatocellular Cancer: Based on solid evidence, immunizing individuals against hepatitis B would lead to a decrease in the incidence of HCC

- **Study Design**: Evidence obtained from cohort or case-control studies.
- **Internal Validity**: Fair (ecologic control; no direct comparison group).
- **Consistency**: Limited number of studies.
- **Magnitude of Effects on Health Outcomes**: Reduction of risk occurs with prevention of hepatitis B infection in one intervention study. A study in Taiwan shows that vaccination of newborns (the vaccination program includes administration of hepatitis B immunoglobulin at birth, followed by a course of hepatitis B vaccine) of mothers infected with hepatitis B virus was associated with a **reduction in the average annual incidence of HCC from 0.70 per 100,000 children between 1981 and 1986 to 0.57 and 0.36 for the time periods of 1986 to 1990 and 1990 to 1994, respectively (*P* < .01])** Although there was no direct control group, the decline in incidence of HCC over time would unlikely be explained by other causes. Failures in a vaccination program may be related to either failure to receive hepatitis B immunoglobulin or failure of the hepatitis B vaccine itself.

NCI PDQ

The JAMA Network

From: **Thirty-Year Outcomes of the National Hepatitis B Immunization Program in Taiwan**

JAMA. 2013;310(9):974-976. doi:10.1001/jama.2013.276701

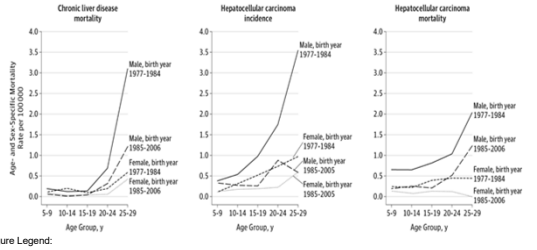


Figure Legend:

Age- and Sex-Specific Mortality and Incidence Rates of Chronic Liver Disease and Hepatocellular Carcinoma for Birth Cohorts Born Before and After the Launch of the Hepatitis B Immunization Program in 1984 in Taiwan

Hepatitis C

- The Centers for Disease Control and Prevention (CDC) recommends one-time HCV testing for everyone born from 1945 to 1965 because people born in these years account for about three-fourths of HCV-infected individuals in the US.
- HCV testing is recommended for those who:
  - Currently injecting drugs
  - Ever injected drugs, including those who injected once or a few times many years ago
  - Have certain medical conditions, including persons:
    - who received clotting factor concentrates produced before 1987
    - who were ever on long-term hemodialysis
    - with persistently abnormal alanine aminotransferase levels (ALT)
    - who have HIV infection
  - Were prior recipients of transfusions or organ transplants, including persons who:
    - were notified that they received blood from a donor who later tested positive for HCV infection
    - received a transfusion of blood, blood components, or an organ transplant before July 1992

cdc.gov/hepatitis/

Evolving Treatment of Hepatitis C

- NO vaccine.
- Initially, before 2011: IFN+ribavirin
- On July 18, 2019, FDA approved a combination tablet (Vosevi) to treat adults with chronic hepatitis C virus genotypes 1-6 without cirrhosis or with mild cirrhosis. This fixed-dose, combination tablet contains two previously approved drugs—sofosbuvir and velpatasvir—and a new drug, voxilaprevir. Approved for patients who have been previously treated with the direct-acting antiviral drug sofosbuvir.
- Selection is part based on genotype
- Goals: SVR (sustained virologic response): 90% achieve SVR with 8-12 weeks of oral treatment
- Benefits with newer agents: high SVR, shorter therapy, oral
- Downsides: some treatments restricted to certain genotypes; increased side effects; $$$$...cheapest ~$25,000 for 2 month Rx
- ~10% of HepC patients are under treatment in US
  - ? Impact on HCC in US and ROW (especially Asia)

Modified Stage System (pTNM)

T0	Tumor not found
T1	1 nodule ≤ 1.9 cm
T2	1 nodule 2.0-5.0 cm; 2 or 3 nodules, all ≤ 3.0 cm
T3	1 nodule > 5.0 cm; 2 or 3 nodules, at least one > 3.0 cm
T4a	4 or more nodules, any size
T4b	Gross intrahepatic portal or hepatic vein involvement

N0 :	No lymph node involvement
N 1 :	Regional (porta hepatis) nodes involved
M0 :	No distant metastasis
M1 :	Metastatic disease

- Including extrahepatic portal or hepatic vein involvement

Child's Pugh Score: Liver Cirrhosis

Parameter	Points		
	1	2	3
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Bilirubin (mg/dL)	< 2	2 - 3	> 3
Ascites	Absent	Slight	Moderate
Encephalopathy	None	I - II	III – IV
PT (INR)	< 1.7	1.8 – 2.3	> 2.3

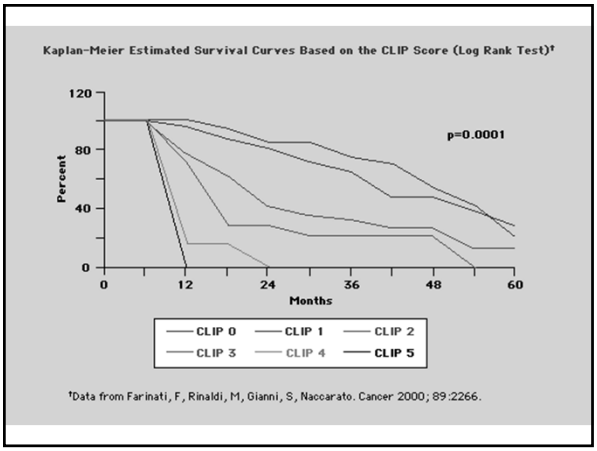
Score	A	B	C
Points	5 - 6	7 - 9	10 - 15

Pugh, RNH, et al. British Journal of Surgery. 60(8): 646-649, 1973

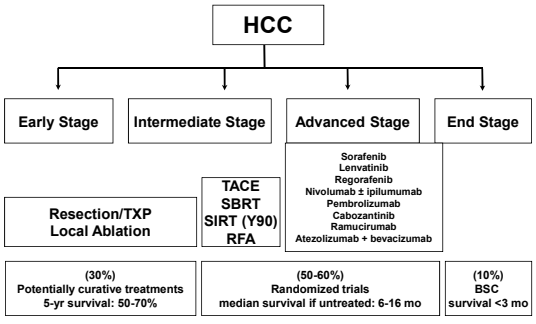
CANCER of the LIVER ITALIAN PROGRAM (CLIP) SCORE*

CHILD-PUGH STAGE	A	0
	B	1
	C	2
TUMOR MORPHOLOGY		
Uninodular/extension <50%		0
Multinodular/extension<50%		1
Massive/extension > 50 %		2
AFP	< 400	0
	> 400	1
PORTAL VEIN THROMBOSIS		
No		0
Yes		1

*CLIP Investigators.Hepatology 1998;28:751.



HCC treatment



Llovet JM, & Bruix J, BCLC. Lancet, 2003

Treatment of HCC
Role of Liver Transplantation

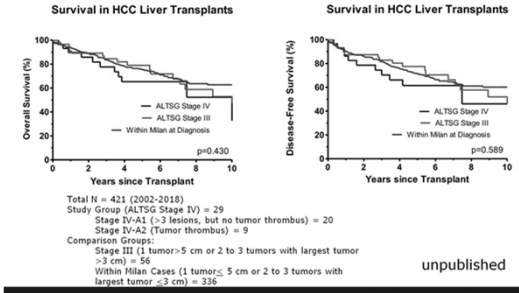
PROS

- "Cures" underlying disease as well as treating HCC
  - Avoids complications associated with resection in cirrhosis
- Excellent outcome in selected patients
  - Equivalent to benign disease; OLT currently has a 5-year survival of 70-80%
- "Optimal" candidate –Milan, UCSF Criteria
  - Single lesion < 5cm
  - Multiple lesions up to 3 nodules, adding to < 3 cm
- Treatments available for Hepatitis B and C to prevent reinfection

Treatment of HCC
Role of Liver Transplantation
CONS

- Difficult to accurately stage preoperatively
  - Tumor burden frequently underestimated
- Lack of prospective, randomized studies to determine who is a good candidate
- Limited organ supply
  - Increasing waiting times is associated with tumor growth and patient drop out because of primary liver failure
  - Differential waiting times depending on region

UpDated treatment of HCC and transplant including stage III and IV disease



Total N = 421 (2002-2018)
Study Group (ALTSG Stage IV) = 29
Stage IV-A1 (>3 lesions, but no tumor thrombus) = 20
Stage IV-A2 (Tumor thrombus) = 9
Comparison Groups:
Stage III (1 tumor>5 cm or 2 to 3 tumors with largest tumor >3 cm) = 56
Within Milan Cases (1 tumor≤ 5 cm or 2 to 3 tumors with largest tumor ≤3 cm) = 336

unpublished

Washington University in St.Louis · School of Medicine

Presented By Maria Doyle at 2019 Gastrointestinal Cancer Symposium

Liver Directed Therapies

- Ablation - Radiofrequency, MW ablation, cryotherapy, IRE, PEI
- TransArterial Chemoembolization TACE, cTACE,
- Bland Embolization - TAE
- Radioembolization Sir Spheres and Theraspheres
- Hepatic arterial pump therapy (HAP)
- External Beam (EBRT) and Stereotactic Radiation Therapy (SBRT)

Washington University in St.Louis · School of Medicine

Presented By Maria Doyle at 2019 Gastrointestinal Cancer Symposium

CHEMOEMBOLIZATION/TACE

- Developed c. 1980 in Japan for treatment of hepatoma
- Procedure has disseminated world-wide for primary and secondary hepatic malignancies

Advantages:

- Tumor ischemia
- Increased drug concentration
- Increased dwell time
- Decreased systemic toxicity
- Wide availability

CHEMOEMBOLIZATION

- Disadvantages
  - Lack of standardization
  - Operator dependent
  - Difficult to access patients for trials through interventional radiology
  - Highest rates of HCC in countries with least mature clinical trials mechanisms

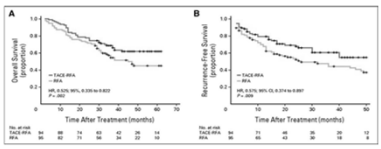
TACE+RFA vs RFA Alone

- A randomized controlled trial was conducted on 189 patients with HCC less than 7 cm at a single tertiary referral center between October 2006 and June 2009. Patients were randomly assigned to receive TACE combined with RFA (TACE-RFA; n = 94) or RFA alone (n = 95). The primary end point was overall survival. The secondary end point was recurrence-free survival, and the tertiary end point was adverse effects.
- Patients in the TACE-RFA group had better overall survival and recurrence-free survival than patients in the RFA group (hazard ratio, 0.525; 95% CI, 0.335 to 0.822; *P* = .002; hazard ratio, 0.575; 95% CI, 0.374 to 0.897; *P* = .009, respectively).

Peng et al. *JCO February 1, 2013 vol. 31 no. 4 426-432*

TACE+RFA vs RFA Alone

Overall (A) and recurrence-free (B) survival curves for the transcatheter arterial chemoembolization (TACE) plus radiofrequency ablation (RFA) and RFA groups.



Peng Z, et al. JCO 2013;31:426-432

TACE+RFA vs RFA Alone

- the sample size was small, with a mainly HBV population conducted in a single tertiary center in China, making it difficult to extrapolate these results.
- the selection of patients participating in this study was stringent, and the findings may only be applicable to a relatively small percentage of patients with HCC.
- the study only had two arms without the potential third arm of TACE alone, making it difficult to assess the relative added contribution of TACE or RFA in the TACE-RFA arm.
- only approximately 50% of lesions were larger than 3 cm and there were no specification on the number of patients with lesion size from 3 to 7 cm; it remained unclear whether the benefits of TACE-RFA were only applicable to smaller lesions (i.e., less than 5 cm), as has been previously suggested

Editorial, Zhu and Salem, *JCO February 1, 2013 vol. 31 no. 4 406-408*

A multicenter randomized controlled trial to evaluate the efficacy of SUrgery vs. RadioFrequency ablation for small hepatocellular carcinoma

SURF
Efficacy of SUrgery vs. Radio-Frequency ablation (RFA) on primary hepatocellular carcinoma: a multicenter clinical trial

SURF Trial Group
Namiki izumi
Kiyoshi Hasegawa, Yujiro Nishioka, Tadatoshi Takayama
Naoki Yamanaka, Masatoshi Kudo, Mitsuo Shimada
Masahumi Inomata, Shuichi Kaneko, Hideo Baba
Kazuhiko Koike, Masao Omata, Masatoshi Makuuchi
Yutaka Matsuyama, Norihiro Kokudo

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19 PRESENTED BY: Namiki Izumi 1

Presented By Namiki Izumi at 2019 ASCO Annual Meeting

RCT Design (from April 2009)

Initial HCC
≤3 HCCs, ≤3cm
Child-Pugh ≤7
20-79 y.o.

Both Applicable

R

Surgery n=300

RFA n=300

Follow -Up

joint chart review by surgeons & hepatologists

Allocation adjustment factors:
✔ Trial site
✔ HCV infection
✔ Tumor diameter
✔ Age
✔ Number of tumors

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Summary of Previous RCTs

Author	Year	Site	Size	Tumor No.	Child -Pugh	n	Conclusion
Chen DS Liang J-D	2005	Taiwan	≤3cm	≤2	A,B	76	NS
Chen M-S Lau WY	2005	Hongkong, Guangzhou	≤5cm	1	A	180	NS
Huang J Zeng Y	2010	Chengdu	≤3cm (Milan)	≤3	A,B	230	Favor (Surgery)
Feng K Dong J	2012	Chongqing	≤4cm	≤2	A,B	168	NS

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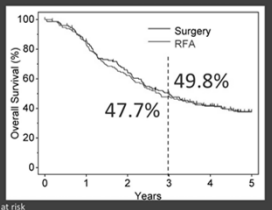
Kaplan-Meier estimate of RFS



median Follow-Up (years)
SUR 5.04 (0.36-9.49)
RFA 4.99 (0.00-8.70)
* median (95%CI)

RFS (years, median)
SUR 2.98 (2.33-3.86)
RFA 2.76 (2.17-3.80)
* median (95%CI)
p= 0.793 (0.72-1.28)

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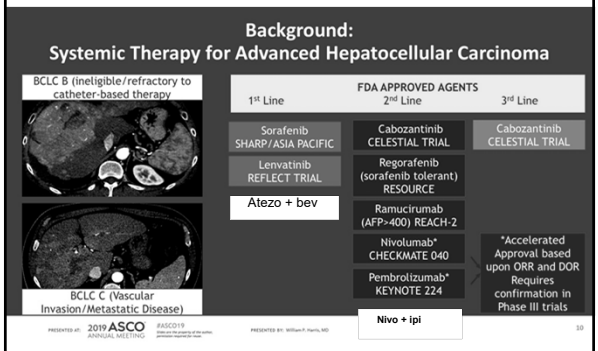
TACE plus Sorafenib Versus TACE alone for Intermediate or Advanced Stage HCC: A Meta-Analysis

- Pubmed and Embase databases were systematically reviewed for studies published up to November 2013, that compared TACE alone or in combination with sorafenib
- Six studies published from 2011 to 2013, with a total of 1254 patients
- The pooled results showed that TACE combined with sorafenib significantly improved
  - OS (HR=0.65; 95% CI: 0.47-0.89, P=0.007)
  - TTP (HR=0.68; 95% CI: 0.52-0.87, P=0.003)
  - ORR (HR=1.06; 95% CI: 1.01-1.12, P=0.021)
- but did not affect PFS (HR=0.84; 95% CI: 0.62-1.14, P=0.267)
- The incidence of grade III/IV adverse reaction was higher in the TACE plus sorafenib group than in the TACE group
- Zhang et al PLoS One 2014 Jun 19;9(6):e100305. doi: 10.1371/journal.pone.0100305

Problems in Assessing Effectiveness of Systemic Therapy for HCC

- Only patients with advanced HCC, and not amenable to surgery or local treatment, are entered onto systemic therapy
- Underlying liver disease(s)—cirrhosis– may be as, or more, important than HCC for pts. prognosis.
- Liver function and drug: metabolism and effects.
- Differences in etiology of HCC in different population and studies – inconsistence of study results.
- HCC is a heterogeneous disease at the molecular level.
- Traditional criteria (methods) for cancer response assessment may be not suitable for HCC: Tumor measurements (RECIST)
  - Especially for radiologic definition of RR, TTF, PFS



Presented By William Harris at 2019 ASCO Annual Meeting

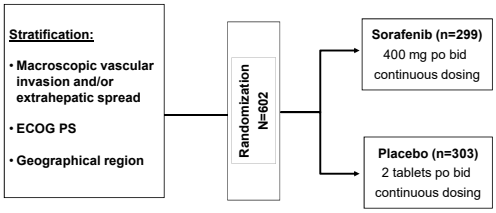
Sorafenib in HCC: Rationale

- Raf kinase is overexpressed and activated in HCC
- RAF/MEK/ERK signaling pathway is implicated in liver tumorigenesis
- Sorafenib, approved in advanced RCC, is the only approved inhibitor of Raf kinase
- Sorafenib is a multikinase inhibitor of RAF, VEGFR, and other kinases[3]
- Sorafenib induces apoptosis in HCC xenograft models
- Sorafenib was active in a Phase II trial of patients with advanced HCC and Child-Pugh class A and B liver function status

1. Hwang et al. *Hepatol Res*. 2. Calvisi et al, *Gastroenterology* 2006
3. Villanueva et al. *Sem Liv Dis* 2007 4. Liu et al. *Cancer Res*. 2006 5. Abou-Alfa et al. *J Clin Oncol*. 2006.

Phase III SHARP Trial
Study Design

- Primary end-points: Overall survival
  Time to symptomatic progression (FHSI8-TSP)
- Secondary end-points: Time to progression (independent review)

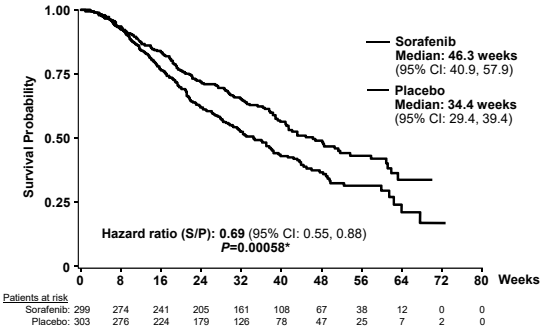


Phase III SHARP Trial
Study Design

Design
- International, multicenter Phase III study
- Inclusion criteria:
  - Histology-proven HCC
  - Advanced HCC
  - At least 1 measurable untreated lesion
  - ECOG 0-2
  - Child-Pugh A class
  - No prior systemic treatment

Randomization
- Double-blind sorafenib 400 mg bid vs placebo; ratio 1:1
- Accrual: March 2005 to April 2006

Phase III SHARP Trial
Overall survival (Intent-to-treat)



*O'Brien-Fleming threshold for statistical significance was P=0.0077.

Phase III SHARP Trial
Response assessment (RECIST; Independent review)
Time to symptom progression (FSHI8-TSP)

	Sorafenib (n=299)	Placebo (n=303)
Overall response		
Complete response (CR)	0	0
Partial response (PR)	7 (2.3%)	2 (0.7%)
Stable disease (SD)	211 (71%)	204 (67%)
Progressive disease	54 (71%)	73 (24%)
Progression-free rate at 4 mo	62%	42%
Duration of treatment (median, weeks)	23	19

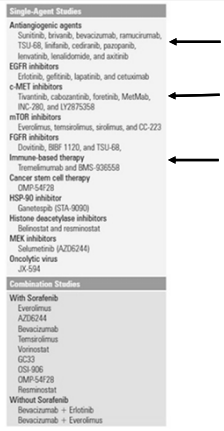
FSHI8-TSP: No significant differences between treatment groups (*P*=0.77).

Comparative trial of Sorafenib Toxicity: Childs A vs B (MSKCC)

	CPA (n=98) %	CPB (n=38) %
Adverse Events	97	97
Serious Adverse Events	52	68
Fatigue	41	37
Hand Foot Skin Reaction	30	13
Diarrhea	59	47
Bilirubin Increase	**18**	**40**
Ascites	**11**	**18**
Encephalopathy	**2**	**11**

Childs A vs B: Outcomes

	CP A (n=98)	CP B (n=38)
SD (≥ 4 months)	49%	26%
TTP	21 weeks	13 weeks
OS	41 weeks	14 weeks



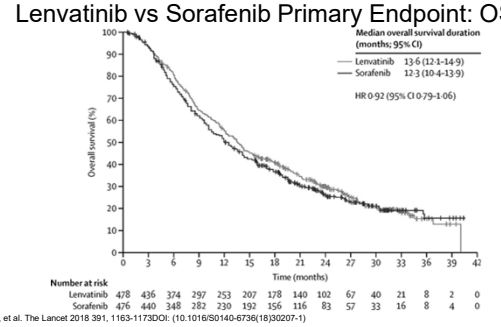
New Agents in HCC

Lenvatinib vs Sorafenib First-line HCC: ASCO 2017
REFLECT trial

- LEN, an inhibitor of vascular endothelial growth factor receptors 1–3, fibroblast growth factor receptors 1–4, platelet derived growth factor receptor α, RET, and KIT
- Randomized, open-label, noninferiority (NI) study; primary endpoint noninferiority for OS
- 1492 Pts enrolled
- 13% Of LEN-treated and 9% of SOR-treated pts discontinued due to adverse events. 33% Of LEN-treated and 39% of SOR-treated pts received second-line therapy.
- FDA approved 8/2018

Lancet 2018 Mar 24;391(10126):1163-1173

Lenvatinib vs Sorafenib Primary Endpoint: OS



Kudo,M, et al. The Lancet 2018 391, 1163-1173DOI: (10.1016/S0140-6736(18)30207-1)

Lenvatinib mRECIST Response

	Lenvatinib (n=478)	Sorafenib (n=476)	Effect size (95% CI)	p value
Objective response (%, 95% CI)	194 (40·6%, 36·2–45·0)	59 (12·4%, 9·4–15·4)	OR 5·01 (3·59–7·01)	<0·0001
Complete response	10 (2%)	4 (1%)	..	..
Partial response	184 (38%)	55 (12%)	..	..
Stable disease	159 (33%)	219 (46%)	..	..
Durable stable disease lasting ≥23 weeks	84 (18%)	90 (19%)	..	..
Progressive disease	79 (17%)	152 (32%)	..	..
Unknown or not evaluable	46 (10%)	46 (10%)	..	..

Kudo, M. et al. Lancet Volume 391, Issue 10126, 24–30 March 2018, Pages 1163-1173

Landscape-Second line therapy for HCC

		Total N	PFS benefit	OS benefit	RR
CHECKMATE040 (SINGLE ARM)	**Nivolumab***	**154**	**NA**	**NA median OS ≈15 mo***	**14%**
RESOURCE	**Regorafenib* v placebo**	**573 (2:1)**	**+1.6 mo HR 0·46 (0.37–0.56); p<0·0001**	**+2.8 mo HR 0.63 (0.50–0.79) p<0.0001)**	**11%**
CELESTIAL**	**Cabozantinib* v placebo**	**707 (2:1)**	**+3.3 mo HR=0.44 [0.36-0.52]; *P* < 0.001**	**+2.2 mo HR=0.76 (0.63-0.92) P = 0.0049**	**4%**
REACH1	**Ramucirumab* v placebo**	**565**	**+0.7mo HR 0.63 [0.52–0.75]; p<0.0001**	**NO**	**7%**
REACH 2 (AFP≥400)	**Ramucirumab* v placebo**	**292 (2:1)**	**+1.2 mo HR 0.452 (0.339, 0.603) p< 0.0001**	**+1.2 mo HR 0.71 (0.531, 0.949); p=0.0199**	**4.6%**
Pooled REACH 1 / 2 (AFP≥400 subgroup)	***Ramucirumab* v placebo***	***542***	***NA***	***+3.1 mo HR 0.694 (0.571, 0.842) P=0.0002***	***NA***

*FDA approved
** included 2nd and 3rd line; 2nd line update: Kelley, et al. Abstr #4088 ASCO 2018

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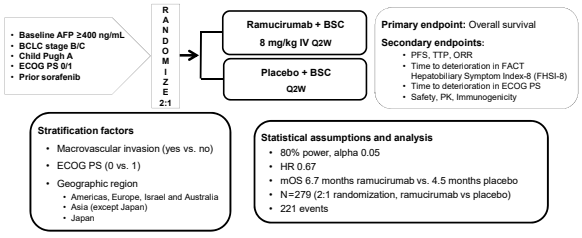
7

Ramucirumab (VEGFR2) versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH)

- 565 patients were enrolled, of whom 283 were assigned to ramucirumab and 282 were assigned to placebo. Median overall survival for the ramucirumab group was 9·2 months (95% CI 8·0–10·6) versus 7·6 months (6·0–9·3) for the placebo group (HR 0·87 [95% CI 0·72–1·05]; p=0·14)
- Subsets benefiting: good CP score; elevated AFP ⩾400 ng/ml
- REACH-2: Child-Pugh score <7 (Child-Pugh Class A), Baseline AFP ≥400 nanograms/milliliter. (NCT02435433)

Zhu, et al. Lancet Oncol. **Volume 16, No. 7**, p859–870, July 2015

Study Design



Abbreviations: AFP=alpha-fetoprotein; BCLC=Barcelona Clinic Liver Cancer; BSC=best supportive care; ECOG PS=Eastern Cooperative Oncology Group performance status; FACT=Functional Assessment of Cancer Therapy; mOS= median overall survival; ORR=objective response rate; PFS=progression-free survival; PK=pharmacokinetics; Q2W=every 2 weeks; TTP=time to progression.

ClinicalTrials.gov NCT02435433

Andrew Zhu, MD, PhD to

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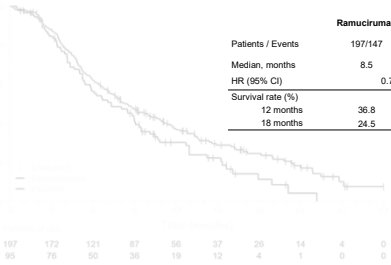
Overall Survival



	Ramucirumab	Placebo	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.5	7.3	1.2	
HR (95% CI)	0.710 (0.531, 0.949)			0.0199
Survival rate (%)				
12 months	36.8	30.3	6.5	0.2930
18 months	24.5	11.3	13.2	0.0187

Andrew Zhu, MD, PhD to

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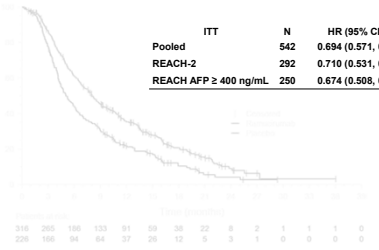
0

Overall Survival in Pooled Population



ITT	N	HR (95% CI)	mOS	P-value
Pooled	542	0.694 (0.571, 0.842)	Δ=+3.1 (8.1 vs. 5.0)	0.0002
REACH-2	292	0.710 (0.531, 0.949)	Δ=+1.2 (8.5 vs. 7.3)	0.0199
REACH AFP ≥ 400 ng/mL	250	0.674 (0.508, 0.895)	Δ=+3.6 (7.8 vs. 4.2)	0.0059

Andrew Zhu, MD, PhD

RESORCE [REgorafenib after SORafenib in patients with hepatoCEllular carcinoma]

- The Ang/TIE-2 pathway is considered a key angiogenic signaling pathway. Combined blockage of VEGFR2 and TIE2 signaling with regorafenib may exert more profound antiangiogenic effects than inhibition of VEGF signaling alone
- HCC is a FGFR-enriched tumor
- Additional activity against FGFR, c-kit, and Ret
- Antiangiogenesis beyond progression
- Other hidden pathways

RESORCE trial design

- HCC patients with documented radiological progression during sorafenib treatment
- Stratified by:
  - Geographic region (Asia vs ROW)
  - Macrovascular invasion
  - Extrahepatic disease
  - ECOG PS (0 vs 1)
  - AFP (<400 ng/mL vs ≥400 ng/mL)

R 2:1

Regorafenib
160 mg po once daily
3 weeks on / 1 week off
(4-week cycle)
(n=379)

N= 573

Placebo
(n=194)

- 152 centers in 21 countries in North and South America, Europe, Australia, Asia
- All patients received best supportive care
- Treat until progression, unacceptable toxicity, or withdrawal

Bruix J et al, Lancet 2017; 389: 56–66

RESORCE: efficacy

	Regorafenib n=379	Placebo n=194
Events	232 (61%)	140 (72%)
Censored	147 (39%)	54 (28%)
Median OS (95% CI)	10.6 months (9.1, 12.1)	7.8 months (6.3, 8.8)
HR 0.62 (95% CI: 0.50, 0.78)		
P<0.001 (2-sided)		

	Regorafenib n=379	Placebo n=194
Events	291 (77%)	181 (93%)
Censored	88 (23%)	13 (7%)
Median PFS (95% CI)	3.1 months (2.8, 4.2)	1.5 months (1.4, 1.6)
HR 0.46 (95% CI: 0.37, 0.56)		
P<0.001 (2-sided)		

	mRECIST		RECIST 1.1	
	Regorafenib n=379	Placebo n=194	Regorafenib n=379	Placebo n=194
Response rate	10.6%	4.1%	6.6%	2.6%
	P=0.01 (2-sided)		*P*=0.04 (2-sided)	
Disease control rate	65.2%	36.1%	65.7%	34.5%
	P<0.001 (2-sided)		*P*<0.001 (2-sided)	

Bruix J et al, Lancet 2017; 389: 56–66

Cabozantinib in HCC
CELESTIAL trial; ASCO GI 2018

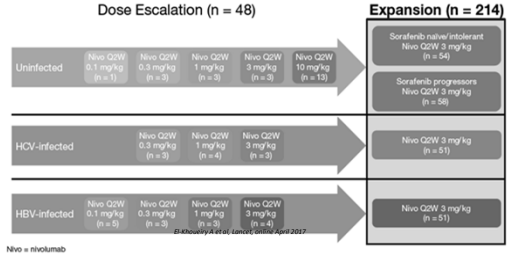
- Cabozantinib: an inhibitor of MET, VEGFR, and AXL
- 707 pts with prior sorafenib; 27% had 2 Rx; primary endpoint OS

	Cabozantinib	Placebo
OS	10.2 mos	8.0 mos
PFS	5.2 mos	1.9 mos
ORR	4%	0.4%

FDA approval: January 2019

Nivolumab in patients with advanced hepatocellular carcinoma (CheckMate 040): an open-label, non-comparative, phase 1/2 dose escalation and expansion trial

Anthony B El-Khoueiry, Bruno Sangro,* Thomas Yau, Todd S Crocenzi, Masatoshi Kudo, Chiun Hsu, Tae-You Kim, Su-Pin Choo, Jörg Trojan, Theodore H Welling Jr, Tim Meyer, Yoon-Koo Kang, Winnie Yeo, Akhil Chopra, Jeffrey Anderson, Christine dela Cruz, Lixin Lang, Jaclyn Neely, Hao Tang, Homa B Dastani, Ignacio Melero*



El-Khoueiry A et al, Lancet, online April 2017

Nivo = nivolumab

Checkmate 040: Nivolumab efficacy

	Uninfected untreated/ intolerant (n=56)	Uninfected progressor (n=57)	HCV infected (n=50)	HBV infected (n=51)	All patients (n=214)
Objective response*	13 (23%; 13 to 36)	12 (21%; 11 to 34)	10 (20%; 10 to 34)	7 (14%; 6 to 26)	42 (20%; 15 to 26)
Complete response	0	2 (4%)	0	1 (2%)	3 (1%)
Partial response	13 (23%)	10 (18%)	10 (20%)	6 (12%)	39 (18%)
Stable disease	29 (52%)	23 (40%)	23 (46%)	21 (41%)	96 (45%)
Progressive disease	13 (23%)	18 (32%)	14 (28%)	23 (45%)	
Not evaluable	1 (2%)	4 (7%)	3 (6%)	0	8 (4%)
Duration of response*					
KM median	8·4 (8·3 to NE)	NR	9·9 (4·5 to 9·9)	NR	9·9 (8·3 to NE)
Ongoing, n/N (%)	8/13 (62%)	7/12 (58%)	8/10 (80%)	5/7 (71%)	28/42 (67%)
Disease control*	42 (75%; 62 to 86)	35 (61%; 48 to 74)	33 (66%; 51 to 79)	28 (55%; 40 to 69)	138 (64%; 58 to 71)
Disease control with stable disease for ≥6 months	22 (39%; 27 to 53)	22 (39%; 26 to 52)	17 (34; 21 to 49)	18 (35%; 22 to 50)	79 (37%; 30 to 44)
Overall survival					
6 months	89% (77 to 95)	75% (62 to 85)	85% (72 to 93)	84% (71 to 92)	83% (78 to 88)
9 months	82% (68 to 90)	63% (49 to 74)	81% (66 to 90)	70% (55 to 81)	74% (67 to 79)
KM median	NR	13·2 (8·6 to NE)	NR	NR	NR
Progression-free survival*					
KM median	5·4 (3·9 to 8·5)	4·0 (2·6 to 6·7)	4·0 (2·6 to 5·7)	4·0 (1·3 to 4·1)	4·0 (2·9 to 5·4)

Unless otherwise indicated, data are n (%; 95% CI); n (%); months (95% CI); or % (95% CI). HCV=hepatitis C virus. HBV=hepatitis B virus. KM=Kaplan-Meier estimate. NR=not reached. NE=not estimable. RECIST=Response Evaluation Criteria In Solid Tumors. *Determined by investigator assessment using RECIST version 1.1.

Table 4: Nivolumab efficacy in the dose-expansion phase

El-Khoueiry A et al, Lancet, online April 2017

KEYNOTE 240: Study Design

- **Key eligibility criteria**
  - **≥18 y**
  - **Pathologically confirmed HCC**
  - **Progression on or intolerance to sorafenib treatment**
  - **Child Pugh class A**
  - **ECOG PS 0-1**
  - **BCLC Stage C or B disease**
  - **Predicted life expectancy >3 mo**

→ **Pembrolizumab 200 mg Q3W for 2y or until PD, intolerable toxicity, withdrawal of consent or investigator decision** → **Survival follow-up**

- **Response assessed Q9W**
- **Primary endpoint: ORR (RECIST v1.1, central review)**
- **Secondary endpoint: DOR, DCR, PFS, OS, and safety and tolerability**

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Response per RECIST version 1.1 by independent central review

	Total N=104
ORR, n (%, 95%CI)*	18 (17, 11-26)
BOR, n (%)†	
CR	1 (1)
PR	17 (16)
SD	46 (44)
PD	34 (33)
No assessment‡	6 (6)
DCR, n (%, 95%CI)§	64 (62, 52-71)
Median time to response, mo (IQR)¶	2.1 (2.1-4.1)
Median DOR, mo (range)¶‖	Not reached (3.1–14.6+)
Response duration ≥9 mo, n (%)¶‖	12 (77)

BOR=best overall response; CR=complete response; DCR=disease control rate; DOR=duration of response; ORR=objective response rate; PD=progressive disease; PR=partial response; SD=stable disease.*ORR includes complete and partial responses. †Confirmed best response by independent central review per RECIST version 1.1. ‡Patients without post-baseline assessment on the data cutoff date were considered not assessable for BOR. §Disease control rate includes CR, PR, and SD. ¶Assessed in patients who had a BOR as confirmed CR or PR. ‖From product-limit (Kaplan-Meier) method for censored data. • Indicates no PD by the time of last disease assessment.

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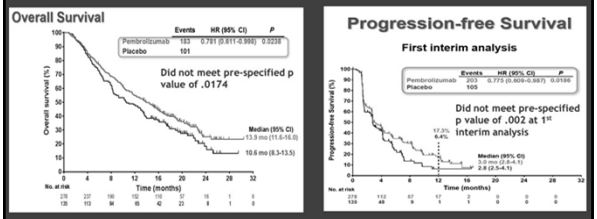
Results: KEYNOTE-240



Presented By William Harris at 2019 ASCO Annual Meeting

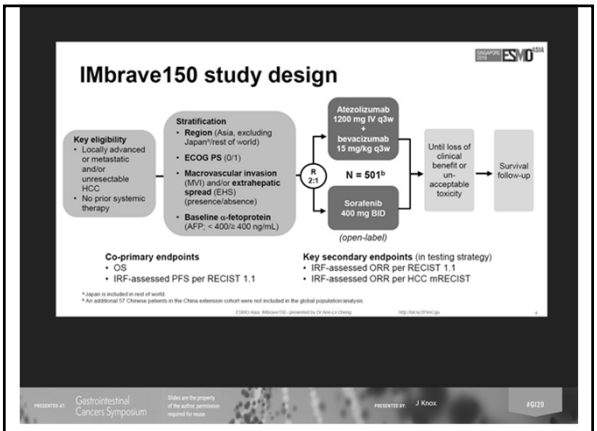
Comments: KEYNOTE-240

- **Response rates, duration of response and mOS similar to Phase II results which had led to conditional approval**
  - **ORR 18.3% by RECIST 1.1**
  - **Median DOR 13.8 months**
  - **mOS 13.9 months**
- **Type I error with rigorous cutoffs, ? underpowered**
  - **α spent with 2 interim analyses**
  - **α split for co-primary endpoints**
  - **Power calculations based upon estimated HR of 0.65 for OS**
- **Placebo group performed better than in other trials**
  - **patient selection/exclusion of main portal vein invasion?**
  - **high rate of subsequent systemic therapy (47.4%, including 10.4% α–PD1/PD-L1)**

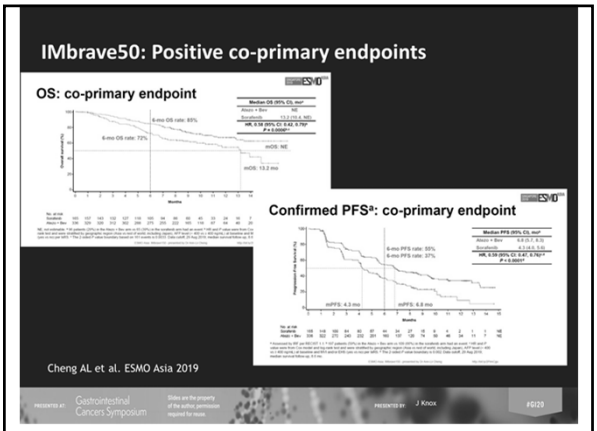
Presented By William Harris at 2019 ASCO Annual Meeting

CheckMate 459

- Phase III Study of Nivolumab Versus Sorafenib as First-Line Treatment
- 726 participants
- Primary endpoint: OS
- Failed to meet primary endpoint: HR, 0.85; 95% CI, 0.72-1.02;*P*= .0752



Presented By Jennifer Knox at 2020 Gastrointestinal Cancer Symposium



Presented By Jennifer Knox at 2020 Gastrointestinal Cancer Symposium

CM 040: Ipilimumab + Nivolumab IO doublet: 2nd line

	nivolumab 1 mg/kg + ipilimumab 3 mg/kg Q3W (n=50)	nivolumab 3 mg/kg + ipilimumab 1 mg/kg Q3W (n=49)	nivolumab 3 mg/kg Every 2 Weeks + ipilimumab 1 mg/kg Q6W (n=49)
ORR, n (%)	16 (32)	15 (31)	15 (31)
CR	4 (8)	3 (6)	0
PR	12 (24)	12 (24)	15 (31)
SD	9 (18)	5 (10)	9 (18)
PD	20 (40)	24 (49)	21 (43)
DCR, % (95% CI)	54 (39-68)	43 (29-58)	49 (34-64)
Median OS, mo (95% CI)	23 (9-NA)	12 (8-15)	13 (7-33)
12-mo OS rate, % (95% CI)	61 (46-73)	56 (41-69)	51 (36-64)
24-mo OS rate, % (95% CI)	48 (34-61)	30 (18-44)	42 (28-56)

- Noteworthy OS
- Double the ORR of single agent nivolumab
- Increase TREA-37% grade 3-4 (rash, pruritis)

(Non-randomised data)

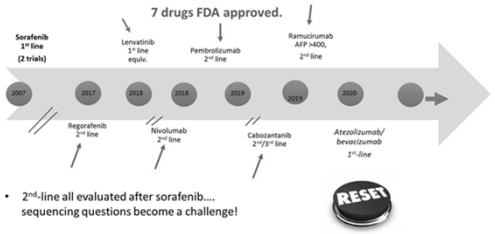
Yau T et al. ASCO 2019 abst 4012

Gastrointestinal Cancers Symposium
J Knox
#GI20

Presented By Jennifer Knox at 2020 Gastrointestinal Cancer Symposium

Changing (Busy) Landscape in HCC

- **Multikinase inhibitors:** sorafenib/lenvatinib
  - cabozantanib, regorafenib
- **PD-1 inhibitors**: nivolumab, pembrolizumab
- **PD-L1 inhibitors**: durvalumab and atezolizumab
- **CTLA-4 inhibitors** : Tremelimumab, Ipiluminab
- **mAB**: bevacizumab, ramucirumab



- 2nd-line all evaluated after sorafenib.... sequencing questions become a challenge!

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Ongoing first-line trials

Combination	Sponsor	Comments
durvalumab vs durv + tremelimumab combo (2 doses) vs sorafenib	AZ	**HIMALAYA**, n=1310, 4 arms, CPA OS Near completion
lenvatinib +pembrolizumab vs lenvatinib + placebo	Merck, Eisai	**LEAP-002**, n=750, CPA OS and PFS Near completion
cabozantinib + atezolizumab vs sorafenib vs cabozantinib	Exelixis, Ipsen	**COSMIC-312**, n=640, 3 arms, CPA 6:3:1 PFS, OS
Nivo 1 + Ipi 3 q 3wks x 4, Nivo 480 q4 vs sorafenib or lenvatinib	BMS	**CHECKMATE 9DW**, n=1084, CPA OS

Gastrointestinal Cancers Symposium
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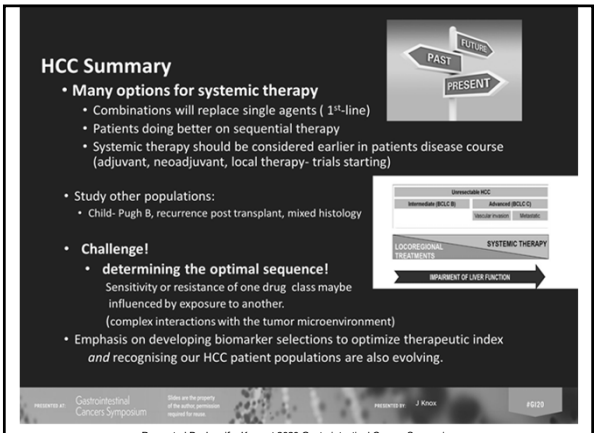
Sorafenib as Adjuvant Treatment in the Prevention Of Recurrence of Hepatocellular Carcinoma (STORM) phase 3, double-blind, placebo-controlled trial

- 1,114 patients with HCC judged to have an intermediate (54%) or high (46%) risk of recurrence after surgical resection (81% of patients) or local ablation. The median age of patients was 59 years, 62% were Asian, and 97% had Child-Pugh class A disease.
- 400 mg orally twice a day (n = 556) or placebo (n = 558) for a maximum of 4 years. The primary endpoint was RFS; Secondary endpoints included TTR and overall survival OS.
- median RFS in the sorafenib and placebo arms of 33.3 months (95% confidence interval [CI], 27.6-44.0 months) and 33.7 months (95% CI, 27.6-39.0 months), respectively (hazard ratio [HR] = 0.94; 95% CI, 0.78-1.134)
- median TTR of 38.6 months (95% CI, 30.4 months to not applicable) in the sorafenib arm and 30.3 months (95% CI, 30.3-41.4 months) in the placebo arm (HR = 0.891; 95% CI, 0.735-1.081)
- OS (median OS not reached in either arm; HR = 0.995; 95% CI, 0.761-1.3).

Bruix, et al. Lancet Oncology. **Volume 16, No. 13, p1344–1354, October 2015**



Presented By Jennifer Knox at 2020 Gastrointestinal Cancer Symposium

Biliary Carcinomas

- Gall Bladder
- Biliary duct
  - intrahepatic cholangiocarcinoma
  - proximal (Klatskin's tumor)
  - middle
  - distal (ampullary)

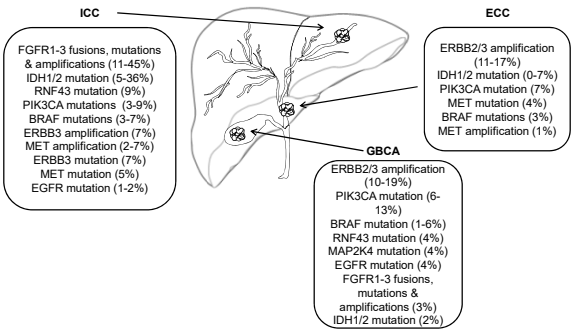
Background

- **Epidemiological data is poor**
- **Worldwide, there is wide geographic variation**
- **South America has highest incidence (up to 13/100,000): GB, Peru**
- **Some European countries, such as Hungary, Poland and Germany have higher incidences (9.2–6.8/100,000)**
- **Variation in the incidence in Asian countries**
  - **Japan 11.9/100,000**
  - **India has been as low as 1/100,000 but is on the rise**
    - **in Delhi, female incidence is 8.9/100,000**
- **Female:male ratio is 2.5–3.0:1**

Reasons for confusion

- Heterogeneous disease
  - **Intrahepatic cholangiocarcinoma**
  - **Extrahepatic biliary tract carcinoma**
    - **including Klatzkin tumors**
  - **Gallbladder carcinoma**
  - **Periampullary carcinoma (?)**
- Not all the above are included in each country's statistics
  - **ACS puts intrahepatic cholangiocarcinoma with HCC for unclear reasons**

Genetic Landscape of Biliary Tract Cancers



Etiology: Biliary Carcinoma

- Cholangiocarcinoma
  - risks include stones, sclerosing cholangitis, UC, PCKD with liver cysts

Biliary Carcinoma

- Gall Bladder
  - – most common biliary site
  - – associated with gallstones
    - 1% of cholecystectomies have carcinoma
  - – increased risks with choledochal cysts
  - – polyps increase risk (Peutz-Jegher's)

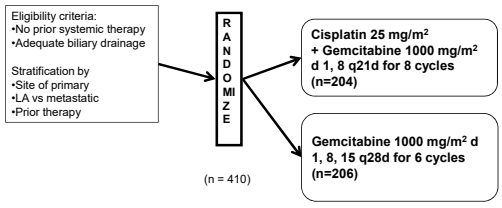
GB Carcinoma

- Treatment
  - – surgical cures most often in incidentalomas
  - – simple cholecystectomy for stage I and II
  - – ? Role of extended (reoperation) in patients with stage III (serosal or N+)
  - – ? Role for combined chemoradiation/embolization in patients at high risk of recurrence

Primary Approaches to GC Ca:
Gallbladder cancer: expert consensus statement

- Adequate lymphadenectomy includes assessment of any suspicious regional nodes, evaluation of the aortocaval nodal basin, and a goal recovery of at least six nodes.
- Patients with confirmed metastases to N2 nodal stations do not benefit from radical resection and should receive systemic and/or palliative treatments.
- Primary resection of patients with early T-stage (T1b-2) disease should include en bloc resection of adjacent liver parenchyma.
- Patients with T1b, T2 or T3 disease that is incidentally identified in a cholecystectomy specimen should undergo re-resection unless this is contraindicated by advanced disease or poor performance status. Re-resection should include complete portal lymphadenectomy and bile duct resection only when needed to achieve a negative margin (R0) resection.
- Patients with preoperatively staged T3 or T4 N1 disease should be considered for clinical trials of neoadjuvant chemotherapy. Following R0 resection of T2-4 disease in N1 gallbladder cancer, patients should be considered for adjuvant systemic chemotherapy and/or chemoradiotherapy.

Gemcitabine ± Cisplatin in Advanced Biliary Tract Cancer: Phase III UK ABC-02 Trial



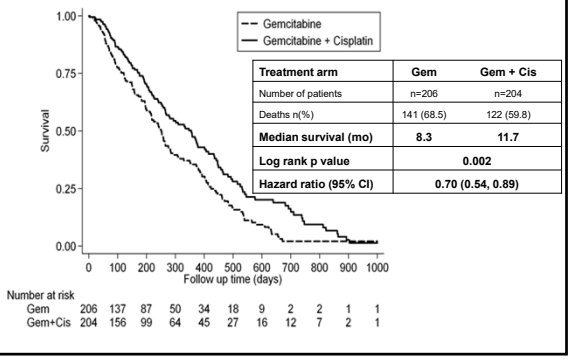
- **Primary endpoint: OS**
- **Secondary endpoints including: PFS, toxicity**

Valle et al. *J Clin Oncol* 2009; 27(suppl):202s (abstract 4503)
N Engl J Med. 2010 Apr 8;362(14):1273-81

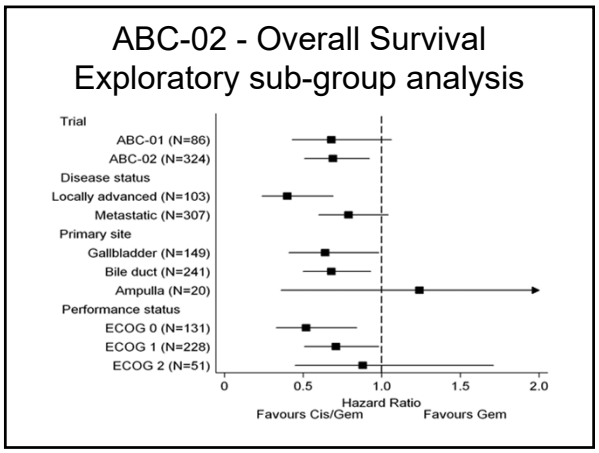
Baseline characteristics of patients

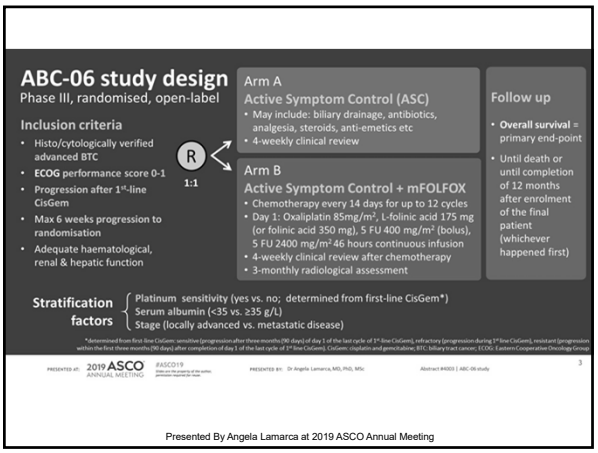
	Gem (n=206)	Cis/Gem (n=204)
Age (yr, median)	63	64
Male/female (%)	48 / 52	47 / 53
Extent of disease Locally advanced / metastatic (%)	23 / 77	27 / 73
Primary site Gallbladder / bile duct / ampulla (%)	37 / 58 / 5	36 / 60 / 4
ECOG Performance score 0 / 1 / 2 (%)	31 / 57 / 12	32 / 54 / 13
Prior therapy		
None (%)	24	25
Biliary stenting (%)	44	46
Surgery (curative / palliative, %)	24 / 20	18 / 19
Radiotherapy (%)	2	1

ABC-02 - Results: Overall Survival (ITT)

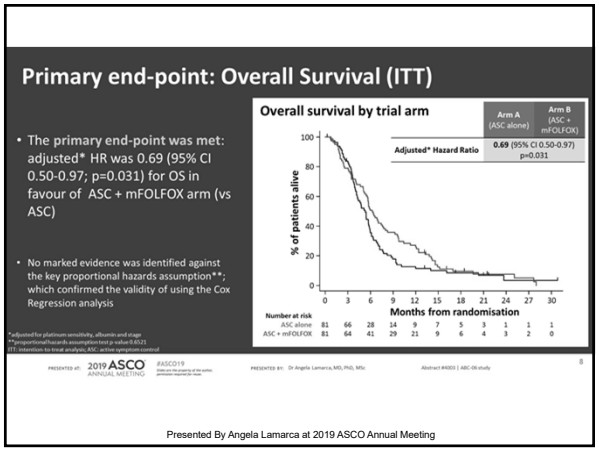


Treatment arm	Gem	Gem + Cis
Number of patients	n=206	n=204
Deaths n(%)	141 (68.5)	122 (59.8)
Median survival (mo)	**8.3**	**11.7**
Log rank p value	**0.002**	
Hazard ratio (95% CI)	**0.70 (0.54, 0.89)**	

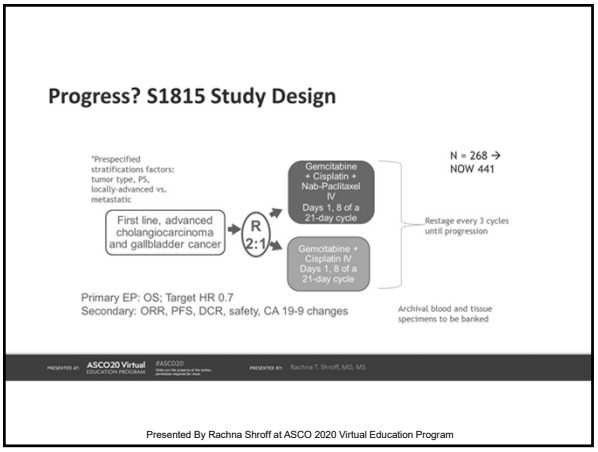




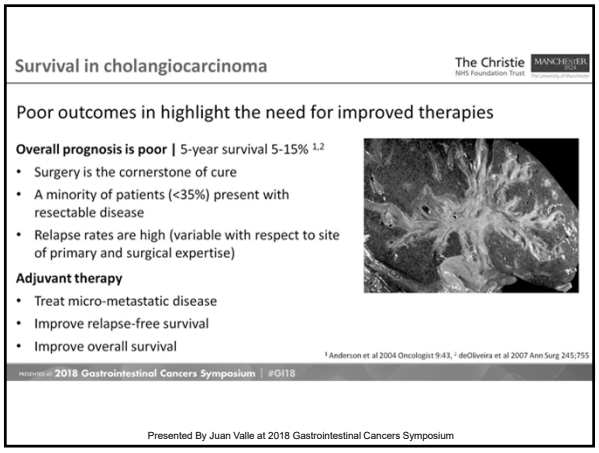
Presented By Angela Lamarca at 2019 ASCO Annual Meeting



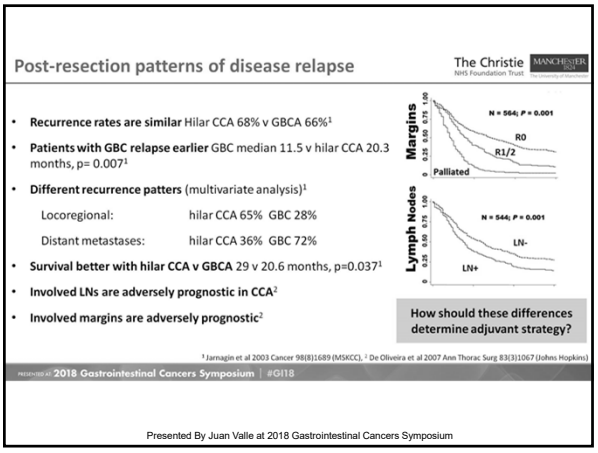
Presented By Angela Lamarca at 2019 ASCO Annual Meeting



Presented By Rachna Shroff at ASCO 2020 Virtual Education Program



Presented By Juan Valle at 2018 Gastrointestinal Cancers Symposium



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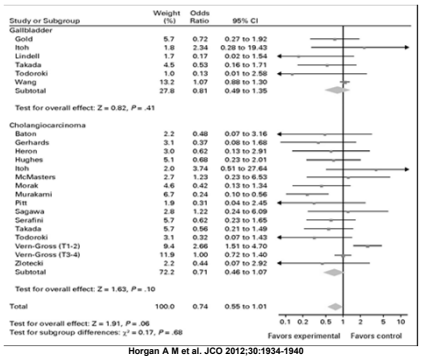
Adjuvant Therapy of Bile Duct Tumors:
6712 pts with CT, XRT, CT+XRT



Those receiving CT or CRT derived statistically greater benefit than RT alone (OR, 0.39, 0.61, and 0.98,respectively; *P* = .02).

The greatest benefit for AT was in those with LN-positive disease (OR, 0.49; *P* = .004) and R1 disease (OR, 0.36; *P* = .002).

Horgan A M et al. JCO 2012;30:1934-1940

JOURNAL OF CLINICAL ONCOLOGY

NCCN guidelines intrahepatic cholangiocarcinoma

The Christie NHS Foundation Trust | The University of Manchester

National Comprehensive Cancer Network®

	Treatment options	Surveillance
Post-resection status	**No residual local disease** (R0 resection): • Observe • Clinical trial • **Fluoropyrimidine-based or gemcitabine-based Cx**	• Multi-phasic abdominal/pelvic CT/MRI with IV contrast and chest CT +/- contrast • Every 6 months for 2 years (if clinically indicated) • Then annually up to 5 years
	Microscopic margins (R1) **or positive regional nodes**: • Clinical trial • **Fluoropyrimidine chemo-Rx** • **Fluoropyrimidine-based or gemcitabine-based Cx**	
	Residual local disease (R2 resection): • Clinical trial • Fluoropyrimidine-based or gemcitabine-based Cx • Loco-regional therapy • Best supportive care	

*"There are **no randomised Phase III** clinical trial data to support a standard **adjuvant regimen**"*

Adapted from NCCN Guidelines Version 4.2017

PRESENTED AT 2018 Gastrointestinal Cancers Symposium | #GI18

Presented By Juan Valle at 2018 Gastrointestinal Cancers Symposium

Adjuvant Therapy of Bile Duct Tumors

	SWOG S0809 (U.S.)	PRODIGE 12 (France)	BILCAP (U.K.)
Design	Single-arm phase 2	Randomized phase 3	Randomized phase 3
Treatment	Gemcitabine/capecitabine + capecitabine/XRT	Gemcitabine/oxaliplatin versus observation	Capecitabine versus observation
n	79	196	440
BTC tumor type	Gallbladder 32% Perihilar 48% Distal 20% Intrahepatic 0%	Gallbladder 19% Perihilar 8% Distal 28% Intrahepatic 45%	Gallbladder 18% Perihilar 28% Distal 35% Intrahepatic 19%
Positive margin (%)	32	15	38
Positive lymph nodes (%)	N/A	37	54
Endpoint/summary	•Two-year OS 65% •Treatment well tolerated •R0/R1 OS similar at 35 and 34 months	•RFS similar between treatment and control groups (p = 0.47) •Treatment well tolerated based on QOL	•ITT median OS 51 versus 36 months (p = 0.097) •Per protocol analysis median OS 53 versus 36 months (p = 0.028)

BTC = biliary tract cancer; XRT = external beam radiation therapy; OS = overall survival; RFS = recurrence free survival; QOL = quality of life; ITT = intention to treat

PRODIGE-12 study schema

The Christie NHS Foundation Trust | The University of Manchester

- Biliary Tract Cancer (iCCA/eCCA/GBC)
- R0 or R1 surgery
- ECOG PS 0-2
- Adequate liver function
- Randomisation within 3 months

N=196 patients

R 1:1

Surveillance (Follow-up only)
- CEA, CA19-9 and CT scans
- Every 3 months for 2 years
- Every 6 months for Y3-Y5

GEMOX 85
- 12 cycles
- Gemcitabine 1000mg/m² D1
- Oxaliplatin 85mg/m² D2

Stratification factors | Tumour site (ICC vs ECC/Hilar vs GBC), R0 v R1, N0 v N+ v Nx, centres

2 co-primary endpoints | Relapse-Free Survival (RFS) and Quality of Life (QoL)

Edeline *et al* (ASCO-GI 2017) J Clin Oncol 35 (45)225, updated at ESMO 2017 LBA29

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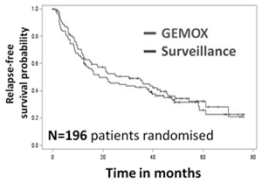
PRODIGE-12 study relapse-free survival results

The Christie NHS Foundation Trust | The University of Manchester



	Surveillance	GEMOX
Disease progression	N=61	N=55
Deaths	N=6	N=4
Median RFS*	**18.5 months**	**30.4 months**
95% CI (months)	12.6-38.2	15.4-43.0

***HR=0.88** [95% CI 0.62-1.25], p=0.47

Median follow-up 46.5 months, N=126 events

Edeline *et al* (ASCO-GI 2017) J Clin Oncol 2017;35 (45)225, updated at ESMO 2017 LBA29

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BILCAP | design

The Christie NHS Foundation Trust | The University of Manchester

- Developed by the Hepatobiliary group, UK National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group in March 2005

- ICC, Hilar CC, muscle-invasive GBC, Lower common bile duct CC
- Radical & macroscopically complete surgery
- ECOG PS 0-2
- No prior treatment
- Adequate organ function
- Randomisation within 3 months

N=360 patients

R 1:1

Observation

Capecitabine
1250mg/m² capecitabine twice a day, days 1-14 of a 3 weekly cycle for 24 weeks (8 cycles)

Primary endpoint; OS

Secondary endpoints; relapse-free survival, toxicity, QoL, health economics

Primrose *et al* (ASCO 2017) J Clin Oncol 35 (15) 4006

PRESENTED AT 2018 Gastrointestinal Cancers Symposium | #GI18

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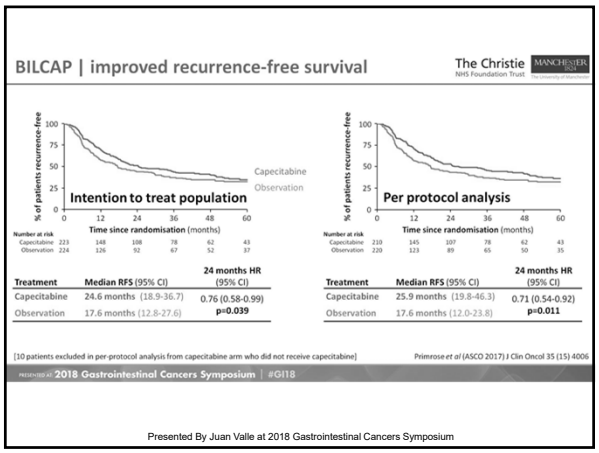

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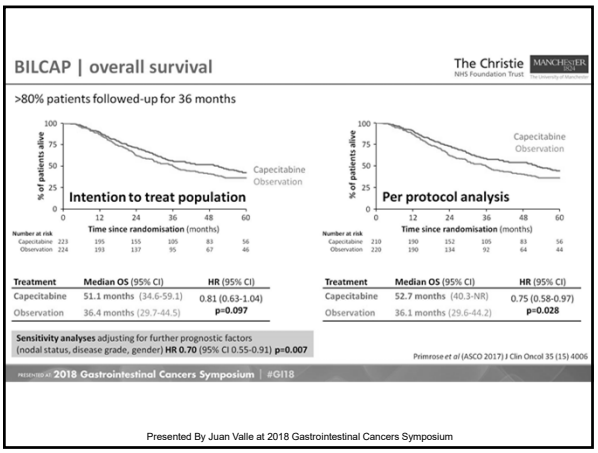

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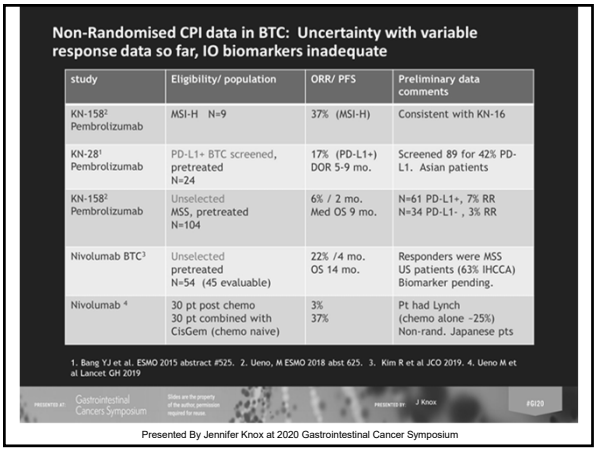
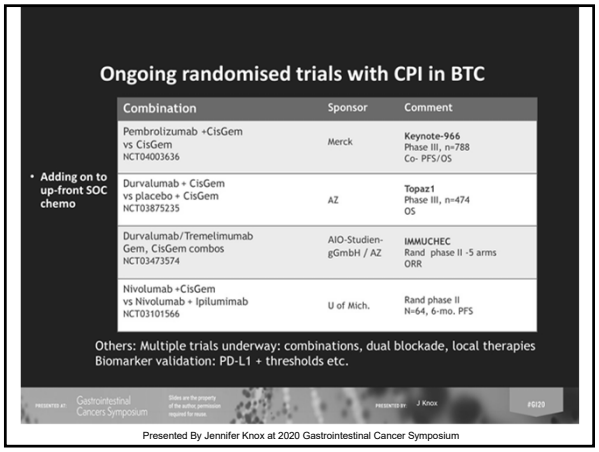
MRD and PD-1 in biliary cancers

- Mismatch repair deficiency (MRD)/MSI is feature of many cancers at a frequency of approximately 1 in 30 patients independent of tumor histology. Tumors with MRD are deficient in the repair of specific DNA replication errors and as a result accumulate hundreds to thousands of mutations per tumor genome
  - MSI-H present in 5-15% of biliary tumors
- Phase 2 study to evaluate the activity of pembrolizumab; co-primary endpoints were response and progression-free survival rate at 20 weeks in previously treated patients
- endometrial: 9; pancreatic: 4; ampullary: 4; biliary: 3; small bowel: 3; gastric: 3; thyroid: 1; prostate: 1; sarcoma: 1
- Objective response and disease control rates were 48% (14/29, 95% confidence interval: 29-67%) and 72% (21/29), respectively. Twenty of 29 patients remain on treatment due to clinical benefit. Median overall Survival (OS) and progression-free survival (PFS) were 21 months and not reached (NR).
- 5/23/17: FDA gave accelerated approval for pembrolizumab for MSI-H tumors, independent of organ site

Le, et al. N Engl J Med 2015; 372:2509-2520; J Clin Oncol 34, 2016 (suppl; abstr 3003)



Presented By Jennifer Knox at 2020 Gastrointestinal Cancer Symposium



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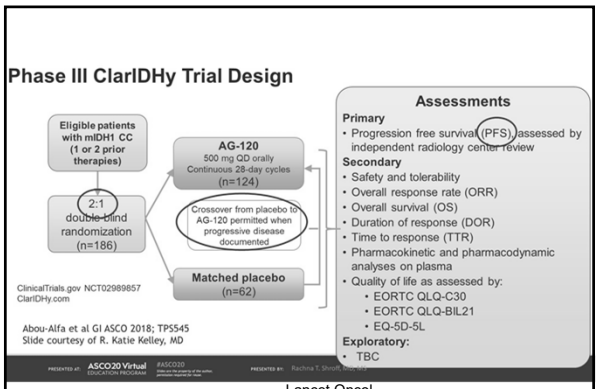
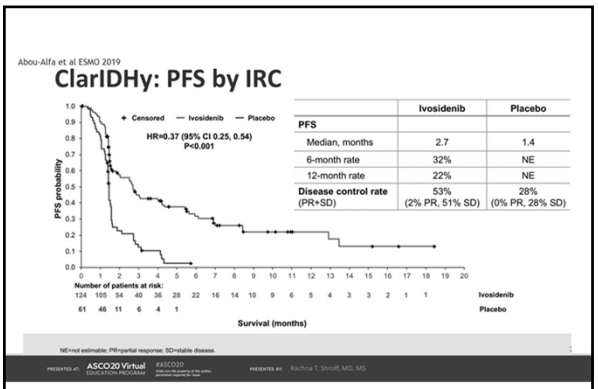
ESMO 2019

- FIGHT 202
- Phase 2b trial of pemigatinib (TAS 102) an FGFR2 inhibitor (10-16% of pts)
- 36% response rate in FGFR2 fusions/rearrangements(primary endpoint)
- PFS 6.9 mos, OS 21.1 mos
- Approved by FDA 4/20/20
- 1st line NCT03656536 phase III trial vs gemcis underway



Lancet Oncol
2020 Jun;21(6):796-807

Presented By Rachna Shroff at ASCO 2020 Virtual Education Program



	Ivosidenib	Placebo
PFS		
Median, months	2.7	1.4
6-month rate	32%	NE
12-month rate	22%	NE
Disease control rate (PR+SD)	53% (2% PR, 51% SD)	28% (0% PR, 28% SD)

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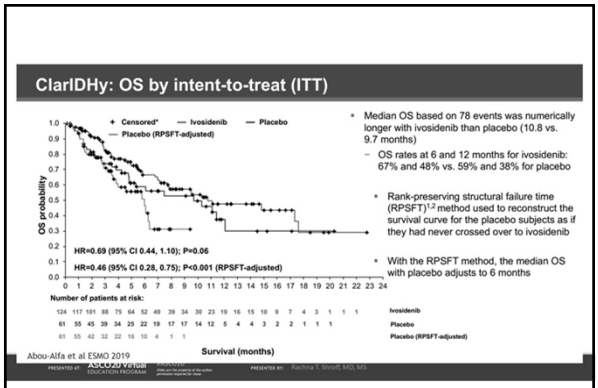

- Median OS based on 78 events was numerically longer with ivosidenib than placebo (10.8 vs. 9.7 months)
  - OS rates at 6 and 12 months for ivosidenib: 67% and 48% vs. 59% and 38% for placebo
- Rank-preserving structural failure time (RPSFT)[1,2] method used to reconstruct the survival curve for the placebo subjects as if they had never crossed over to ivosidenib
- With the RPSFT method, the median OS with placebo adjusts to 6 months

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73

Sarcomas

Mark Agulnik, MD

August 20, 2020

HEMATOLOGY AND MEDICAL ONCOLOGY

BEST PRACTICES COURSE

73 – Sarcomas

Mark Agulnik, MD

Disclosures

Disclosures of Financial Relationships with Relevant Commercial Interests

- **Advisory Board/ Speaker's Bureau: Lilly, BMS, Sanofi Genzyme, Regeneron, Blueprint Medicine, Deciphera**

Off-Label Usage

- **None**

Outline

Background	• Incidence • Epidemiology • Etiology
Soft tissue sarcomas (STS)	• GIST vs non-GIST
Bone sarcomas	• Osteosarcoma • EFTS • Chondrosarcoma • Rare Tumors with FDA approved drugs

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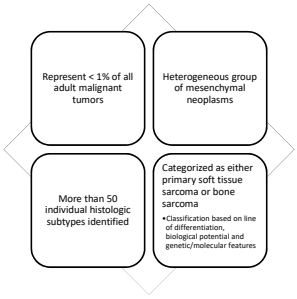
Sarcomas



Skubitz KM, D'Adamo DR. *Mayo Clin Proc.* 2007; 82:1409-1432
Doyle L. *Cancer* 2014;120:1763–1774 & Fletcher C. WHO classification of tumours of soft tissue and bone

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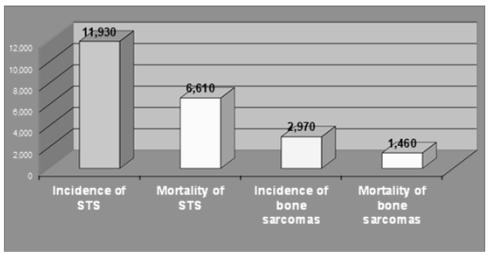
Sarcoma: Incidence



- True incidence of Gastrointestinal stromal tumors (GIST) are likely underestimated as they are included under GI malignancies

Siegel RA et al. Cancer Statistics, 2015. *CA Cancer J Clin* 2015; 65(1): 5-29.

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Sarcomas: Epidemiology

- Slight male predominance
- No race predilection
- Age distribution for soft tissue sarcomas:
  - increases with increasing age
  - Age > 60 y/o: > 51.7%
- Age distribution of bone sarcomas:
  - Children and young adults: osteosarcoma and EFTs
  - Adults: chondrosarcomas

SEER Database. http://seer.cancer.gov/statfacts/html/soft.html

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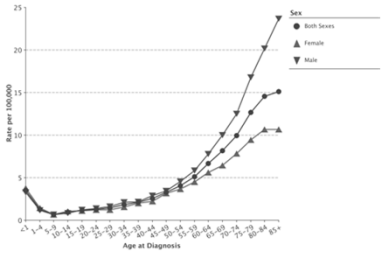
Soft Tissue: SEER Incidence Rates by Age at Diagnosis , 2011-2015, by sex



https://seer.cancer.gov/

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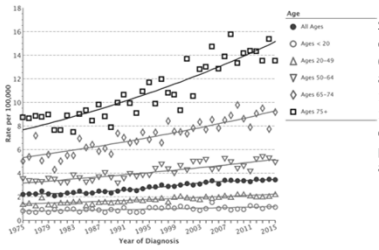
Soft Tissue: Long Term Trends in SEER Incidence Rates, 1975-2015



STSs are common in elderly patients aged ≥ 65 years, with an age-adjusted incidence of 11.3 cases per 100,000 population compared to 2.3 cases per 100,000 in those age < 65 years.

https://seer.cancer.gov/

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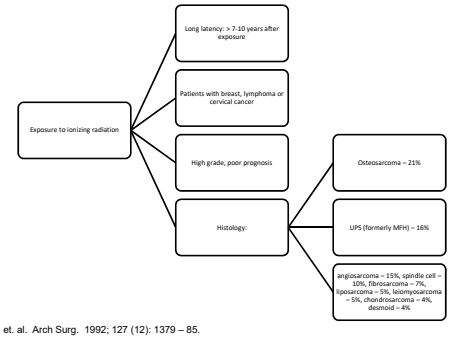
Sarcomas: Etiology- Spontaneous Vs Risk Factor



Brady MS, et. al. Arch Surg. 1992; 127 (12): 1379 – 85.

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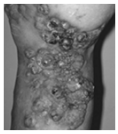
Sarcomas: Etiology



- Chronic lymphedema (Stewart-Treves)
  - Angiosarcoma
- Exposure to chemicals:
  - Vinyl chloride: Hepatic angiosarcoma
- Viruses
  - Human herpesvirus 8 – Kaposi's sarcoma
  - Epstein-Barr virus and leiomyosarcoma

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Soft Tissue Sarcoma: Subgroups

3 most common subgroups (other than GIST):	• Undifferentiated Pleomorphic Sarcoma (UPS, formerly MFH), • Liposarcoma • Leiomyosarcoma
Other histologies:	• synovial sarcoma • angiosarcoma
Biological classification:	• Benign: usually do not recur • Intermediate, locally aggressive or rarely metastasizing • Malignant

*some slides courtesy of Dr. Maki

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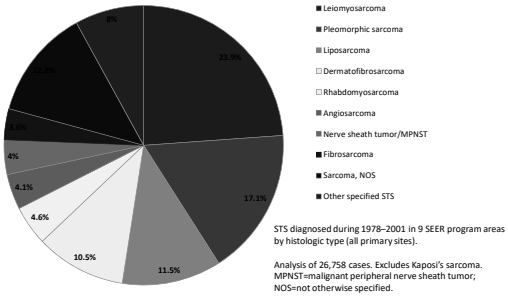
Epidemiology and Etiology



STS diagnosed during 1978–2001 in 9 SEER program areas by histologic type (all primary sites).

Analysis of 26,758 cases. Excludes Kaposi's sarcoma. MPNST=malignant peripheral nerve sheath tumor; NOS=not otherwise specified.

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- Diagnosis
  - core needle biopsy
- Biopsy/needle track site chosen should lie within a future en bloc resection of the tumor
- Imaging used: CT/MRI
  - PET: may be useful for prognostication, following response to treatment

Clark M. Soft tissue sarcoma. NEJM. 2005; 353:7: 701-711

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Soft Tissue Sarcoma: Staging

- Performed to determine extent of disease spread[1]
- Based on grade and tumor size[1]
- Important to prognosis and treatment planning[1]
- TNM system is most widely used[2]
- No standard staging system—different systems depending on where the cancer is in the body[1]
- Can recur in same location or in other parts of the body[1]

Staging for STS of the Extremity or Trunk (AJCC 8th Ed.)[3,4]

Stage	T	N	M	Grade
I	Any	--	--	1
	≤5 cm*, superficial	--	--	2
II	≤5 cm*, deep	--	--	2
	>5 cm* and ≤10 cm*, superficial or deep	--	--	2
	>10 cm* superficial or deep	--	--	2
IIIA	≤5 cm* and ≤10 cm*, superficial or deep	--	--	3
	>5 cm* and ≤10 cm*, superficial	--	--	3
	>5 cm* and ≤10 cm*, deep	--	--	3
	>10 cm*, superficial	--	--	3
IIIB	>10 cm*, deep	--	--	3
	Any	Regional lymph node metastasis	--	Any
IV	Any	Any	Distant metastasis	1
	Any	Any	Distant metastasis	2/3

*=greatest dimension.
TNM, primary tumor, regional lymph nodes, distant metastasis.

1. NIH-NCI. Adult Soft Tissue Sarcoma Treatment (PDQ®)–Patient Version. Available: https://www.cancer.gov/types/soft-tissue-sarcoma/patient/adult-soft-tissue-treatment-pdq. Revised May 6, 2020. Accessed June 10, 2020. 2. Zhang, et al. In: Henshaw RM, ed. *Sarcoma: A Multidisciplinary Approach to Treatment*. 2017:573-586. 3. Pollock RE, Maki RG. In: Amin MB, et al, eds. *AJCC Cancer Staging Manual*, 8th edn. 2017:489-497.
4. NCCN Guidelines. Soft Tissue Sarcoma. Version 2.2020–May 28, 2020.

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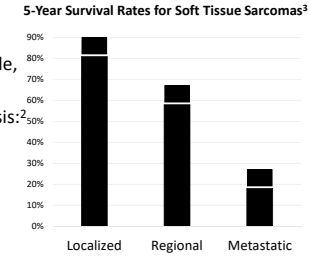
Soft Tissue Sarcoma: Prognosis

- Prognostic factors:[1]
  - patient age
  - tumor size, histologic grade, and stage at diagnosis
- Factors with a poor prognosis:[2]
  - age >60 years
  - tumors >5 cm
  - high-grade histology
  - R1/R2 resection

5-Year Survival Rates for Soft Tissue Sarcomas[3]



1. NIH-NCI. Adult Soft Tissue Sarcoma Treatment (PDQ®)–Patient Version. Available: https://www.cancer.gov/types/soft-tissue-sarcoma/patient/adult-soft-tissue-treatment-pdq. Revised May 6, 2020. Accessed June 10, 2020. 2. NIH NCI. Adult Soft Tissue Sarcoma Treatment (PDQ®)–Health Professional Version. Available: https://www.cancer.gov/types/soft-tissue-sarcoma/hp/adult-soft-tissue-treatment-pdq. Accessed June 9, 2020.
3. American Cancer Society. Survival rates for soft tissue sarcoma. https://www.cancer.org/cancer/soft-tissue-sarcoma/detection-diagnosis-staging/survival-rates.html. Updated 6 March 2019. Accessed 19 March 2019.

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Sarcoma-Specific Survival by depth, grade and size

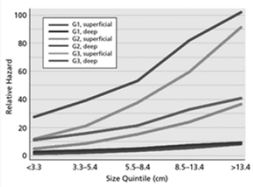

Figure 2.

Predicted relative hazard ratios for sarcoma-specific survival for cases without nodal or distant metastasis by tumor depth and histologic grade over quintiles of tumor size. Plots are relative to superficial, low-grade tumors <3.3 cm in greatest dimension and are adjusted for interactions between tumor depth and size. Abbreviations: G1, low-grade (grade 1); G2, intermediate-grade (grade 2); G3, high-grade (grade 3).

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J Natl Compr Canc NetwFebruary 1, 2018 vol. 16 no. 2 144-152

General Principles of Therapy for Soft Tissue Sarcomas

Local control

- Surgical en bloc resection is the goal
- Radiation of benefit for close surgical margins or residual disease (especially for extremity sarcomas)

Systemic control

- Chemotherapy – role for palliation in metastatic disease
- Targeted therapies

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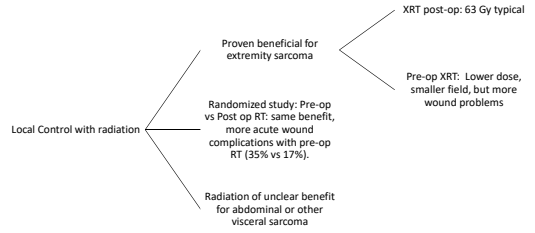
Soft Tissue Sarcoma: Radiation therapy



Davis AM et al. Radiother Oncol 2005; 75: 48
O'Sullivan B et al. Lancet 2002; 359: 2235; O'Sullivan et al. ASCO 2004, abst 9007

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Treatment of Soft Tissue Sarcomas

Adjuvant Chemotherapy

The role of chemotherapy in the adjuvant setting for standard adult soft tissue sarcoma remains controversial.

There are situations when adjuvant therapy clearly is not indicated.
- no benefit for soft tissue sarcomas that arise from visceral or abdominal sites, and surgery alone remains the standard of care.

Specific subtypes of adult soft tissue sarcomas may benefit from adjuvant chemotherapy:
- synovial sarcoma
- high-grade myxoid/round cell liposarcoma.

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Adjuvant Chemotherapy for STS

- Meta-analysis 1997 and 2008
  - 14 trials: 1568 pts: Increased DFS, RFS, distant mets in favor of chemotherapy, not OS
    - no ifosfamide
  - 18 trials: 1953 pts: marginal efficacy in favor of chemotherapy with doxorubicin and ifosfamide with respect to local, distant, overall recurrence and OS (11% absolute risk reduction: (30 vs 41% risk of death).

Sarcoma Meta-Analysis Collaboration, Lancet 350:1647, 1997.; Pervaiz N et a. Cancer 2008; 112:573

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Conclusions: Adjuvant chemotherapy for STS

- **Disease-free survival is longer** in patients who receive chemotherapy.
- **Overall survival may be improved** with chemotherapy for all STS based on studies using doxorubicin-based therapy, but if there is a benefit, it appears to be a small one. The risks and benefits of adjuvant therapy should be discussed on a case-by-case basis.

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Classic Chemotherapy Drugs for Metastatic Sarcoma: Response Rates

Doxorubicin	20%
Ifosfamide	20%
Cyclophosphamide	12%
Paclitaxel	12%
Dacarbazine	10%
Pegylated doxorubicin	10%
Trabectedin	10%
Gemcitabine	8%
Eribulin	7%

Edmonson JH, et. al. J Clin Oncol 1993; 11:1269 – 1275.; Santoro A., et. al. J Clin Oncol. 1995; 13: 1537-1545.;Patel A, et. Al. J Clin Oncol. 1997; 15 – 2378.; van Oosterom et. al., Eur J Cancer. 2002; 2397 – 2406; Judson I, et. Al. Eur J Cancer. 2001; 37:870-77.;Demetri G, et. al. Hematol Oncol Clin North Am. 1995; 9 (4): 765-85.;Antman K, et. al. Semin Surg Oncol. 1988; 4: 53 – 58.;Skubitz KM, D'Adamo DR. Sarcoma. Mayo Clin Proc. 2007; 82:1409-1432, Demetri GD, et. al. PNAS 1999;96: 3951-56; Debrock G, et. Al. Br J Cancer. 2003; 89:1409-12;Schoffski P et. al. Lancet Oncol 2011: 12: Demetri GD et al. JCO 2015: 33: Abst 10503^; Schoffski P et al. JCO 2015: 33 Abstr LBA10507^

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Combination Therapy

Adriamycin/Olaratumab vs Adriamycin	• RR in a phase Ib/II trial: ~18% vs 12%
AIM	• ~40% RR
MAID	• ~40% RR
Gemcitabine/Docetaxel vs Gemcitabine	• RR in a phase II trial: ~18% vs 8%
Gemcitabine/DTIC vs DTIC	• RR in a phase II trial: ~12% ORR vs 4%

Elias A, et. al. J Clin Oncol. 1989; 7:1208 – 1216.; Antman K et. al. J Clin Oncol. 1993; 11: 1276 – 1285; Judson, et. al. Lancet Oncol 2014; Maki RG et al. J Clin Oncol. 2007; 25:2755; Hensley et. al. JCO 2002; Garcia-del-Muro, X, et. al. JCO 2011, Tap, William D et al.The Lancet , Volume 388 , Issue 10043 , 488 - 497

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Soft Tissue Sarcoma: NCCN Guideline Recommended Agents/Regimens

- Systemic therapy agents and regimens with activity for general STS subtypes[a,b,c,*] are shown below:[1]

Neoadjuvant / Adjuvant	1L Advanced / Metastatic	2L+ Advanced / Metastatic
Preferred: – AIM (doxorubicin, ifosfamide, mesna – Ifosfamide, epirubicin, mesna **Other recommendations:** – AD (doxorubicin + dacarbazine[†]) – Doxorubicin – Gemcitabine + docetaxel **Useful in certain circumstances:** – Ifosfamide	**Preferred:** – Doxorubicin **or** epirubicin **or** liposomal doxorubicin – AD **or** AIM **or** MAID (mesna, doxorubicin, ifosfamide, dacarbazine) – Ifosfamide, epirubicin, mesna **Other recommendations:** – Gemcitabine-based regimens **Useful in certain circumstances:** – Pazopanib[‡] – Larotrectinib[‖, §] – Entrectinib[‖, §]	**Preferred:** – Eribulin[‖,#, ‡] – Pazopanib[‡, ¶] – Trabectedin[‖,^,#] **Other recommendations:** – Dacarbazine – Ifosfamide – Temozolomide[‡] – Vinorelbine[‡] – Regorafenib[‡]

*Soft tissue sarcoma subtypes with non-specific histologies. Regimens appropriate for general STS[a,b,c]; see other NCCN guideline sections for histology-specific recommendations. Category 2A recommendations unless otherwise noted. See Notes for NCCN alphabetical footnotes. †If ifosfamide is not considered appropriate. ‡Patients ineligible for IV chemotherapy. §For NTRK gene-fusion sarcomas. ‖Category 1 recommendation for liposarcoma, Category 2A recommendation for other subtypes. ¶For non-adipocytic sarcoma. #Category 1 for liposarcoma and leiomyosarcoma.
1L, first-line; 2L+, subsequent lines of therapy; STS, soft tissue sarcoma.
1: NCCN Guidelines. Soft Tissue Sarcoma. Version 2.2020–May 28, 2020.

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Overview of Targeted Therapies for Cancer

- Targeted cancer therapies are drugs designed to interfere with specific molecules necessary for tumor growth and progression.
- Ideally- A primary goal of targeted therapies is to fight cancer cells with more precision and potentially fewer side effects.
- Targeted cancer agents are broadly classified as:
  - **Therapeutic monoclonal antibodies** target specific antigens found on the cell surface.
  - **Small molecules** can penetrate the cell membrane to interact with targets inside a cell.

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Agent	Target(s)	FDA-approved indication(s)
Ado-trastuzumab emtansine (Kadcyla)	HER2 (ERBB2/neu)	Breast cancer (HER2+)
Afatinib (Gilotrif)	EGFR (HER1/ERBB1), HER2 (ERBB2/neu)	Non-small cell lung cancer
Aldesleukin (Proleukin)		Renal cell carcinoma Melanoma
Alectinib (Alecensa)	ALK	Non-small cell lung cancer
Avapritinib	KIT and PDGFR	GIST
Atezolizumab (Tecentriq)	PD-L1	Urothelial carcinoma Non-small cell lung cancer
Axitinib (Inlyta)	KIT, PDGFRβ, VEGFR1/2/3	Renal cell carcinoma
Bevacizumab (Avastin)	VEGF ligand	Cervical, Fallopian tube and Ovarian cancer Colorectal cancer Glioblastoma Non-small cell lung cancer Renal cell carcinoma
Cabozantinib (Cabometyx [tablet], Cometriq [capsule])	FLT3, KIT, MET, RET, VEGFR2	Medullary thyroid cancer Renal cell carcinoma
Ceritinib (Zykadia)	ALK	Non-small cell lung cancer
Cetuximab (Erbitux)	EGFR (HER1/ERBB1)	Colorectal cancer Squamous cell cancer of the head and neck
Cobimetinib (Cotellic)	MEK	Melanoma
Crizotinib (Xalkori)	ALK, MET, ROS1	Non-small cell lung cancer

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Agent	Target(s)	FDA-approved indication(s)
Dabrafenib (Tafinlar)	BRAF	Melanoma
Denosumab (Xgeva)	RANKL	Giant cell tumor of the bone
Erlotinib (Tarceva)	EGFR (HER1/ERBB1)	Non-small cell lung cancer Pancreatic cancer
Everolimus (Afinitor)	mTOR	neuroendocrine tumor Renal cell carcinoma Breast cancer
Gefitinib (Iressa)	EGFR (HER1/ERBB1)	Non-small cell lung cancer
Imatinib (Gleevec)	KIT, PDGFR, ABL	GI stromal tumor Dermatofibrosarcoma protuberans
Ipilimumab (Yervoy)	CTLA-4	Melanoma
Lapatinib (Tykerb)	HER2 (ERBB2/neu), EGFR (HER1/ERBB1)	Breast cancer
Lenvatinib (Lenvima)	VEGFR2	Renal cell carcinoma Thyroid cancer
Necitumumab (Portrazza)	EGFR (HER1/ERBB1)	Squamous non-small cell lung cancer

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Agent	Target(s)	FDA-approved indication(s)
Nivolumab (Opdivo)	PD-1	Head and neck squamous cell carcinoma Melanoma Non-small cell lung cancer Renal cell carcinoma Urothelial carcinoma
Olaparib (Lynparza)	PARP	Ovarian cancer
Osimertinib (Tagrisso)	EGFR	Non-small cell lung cancer
Palbociclib (Ibrance)	CDK4, CDK6	Breast cancer
Panitumumab (Vectibix)	EGFR (HER1/ERBB1)	Colorectal cancer
Pazopanib (Votrient)	VEGFR, PDGFR, KIT	Renal cell carcinoma Soft tissue sarcoma
Pembrolizumab (Keytruda)	PD-1	Melanoma Non-small cell lung cancer (PD-L1+) Head and neck squamous cell carcinoma
Pertuzumab (Perjeta)	HER2 (ERBB2/neu)	Breast cancer
Pexidartinib	CSF1R	tenosynovial giant cell tumor
Ramucirumab (Cyramza)	VEGFR2	Colorectal cancer Gastric cancer or Gastroesophageal junction Non-small cell lung cancer
Regorafenib (Stivarga)	KIT, PDGFRβ, RAF, RET, VEGFR1/2/3	Colorectal cancer Gastrointestinal stromal tumors

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Agent	Target(s)	FDA-approved indication(s)
Ribociclib (Kisqali)	CDK4, CDK6	Breast cancer
Ripretinib	KIT and PDGFRα inhibitor	GIST
Sipuleucel-T (Provenge)		Prostate cancer
Sonidegib (Odomzo)	Smoothened	Basal cell carcinoma
Sorafenib (Nexavar)	VEGFR, PDGFR, KIT, RAF	Hepatocellular carcinoma Renal cell carcinoma Thyroid carcinoma
Sunitinib (Sutent)	VEGFR, PDGFR, KIT, RET	Renal Cell Carcinoma GIST Pancreatic NET
Tazemetostat	EZH2	Epithelioid Sarcoma
Temsirolimus (Torisel)	mTOR	Renal cell carcinoma
Trametinib (Mekinist)	MEK	Melanoma
Trastuzumab (Herceptin)	HER2 (ERBB2/neu)	Breast cancer Gastric cancer
Vandetanib (Caprelsa)	EGFR (HER1/ERBB1), RET, VEGFR2	Medullary thyroid cancer
Vemurafenib (Zelboraf)	BRAF	Melanoma
Vismodegib (Erivedge)	PTCH, Smoothened	Basal cell carcinoma
Ziv-aflibercept (Zaltrap)	PlGF, VEGFA/B	Colorectal cancer

Soft Tissue Sarcoma: NCCN Guideline Recommended Targeted Agents

- NCCN recommended non-chemotherapy targeted agents are described in the table below

Drug Name	Brand Name	Mechanism of Action	Recommended for:
Pazopanib[2]	Votrient®	Inhibits VEGFR, PDGFR, FGFR, c-Kit	Option for 1L advanced/metastatic disease in patients ineligible for IV chemotherapy
Larotrectinib[3]	VITRAKVI®	Inhibits TRKA, TRKB, TRKC, TNK2	Option for 1L advanced/metastatic disease
Entrectinib[4]	Rozylytrek®	Inhibits TRKA, TRKB, TRKC, ROS1, ALK, JAK2 and TNK2	Option for 1L advanced/metastatic disease
Regorafenib[5]	STIVARGA®	Inhibits c-Kit, VEGFR, PDGFR, RET, BRAF	Option for 2L+ advanced/metastatic disease
Tazemetostat[6]	Tazverik®	Inhibits EZH2, EZH2 gain-of-function mutations Y646X and A687V	Option for metastatic or locally advanced epithelioid sarcoma not eligible for complete resection
Pembrolizumab[7]	Keytruda®	Inhibits PD-L1/PD-L2 and PD-1; immunotherapy	Option for metastatic undifferentiated pleomorphic sarcoma
Palbociclib[8]	Ibrance®	Inhibits CDK-4 and 6, preventing downstream cell proliferation	Option for unresectable well-differentiated / dedifferentiated liposarcoma (WD-DDLS)

BRAF, B-Raf proto-oncogene; FGFR, fibroblast growth factor receptor; Kit, hematopoietic growth factor receptor; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.
1. NCCN Guidelines. Soft Tissue Sarcoma. Version 2.2020–May 28, 2020. 2. Votrient (pazopanib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; June 2020. 3. VITRAKVI (larotrectinib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; July 2019. 4. Rozyltrek (entrectinib) [prescribing information]. South San Francisco, CA: Genentech, Inc; August 2019. 5. STIVARGA (regorafenib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; February 2020. 6. Tazverik (tazemetostat) [prescribing information]. Cambridge, MA: Epizyme, Inc; January 2020. 7. Keytruda (pembrolizumab) [prescribing information]. Whitehouse Station, NJ: MERCK & Co., Inc; April 2020. 8. Ibrance (Palbociclib) [prescribing information]. New York, NY: Pfizer Inc; February 2018.

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Pazopanib- Multi-tyrosine Kinase Inhibitor

Pazopanib is a small-molecule TKI of growth factor receptors associated with angiogenesis and tumor cell proliferation

Pazopanib exhibits inhibition of:

- Vascular endothelial growth factor receptors (VEGFR-1, -2, and -3)
- Platelet-derived growth factor receptors (PDGFR-α and -β)
- Fibroblast growth factor receptors (FGFR-1 and -3)
- Stem cell factor receptor (c-Kit)
- Interleukin-2 receptor inducible T-cell kinase (Itk)
- Leukocyte-specific protein tyrosine kinase (Lck)
- Transmembrane glycoprotein receptor tyrosine kinase (c-Fms)

Sleijfer et. al., J Clin Oncol 2009; 3126

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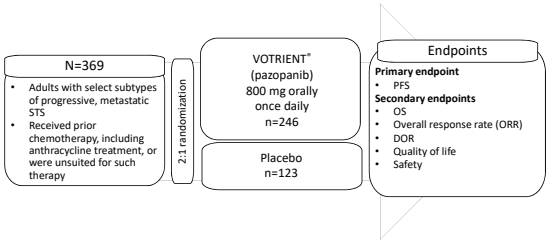
PALETTE Study
Objective and design

- **PA**zopanib exp**L**or**E**d in Sof**T**-**T**isue Sarcoma—a phas**E** 3 study (PALETTE) was a multicenter, randomized, double-blind, placebo-controlled trial in patients with metastatic STS who received prior chemotherapy



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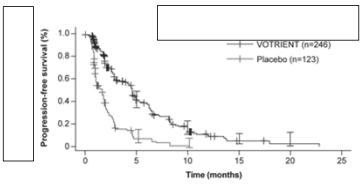
PALETTE Study
Efficacy: primary endpoint

Median PFS	pazopanib (n=246)	Placebo (n=123)
Months	4.6	1.6
HR (95% CI)	0.35 (0.26-0.48)	
	P<0.001	

HR, Hazard ratio



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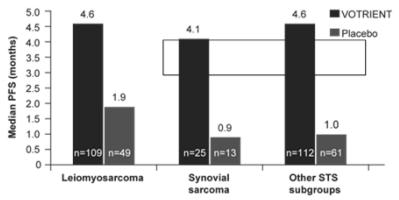
PALETTE Study
Efficacy: primary endpoint (cont'd)

- Pazopanib demonstrated PFS benefit in prespecified subgroups based on STS histology



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PALETTE Study
Efficacy: secondary endpoints

Endpoint	pazopanib (n=246)	Placebo (n=123)
Median OS (months)	12.6	10.7
HR (95% CI)	0.87 (0.67-1.12)	
ORR (CR+PR), % (95% CI)	4 (2.3-7.9)	0 (0.0-3.0)
Duration of response Median (months) (95% CI)	9.0 (3.9-9.2)	

CR: complete response; HR: hazard ratio; ORR: overall response rate; OS: overall survival; PR; partial response

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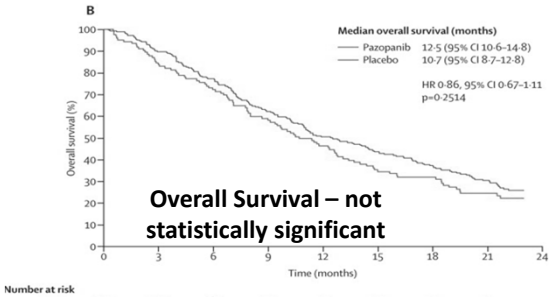
PALETTE (EORTC 62072) Overall Survival



Overall Survival – not statistically significant

Van Der Graaf et. al. Lancet 2012; 379: 1879

Pazopanib

- On April 26, 2012, the U.S. Food and Drug Administration granted approval for pazopanib for the treatment of patients with advanced soft tissue sarcoma who have previously received chemotherapy

STS Subgroups

Liposarcomas (Adipocytic)

- Tied 2nd most common
- Subtypes (WHO 2013):
  - Atypical lipomatous tumor/Well-differentiated liposarcoma
  - Myxoid liposarcoma
  - *round-cell liposarcoma*
  - dedifferentiated liposarcoma
  - Pleomorphic liposarcoma
- Well-differentiated liposarcoma and dedifferentiated: retroperitoneum
- Myxoid and pleomorphic liposarcomas: extremities
- Myxoid, dedifferentiated and pleomorphic: more aggressive
- Well-differentiated - unlikely to metastasize, treated with surgery

Liposarcoma

Well-differentiated/ Dedifferentiated Liposarcoma	• MDM2 and CDK4 amplification • Variable clinical course and chemo sensitivity
Myxoid/ Round Cell Liposarcoma	• FUS-CHOP translocation • Some P13K mutations • Peculiar pattern of metastases • Relatively sensitive to anthracyclines, alkylators and trabectedin
Pleomorphic Liposarcoma	• Frequent p53 mutation • Aggressive clinical course

Well-Differentiated or Dedifferentiated Liposarcoma

More than 90% of well-differentiated or dedifferentiated liposarcomas (WD/DDLS) have CDK4 amplification.

Phase 2 Trial of Palbociclib

	2/1 schedule	3/1 schedule
Sample size	30	60
PFS at 12 weeks	66%	57%
Median PFS	18 weeks	18 weeks
Response Rate	3%	2%
Grade 3/4 Anemia	17%	22%
Grade 3/4 Neutropenia	50%	36%
Grade 3/4 Thrombocytopenia	30%	7%

Dickson et al., J Clin Oncol 2013; JAMA Oncol 2016

Results of previous and current study in dedifferentiated liposarcoma

	palbociclib	palbociclib	abemaciclib
	14/21d schedule 200 mg OD	21/28d schedule 125 mg OD	Continuous 200 mg BID
Sample size	30	60	30
PFS at 12 weeks	66%	57%	76%
Median PFS	18 weeks	18 weeks	30 weeks
Response Rate	3%	2%	3%

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High grade Myxoid (formerly Round cell Liposarcoma)

- Myxoid/round cell with t(12;16) TLS-CHOP
  - 40% of liposarcomas
  - Younger patients (age 15-45)
  - Most chemotherapy sensitive liposarcoma subtype
    - Doxorubicin, ifosfamide
    - Trabectedin (ET-743) (Phase III)
    - Eribulin (Phase III)

Demetri GD, et. al. PNAS 1999;96: 3951-56; Debrock G, et. Al. Br J Cancer. 2003; 89:1409-12;Schoffski P et. al. Lancet Oncol 2011: 12:
Demetri GD et al. JCO 2015: 33: Abst 10503*; Schoffski P et al. JCO 2015: 33 Abstr LBA10502**

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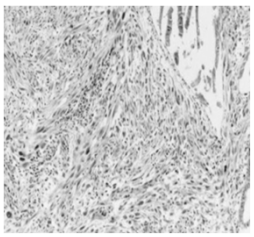
Leiomyosarcoma

- uLMS- may represent a distinct phenotype;
- Doxorubicin, DTIC, Gemcitabine or Gemcitabine-Docetaxel combinations useful
- Trabectedin (ET-743)
- Eribulin



Maki RG et al. J Clin Oncol. 2007; 25:2755; Hensley ML. Curr Opin Oncol. 2010; 22 (4): 356 - 61.
Demetri GD et al. JCO 2015: 33: Abst 10503*; Schoffski P et al. JCO 2015: 33 Abstr LBA10502**

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Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial

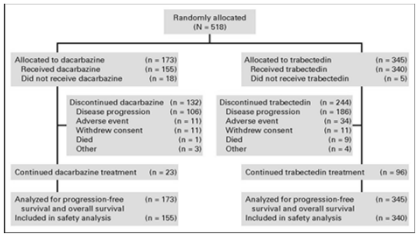

Fig 1. CONSORT diagram.

Published in: George D. Demetri; Margaret von Mehren; Robin L. Jones; Martee L. Hensley; Scott M. Schuetze; Arthur Staddon; Mohammed Milhem; Anthony Elias; Kristen Ganjoo; Hussein Tawbi; Brian A. Van Tine; Alexander Spira; Andrew Dean; Nushmia Z. Khokhar; Youn Choi Park; Roland E. Knoblauch; Trilok V. Parekh; Robert G. Maki; Shreyaskumar R. Patel; JCO **2016**, 34, 786-793.
DOI: 10.1200/JCO.2015.62.4734

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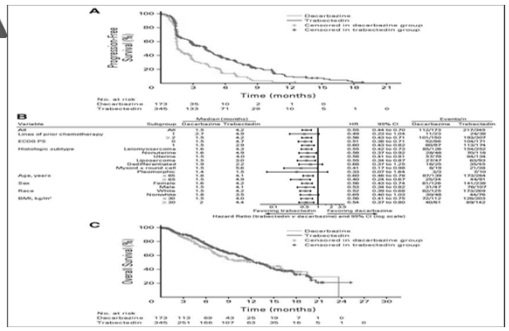

Fig 2. Kaplan-Meier estimates of progression-free survival, subgroup analyses, and overall survival at the interim analysis. (A) Progression-free survival; (B) subgroup analysis (hazard ratios [HRs] and 95% CIs) of progression-free survival; and (C) overall survival. HR was calculated as the hazard in the trabectedin treatment group divided by the hazard in the dacarbazine treatment group. BMI, body mass index.

JCO **2016**, 34, 786-793
DOI: 10.1200/JCO.2015.62.4734

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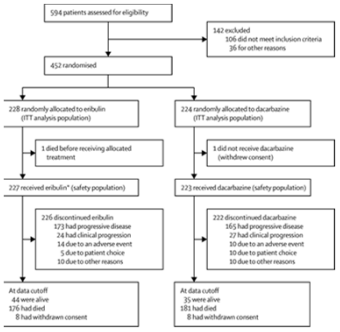
Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial



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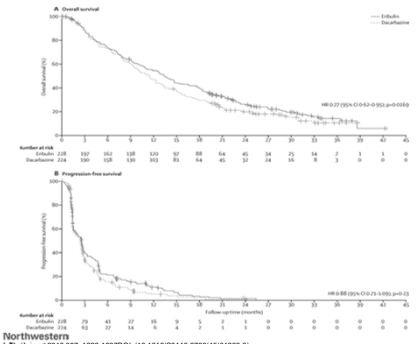
The Lancet Volume 387, Issue 10028, Pages 1629-1637 (April 2016)

Figure 2

OS and PFS

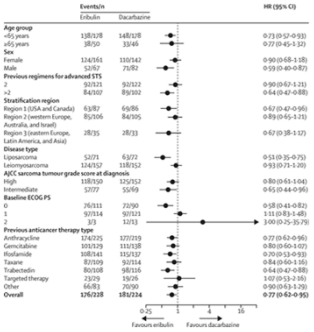


Northwestern Medicine

The Lancet 2016 387, 1629-1637DOI: (10.1016/S0140-6736(15)01283-0)

Figure 3

Subgroup Analysis



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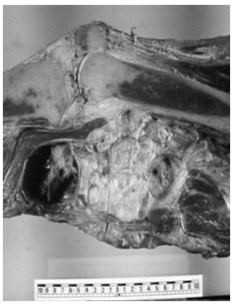
The Lancet 2016 387, 1629-1637DOI: (10.1016/S0140-6736(15)01283-0)

Synovial Sarcoma

- Named for resemblance to synovium
- Considered high-grade
- 2 types: monophasic and biphasic (spindle & epithelial)
- t(X;18) SYT-SSX1 (biphasic) or SYT-SSX2 (monophasic); ***> 90%***
- SSX1 / biphasic better prognosis than monophasic
- Among most sensitive 'adult' sarcoma to chemotherapy especially to ifosfamide regimens



Rosen, et. al. Cancer 1994; 73:2506-2511. Skubitz KM, D'Adamo DR. Mayo Clin Proc. 2007; 82:1409-1432; slides courtesy of R. Maki

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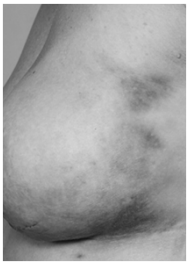
Angiosarcoma

- Uncommon subtype
- Typically on scalp, face and post radiation fields
- Associated with lymphedema, vinyl chloride
- Surgery followed by radiation (scalp/face)
- Taxanes (Docetaxel, Paclitaxel) and anthracyclines (Doxil®) have been used and effective
  - Sorafenib; Bevacizumab



Fury MG, et. al. Cancer J. 2005; 11(3): 241 – 7.; Glazebrook KN, et. al. AJR Am J Roent 2008;190 (2): 533-8; Maki R, et. al. J Clin Oncol. 2009; 27:3133.

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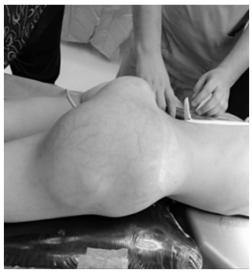
Desmoid Tumors

- "Benign" but locally aggressive tumors arising from fibroblasts.
- Resembles out of control scar tissue
- Arise in any anatomical location and infiltrate the mesentery, neurovascular structures, and visceral organs.
- There is no standard of care.



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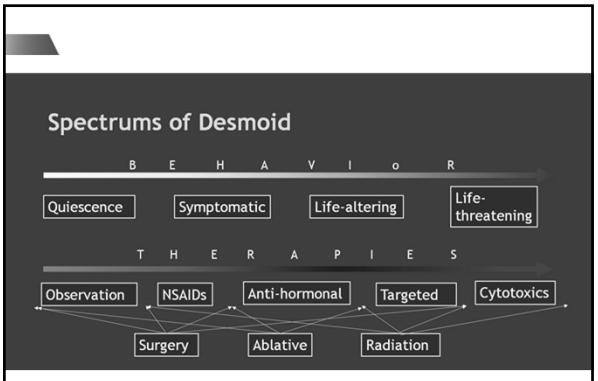

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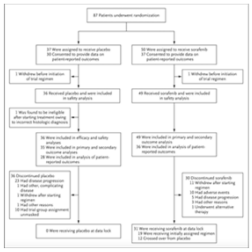
Sorafenib for Advanced and Refractory Desmoid Tumors

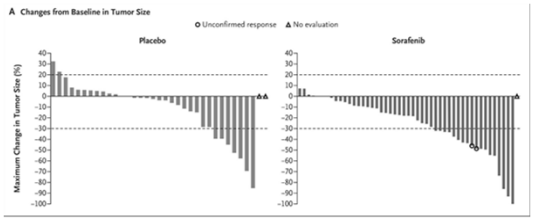
N Engl J Med 2018; 379:2417-2428 DOI: 10.1056/NEJMoa1805052

- double-blind,
- phase 3 trial
- 87 patients with progressive, symptomatic, or recurrent desmoid tumors received either sorafenib (400-mg tablet once daily) or matching placebo.
- Crossover to the sorafenib group was permitted for patients in the placebo group who had disease progression.
- The primary end point was investigator-assessed progression-free survival.
- rates of objective response and adverse events were also evaluated.



Northwestern Medicine

Sorafenib for Advanced and Refractory Desmoid Tumors



Among patients with progressive, refractory, or symptomatic desmoid tumors, sorafenib significantly prolonged progression-free survival and induced durable responses.

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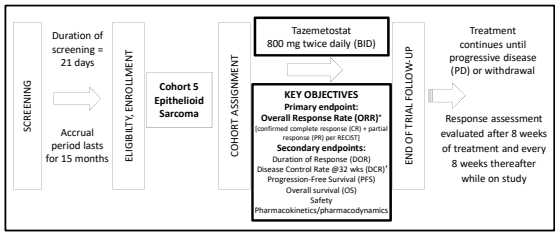
STUDY DESIGN

PHASE 2, OPEN-LABEL, MULTI-CENTER STUDY OF TAZEMETOSTAT



* Objective response: RECIST 1.1 confirmed complete response or partial response at week 24.
† Disease control: RECIST 1.1 confirmed complete.

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STUDY DESIGN

KEY ELIGIBILITY CRITERIA*

Inclusion†	Exclusion
Age ≥16 years	Prior exposure to tazemetostat or other inhibitor(s) of EZH2
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1	Prior malignancy other than the malignancies under study
Life expectancy >3 months	
Advanced disease	
INI1-negative ES by local pathology	
Has measurable disease based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1	

†Although 77% of patients in Stages 1 and 2 had documented disease progression within 6 months prior to study enrollment, disease progression was an inclusion requirement in the expansion phase.

* For a full list of study eligibility criteria, please see Clinicaltrials.gov. ECOG, Eastern Cooperative Oncology Group; ES, epithelioid sarcoma; EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; RECIST, response evaluation criteria in solid tumors.

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RESULTS

PRIMARY STUDY ENDPOINT: OBJECTIVE RESPONSE RATE (ORR) PER RECIST

Endpoint Category (RECIST), n (%)	No Prior Systemic Therapy (n=24)	Prior Systemic Anticancer Therapy (n=38)	Total (N=62)
ORR [CR+PR]¶ 95% CI	6 (25%) (9.8–46.7)	3 (8%) (1.7–21.4)	9 (15%) (6.9–25.8)
CR	0	0	0
PR	6 (25%)	3 (8%)	9 (15%)
SD	15 (63%)	20 (53%)	35 (56%)
PD	2 (8%)	11 (29%)	13 (21%)
Not evaluable	1 (4%)	4 (11%)	5 (8%)

¶ORR is the percentage of subjects achieving a confirmed CR or PR from the start of tazemetostat until PD or the start of subsequent anticancer therapy, whichever is earlier. CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors.

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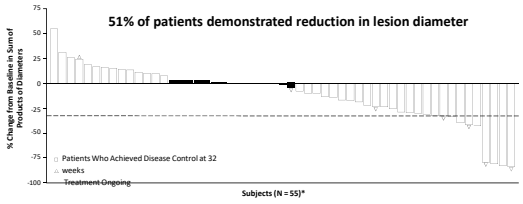
BEST PERCENT CHANGE IN SUM OF DIAMETERS PER INVESTIGATOR ASSESSMENT

RESULTS



* Post-baseline sum of diameters was not calculated for 7 subjects in the Intent-to-Treat population due to a lack of complete tumor diameter measurements at any post-baseline visit. These subjects were excluded from the figure.

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SUMMARY

SUMMARY

- FIRST PROSPECTIVE STUDY CONDUCTED IN EPITHELIOID SARCOMA
- TREATMENT WITH TAZEMETOSTAT, AN INVESTIGATIONAL, FIRST-IN-CLASS ORAL EZH2 INHIBITOR, ACHIEVED
  - AN ORR BY RECIST IN 15% OF ALL PATIENTS
  - A DECREASE IN TUMOR SIZE IN 51% OF ALL PATIENTS
  - DURABLE RESPONSES. AT A MEDIAN FOLLOW-UP OF 59.9 WEEKS, THE MEDIAN DOR WAS NOT REACHED
  - A MEDIAN PFS OF 23.7 WEEKS, WITH 21.3% PATIENTS PROGRESSION-FREE AT 1 YEAR.
  - A MEDIAN OS OF 82.4 WEEKS
- TAZEMETOSTAT WAS GENERALLY WELL TOLERATED WITH NO TREATMENT-RELATED DEATHS AND <2% DEFINITIVE DISCONTINUATIONS
- TAZEMETOSTAT, WAS APPROVED 1/23/2020 FOR ACCELERATED APPROVAL FOR THE TREATMENT OF PATIENTS WITH METASTATIC OR LOCALLY ADVANCED EPITHELIOID SARCOMA NOT ELIGIBLE FOR CURATIVE SURGERY

DOR, duration of response; ES, epithelioid sarcoma; EZH2, enhancer of zeste homolog 2; INI1, integrase interactor 1; ORR, objective response rate; PFS, progression-free survival; RECIST, response evaluation in solid tumors.

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Gastrointestinal stromal tumor (GIST)

- Exact incidence is unknown, estimated annual US incidence ~ 3000 - 6000 cases/ year *
- Median age 63 – 69 y/o
- Most common mesenchymal tumor of intestinal origin
  - Originates from interstitial cells of Cajal
- Symptoms variable, median size at diagnosis: 5 cm
- Stomach is most common site (60 – 70%) -> small intestine (20 – 30%)

Von Mehren M. NCCN Task Force Report: Gastrointestinal Stomal Tumors; *NCI data

Northwestern Medicine

Gastrointestinal stromal tumor (GIST)

- Surgery - mainstay of treatment
- Poor response to chemotherapy (< 5% response to doxorubicin)
- Commonly results from activating/gain-of-function mutations in the KIT (CD117)* or PDGFRA (Platelet derived growth factor alpha)

*Hirota S et al. Science. 1998 Jan 23;279(5350):577-80;

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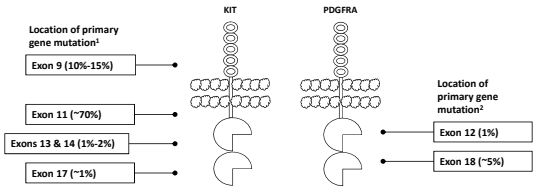
The Majority of GISTs Harbor Primary Mutations in *KIT* or *PDGFRA*[1]

While most primary mutations occur in exon 11 of *KIT* (70%), others may occur in *KIT* at exons 9, 13, 14, and 17 and in *PDGFRA* at exons 12 and 18[1]



KIT=KIT proto-oncogene receptor tyrosine kinase; PDGFRA=platelet-derived growth factor receptor a.
1. Oppelt PJ et al. *J Gastrointest Oncol*. 2017;8(3):466-473. 2. Corless CL et al. *Nat Rev Cancer*. 2011;11(12):865-878.

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Mutation Testing Can Reveal a Driver Mutation in GIST

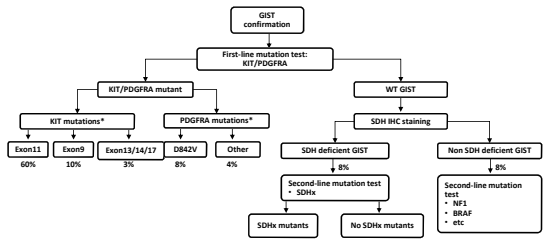

Image adapted from Wang Y et al. *Curr Cancer Drug Targets*. 2019.

*Percentages reflect primary mutations found in all GIST.
GIST=gastrointestinal stromal tumor; IHC=immunohistochemistry; KIT=KIT proto-oncogene receptor tyrosine kinase; NGS=next generation sequencing; PDGFRA=platelet-derived growth factor receptor a; SDHx=succinate dehydrogenase x; WT=wild-type.
Wang Y et al. *Current Cancer Drug Targets*. 2019;19(1):1-10.

Northwestern Medicine

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Phase III Trials of Imatinib in GIST

SWOG S0033/CALGB 150105

- N=746 patients
- Median PFS of 18 months on 400 mg vs 20 months on 800 mg imatinib.
- Median OS was 55 and 51 months, respectively.
- 22% alive at 10 years*
- After progression on 400 mg imatinib, 33% of patients who crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease.

EORTC 62005

- N=946 patients
- 263 (56%) of 473 patients on imatinib once daily had progressed compared with 235 (50%) of 473 on imatinib twice daily treatment
- Responses: CR: 52 (5%); PR: 442 (47%); SD: 300 (32%), no difference between groups.
- Median time to best response was 107 days.

Blanke C et al. J Clin Oncol 2008; 26:626-32; Veerweij et. al. Lancet 2004; 364:1127-134; *Demetri G et al. ASCO 2014: Abstr 10508.

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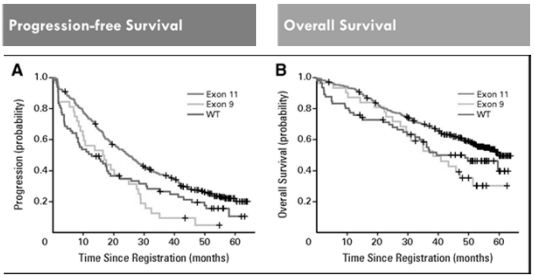
KIT Exon 11 predicts better survival with metastatic GIST patients on imatinib



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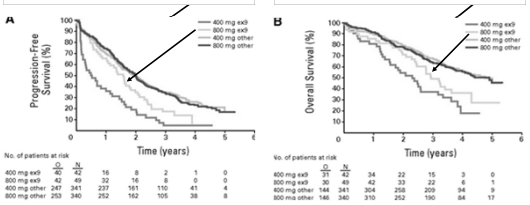
Heinrich MC et al. J Clin Oncol 2008; 21: 5360

MetaGIST Analysis: Predictive factors for the benefit of high-dose Imatinib therapy with regard to PFS and OS

Progression-free Survival

Overall Survival



Presence of *KIT* exon 9 mutation was the only significant predictive factor for the benefit of high-dose therapy

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Heinrich M, et. al. JCO Mar 1 2010: 1247-1253.

Use of Imatinib for KIT mutations

- Standard starting dose of 400 mg daily
- Increase to 800 mg can be considered as up to 30% response can be seen
- Start at 800 mg daily (may dose-escalate 4-8 wks)
  - KIT exon 9 mutations
  - Potentially delay the first occurrence of disease progression and increase objective response rate

Zalcberg JR et al. Eur J Cancer 2005;41:1751–1757.

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Resistance to Imatinib

- **Primary resistance** - progression during the first 6 months of imatinib
  - commonly seen with *KIT* exon 9, *PDGFRA* D842V -mutant or exon 18, or wild-type GIST
- **Secondary resistance** - > 6 months of imatinib or those with an initial response who then experience progression
- Mechanisms: secondary kinase mutations
  - Newly acquired kinase mutations (ATP Binding or Activation loop)
  - Genomic amplification of target receptor
  - Drug transporters

Benjamin RS et. al. Semin Oncol 2009;36:302–311; Antonescu CR et. al. Clin Cancer Res 2005;11:4182–4190.
Maleddu A. et. al. Oncol Rep 2009;21:1359–1366

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Efficacy of Sunitinib in Imatinib-resistant or intolerant patients

Efficacy parameter	Sunitinib (n=207)	Placebo (n=105)	p Value (log-rank test)	HR	95%CI
Median TTP [weeks (months)]	27.3 (6.4)	6.4 (1.5)	<0.0001	0.33	0.23 to 0.47
Median PFS [weeks (months)]	24.1 (5.6)	6.0 (1.4)	<0.0001	0.33	0.24 to 0.47
Partial response (%)	6.8	0			
Durable stable disease(%)	17.4	1.9			
Objective response rate (%)	7	0	0.006		

Demetri et. al. Lancet. 2006 Oct 14;368(9544):1329-38; Younous et. al. Curr Oncol. 2010 17: 4

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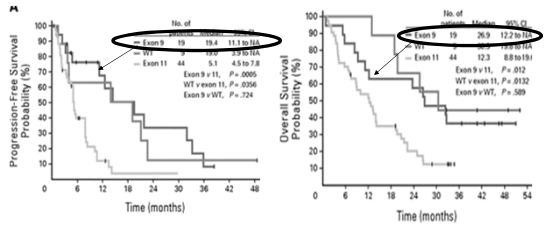
KIT Genotype and Efficacy of Sunitinib

Progression-Free Survival | **Overall Survival**



Opposite sensitivity pattern to imatinib: *KIT* exon 9 mutation and WT better

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Heinrich M C. et. al. J Clin Oncol 2008; 26: 5352 - 5359

Regorafenib in the GRID Study (GIST Regorafenib in Progressive Disease)

- Oral multikinase inhibitor
- 199 patients with metastatic or unresectable GIST with disease progression while on, or intolerance to, previous imatinib and sunitinib
- 2:1 randomization on regorafenib 160 mg daily vs placebo 3 out of 4 weeks cycle
- Cross-over to regorafenib allowed upon progression (85%).
- The primary endpoint was PFS

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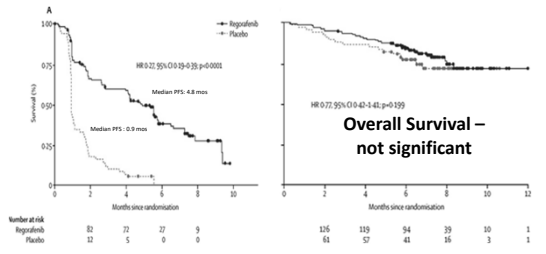
Demetri G et al. Lancet 2013; 81: 295 - 302

Regorafenib

Progression-Free Survival | **Overall Survival**



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Demetri G et al. Lancet 2013; 81: 295 - 302

Avapritinib

- Avapritinib is a kinase inhibitor indicated for the treatment of adults with unresectable or metastatic gastrointestinal stromal tumor (GIST) harboring a platelet-derived growth factor receptor alpha (PDGFRA) exon 18 mutation, including PDGFRA D842V mutations.[1]
- Avapritinib binds directly to the active conformation of PDGFRA and PDGFRA D842 mutants as well as multiple KIT exon 11, 11/17 and 17 mutants[1,2]
- In in vitro assays, avapritinib was shown to be a selective KIT/PDGFRA kinase inhibitor[1,2]
- Avapritinib demonstrated potent cellular in vitro activity on PDGFRA D842V mutants associated with resistance to approved kinase inhibitors[1]

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1. AYVAKIT Prescribing Information. Blueprint Medicines Corporation, Cambridge, MA. January 2020. 2. Data on file (DOF-REF-00206). Blueprint Medicines Corporation, Cambridge, MA. 2019.

Avapritinib in advanced PDGFRA D842V-mutant GIST(NAVIGATOR): a multicentre, open-label, phase 1 trial

- A multi-center, single-arm, open-label clinical trial where patients received avapritinib 300 mg or 400 mg orally once daily until disease progression or unacceptable toxicity
- **Eligibility:** Patients were required to have a confirmed diagnosis of GIST and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2

Endpoints:

- **Primary Endpoint:** Overall response rate (ORR) as defined by patients who achieved a complete response (CR) or partial response (PR)
- **Secondary Endpoint:** Duration of response (DOR)

https://doi.org/10.1016/S1470-2045(20)30269-2

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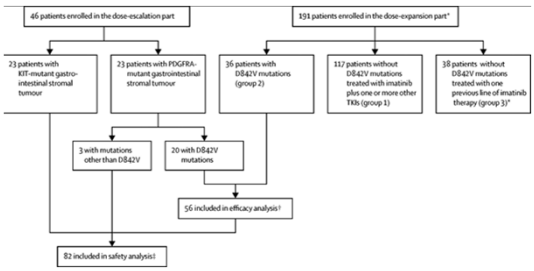
Patient disposition



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Best confirmed response by central assessment per mRECIST (version 1.1) in patients with PDGFRA D842V-mutant gastrointestinal stromal tumor

	All doses (n=56)	300 mg (n=28)
Complete response	5 (9%)	1 (4%)
Partial response	44 (79%)	25 (89%)
Overall response (partial plus complete response)	49 (88%; 95% CI 76–95)	26 (93%; 95% CI 77–99)
Stable disease	7 (13%)	2 (7%)
Clinical benefit (complete response or partial response plus stable disease lasting at least 16 weeks)	55 (98%; 95% CI 90–100)	28 (100%; 95% CI 88–100)
Progressive disease	0	0

mRECIST=Response Evaluation Criteria in Solid Tumors modified for patients with gastrointestinal stromal tumour.

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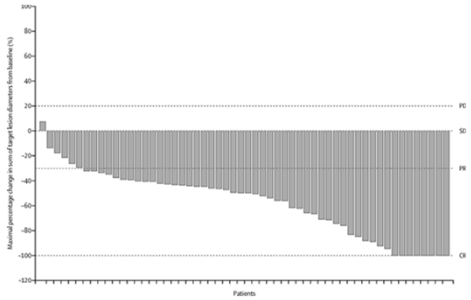
Maximal percentage change in sum of target lesion diameters from baseline in patients with PDGFRA D842V-mutant GIST



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Ripretinib

Ripretinib (DCC-2618) is a switch-control TKI that broadly inhibits KIT and PDGFRA kinase signalling through a dual mechanism of action.

Specifically and durably binds to both the switch pocket and the activation loop to lock the kinase in the inactive state, preventing downstream signaling and cell proliferation.

This dual mechanism of action provides broad inhibition of *KIT* and PDGFRA kinase activity, including for wild-type *KIT* and *PDGFRA* mutations and multiple primary and secondary mutations associated with drug-resistant gastrointestinal stromal tumors.

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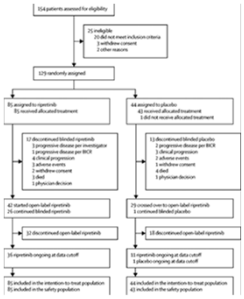
Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomized, placebo-controlled, phase 3 trial



https://doi.org/10.1016/S1470-2045(20)30168-6

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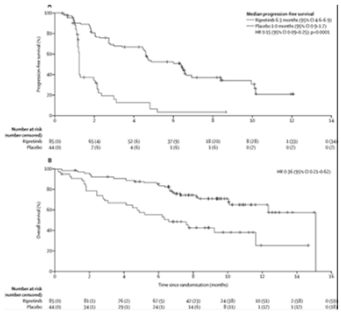
A: Median PFS
B: OS



Median overall survival was 15·1 months (95% CI 12·3–15·1) in the ripretinib group and 6·6 months (4·1–11·6) in the placebo group (HR 0·36, 95% CI 0·21–0·62

Northwestern Medicine

Ripretinib

Results from the INVICTUS study showed the efficacy and safety of ripretinib as fourth-line (or further-line) therapy in patients who have advanced GIST.

In May, 2020, the US FDA approved ripretinib for the treatment of adult patients with advanced GIST who have received previous treatment with three or more kinase inhibitors, including imatinib.

Ripretinib is being evaluated in an ongoing phase 3 study (INTRIGUE) in second-line treatment compared with sunitinib.

Northwestern Medicine

GIST: Current Treatment Approaches

- Surgery remains the only curative intervention in patients with primary, localized GIST (where avoiding tumor rupture is possible, and the associated risk of injury or death is acceptable)[1,2]
- Tumors often recur or metastasize[2]
- NCCN recommended systemic agents and regimens for unresectable or metastatic GIST are shown below:*[3]

1L Therapy for Unresectable, Recurrent, or Metastatic Disease	2L Therapy for Unresectable, or Metastatic Disease (PD after Imatinib)	3L Therapy for Unresectable, or Metastatic Disease (PD after Imatinib and Sunitinib)	4L Therapy for Unresectable, or Metastatic Disease (PD after Imatinib, Sunitinib, and Regorafenib)
Preferred: – Imatinib[A] (category 1) – Avapritinib[A,‡]	**Preferred:** – Sunitinib[A] (category 1)	**Preferred:** – Regorafenib[A] (category 1)	**Preferred:** – Ripretinib[A] **Useful Under Certain Circumstances:** – Sorafenib or Nilotinib or Dasatinib[A] or Pazopanib or Everolimus + TKI[E] or Avapritinib[A,‡]

1L, first-line; 2L, second-line; 3L, third-line; 4L, fourth-line; GIST, gastrointestinal stromal tumor; NCCN, National Comprehensive Cancer Network; PD, progressive disease.
*Category 2A recommendations unless otherwise noted. See Notes for NCCN alphabetical footnotes. ‡For GIST with *PDGFRa* exon 18 mutation including *PDGFRa* D842V mutations. ‡For patients with *PDGFRa* D842V mutation.
1. The ESMO/European Sarcoma Network Working Group. *Ann Oncol*. 2014;25(Suppl 3):iii102–iii112. 2. Wang CJ, et al. *World J Gastroenterol*. 2015;21:8398-8407. 3. NCCN Guidelines. Soft Tissue Sarcoma. Version 2.2020–May 28, 2020.

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Scandinavian Sarcoma Group 1979

Abstract #11503

AIO

Three versus one year of adjuvant imatinib for high-risk gastrointestinal stromal tumor (GIST): Survival analysis of a randomized trial after 10 years of follow-up

Heikki Joensuu, Mikael Eriksson, Kirsten Sundby Hall, Annette Reichardt, Barbara Hermes, Jochen Schütte, Silke Cameron, Peter Hohenberger, Philipp J Jost, Salah-Eddin Al-Batran, Lars H Lindner, Sebastian Bauer, Eva Wardelmann, Bengt Nilsson, Raija Kallio, Panu Jaakkola, Jouni Junnila, Thor Alvegård, Peter Reichardt

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Background

- Adjuvant imatinib improved recurrence-free survival (RFS) of GIST patients in 3 large randomized trials[1-3]
  - The target patient populations and the durations of adjuvant imatinib differed in these trials
- The Scandinavian Sarcoma Group XVIII/German (SSGXVIII/AIO) trial found 3 years of adjuvant imatinib to improve also overall survival (OS) when compared to 1 year of imatinib
  - The trial has been analyzed after median patient follow-up durations of 54 months[3] and 90 months[4]
  - In both analyses OS was longer in the 3-year group than in the 1-year group

[1]DeMatteo RP et al. Lancet 2009;373:1097-104
[2]Casali PG et al. J Clin Oncol 2015;33:4276-83
[3]Joensuu H et al. JAMA 2012;307:1265-72
[4]Joensuu H et al. J Clin Oncol 2016;34:244-50

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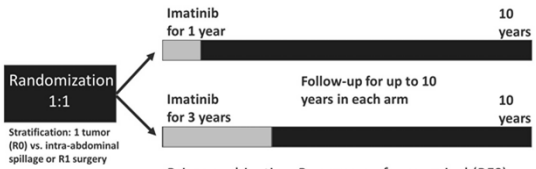
SSGXVIII/AIO design and objectives

- An open-label, multicenter, Phase III trial



- Primary objective: Recurrence-free survival (RFS)
- Secondary objectives include: Safety, overall survival

ClinicalTrials.gov identifier NCT00116935

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Key inclusion criteria

- Histologically confirmed KIT-positive GIST
- High risk of recurrence according to the modified Consensus Criteria[1,2]:
  - Tumor size >10 cm *or*
  - Tumor mitosis count >10/50 HPFs *or*
  - Size >5 cm and mitosis count >5/50 HPFs *or*
  - Tumor rupture spontaneously or at surgery

HPF = high-power field of the microscope

[1]Fletcher CD et al. Hum Pathol 2002; 33:459-65
[2]Joensuu H. Hum Pathol 2008;39:1411-9

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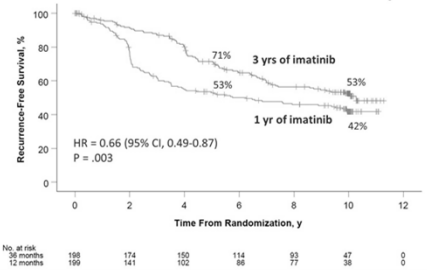
Recurrence-free survival in the Intention-To-Treat Population



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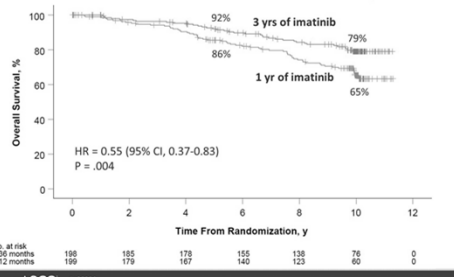
Overall survival in the Intention-To-Treat Population



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Conclusions

- Three years of adjuvant imatinib is superior in efficacy RFS and OS) as compared to 1 year of imatinib
- About 50% of deaths can be avoided during the first 10 years of follow-up after surgery with the longer adjuvant imatinib treatment

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Presented By Peter Reichardt at TBD

Bone Sarcomas

- Rare (2970 cases in the US in 2015 with 1640 deaths)
- Improvement in terms of limb-sparing procedures and survival with chemotherapy
- More common:
  - Osteosarcoma
  - Chondrosarcoma
  - Ewing Sarcoma

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Osteosarcoma

- Osteosarcoma: characterized by osteoid or immature bone
- Most common primary malignant bone tumor present in children and young adults
  - Bimodal peak: adolescents and older at 60 – 80 y/o associated with Paget's disease

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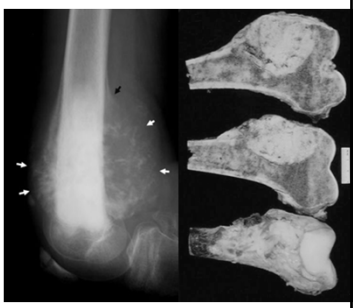
Bone Sarcomas - Osteosarcoma

- Most frequent in the femur, tibia and humerus (metaphysis of long bones)



Codman's triangle, sunburst

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Osteosarcoma Biology

- Associated with p53, Rb deletions
- 20% will present with metastatic disease
- 80% of metastasis will be in the lungs
  - Surgery for lung mets may provide remission
- Prognostic factors:
  - Poor: increased alkaline phosphatase or LDH
  - Good histopathologic response (>90% necrosis) to neoadjuvant chemotherapy predictive of survival

Bacci et. al. Eur J Cancer 2005;41:2079

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Osteosarcoma: Treatment

- Surgery for local control: Wide excision
  - Radiation not often effective
- Chemotherapy is mandatory and a standard of care in the therapy of bone osteosarcoma
  - Chemotherapy effective in either neo-adjuvant or adjuvant setting
- Doxorubicin and cisplatin as neoadjuvant therapy without high dose methotrexate appears to be as useful as a more complex regimen for overall survival: standard of care for adults

Link et al. NEJM 1986; 314:1600.;
Goorin A et al. J Clin Onc 2003; 21:1574
Souhami RL et. al. Lancet 1997; 350: 911
Ferrari S, et. al. JCO 2012; 30:2112–2118

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Osteosarcoma

- Adjuvant chemotherapy shown to decrease recurrence from 80% to 30%
- Standard of care is still doxorubicin + cisplatin +/- methotrexate for adjuvant therapy

Sutow WW, et. al. Cancer 1975; 36: 1598 – 1602;
Link MP, et. Al. NEJM 1986; 314: 1600

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Osteosarcoma MAP Regimen

Weeks	Agents	Dose	Days
Induction MAP (weeks 1 through 10)			
1, 6	Doxorubicin	37.5 mg/m^2 per day by continuous IV infusion or IV push	1 and 2
	Cisplatin	60 mg/m^2 per day IV over four hours	
4, 5, 9, 10	High-dose methotrexate	12 grams/m^2 IV over four hours*	1
	Leucovorin rescue	15 mg (approximately 10 mg/m^2) every six hours IV or orally for 10 doses¶	Starting 24 hours after beginning high-dose methotrexate
Surgery (week 11)			
11	Resection or amputation		
Postoperative MAP (weeks 12 through 29)			
12, 17	Doxorubicin$^{\Delta}$	37.5 mg/m^2 per day by continuous IV infusion or IV push	1 and 2
	Cisplatin	60 mg/m^2 per day IV over four hours	
22, 26	Doxorubicin$^{\Delta}$	37.5 mg/m^2 per day IV over 24 hours	
15, 16, 20, 21, 24, 25, 28, 29	High-dose methotrexate	12 grams/m^2 IV over four hours	1
	Leucovorin rescue	15 mg (approximately 10	Starting 24 hours after

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Bone Sarcomas - Chondrosarcoma

- Chondrosarcomas: commonly arise in benign cartilage abnormality
- 2nd most common tumor of the bone
- More common in older adults
- Typically in the pelvis, femur, knee, shoulder
- Grade, size and tumor location prognostic
- Rx: surgical resection
  - Consider palliative resection even in advanced disease
- Chemotherapy: little role*
- Unresectable: treated with RT

*Dedifferentiated: Treat like osteosarcoma; Mesenchymal: Treat like Ewing's

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Bone Sarcomas – Ewing Sarcoma

- Small, round-cell neoplasms: Ewing sarcoma, primitive neuroectodermal tumor (PNET), PNET of bone, extraosseous Ewing sarcoma
- EWS gene on chromosome 22q12 fuses with various members of the ETS family (FLI1, ERG, ETV1, ETV4, FEV)
- EWS-FLI1 fusion transcript from translocation t(11;22)(q24;q12) – 85% of Ewings sarcoma*

*PNET (removed in the WHO 2013 classification as synonym for Ewings)

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Bone Sarcomas – Ewing Sarcoma

- Adolescents and young adults
- May affect soft tissues or bone
- Most common sites are: femur, pelvis, chest wall
- Diaphysis is most frequent affected site: mottling; onion skin periosteal reaction
- Favorable prognosticators: distal site, normal LDH, no metastasis at presentation

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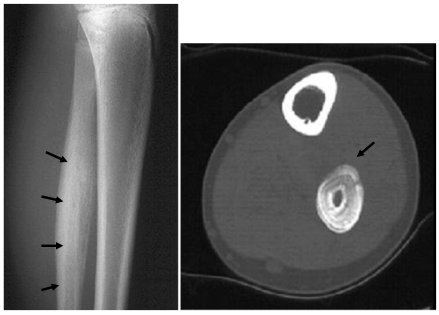
Ewing Sarcoma (Bone)



Infiltrative changes Onion-skinning

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Ewing Sarcoma

- Treatment consists of systemic therapy and local control therapy
- Primary treatment – Neoadjuvant multiagent chemotherapy for 12 – 24 weeks
- Local treatment: surgical wide excision +/- pre-operative RT, definitive chemoRT
- Adjuvant chemotherapy for 28 – 49 weeks

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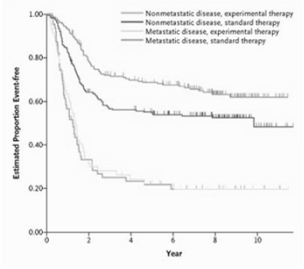
Ewing Sarcoma Adjuvant Study (IESS-III 1988 – 1992)

- 518 pts (398 pts without metastases) randomized
- Age < 30
- VAC +/- I/E arms
- OS 72% vs 61% in favor of 5 drugs
- Standard of care for non-metastatic disease
- I/E did not improve survival when given in this fashion for metastatic disease



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Grier HE et al. NEJM 2003; 348:694

Chemotherapy Protocol for Ewing Sarcoma

Drug	Dose	Regimen	
		VDCA	VDCA/IE
Vincristine	2 mg/m^2 (max 2 mg), day 1	Cycles 1-17	Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17
Doxorubicin	75 mg/m^2, day 1	Cycles 1-9*	Cycles 1, 3, 5, 7, 9
Cyclophosphamide plus mesna	1200 mg/m^2, day 1	Cycles 1-17	Cycles 1, 3, 5, 7, 9, 11, 13, 15, 17
Dactinomycin	1.25 mg/m^2, day 1*	Cycles 6-17*	Cycles 11, 13, 15, 17
Ifosfamide plus mesna	1800 mg/m^2 daily, days 1-5	-	Cycles 2, 4, 6, 8, 10, 12, 14, 16
Etoposide	100 mg/m^2 daily, days 1-5	-	Cycles 2, 4, 6, 8, 10, 12, 14, 16

Courses administered every 21 days for 17 courses.
* Substitute dactinomycin for doxorubicin when cumulative doxorubicin dose is 375 mg/m^2.

Grier H, et al. N Engl J Med 2003; 348:694.

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Conclusions: Bone sarcomas

- Each bone sarcoma has a characteristic radiographic appearance
- Chemotherapy essentially mandatory for osteogenic sarcoma and Ewing sarcoma, in addition to surgery (and XRT for Ewing sarcoma) - cure rate improved
- Conventional chondrosarcomas are treated surgically as a standard of care

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Giant cell tumor of bone (GCTB)

- Priamry osteolytic bone tumor with substantial skeletal morbidity.
- Symptoms include:
  - Localized tenderness swelling
  - Reduced joint mobility
  - Pain that is often severe and intractable
- Surgery, the definitive therapy for GCT, is often associated with significant morbidity
- GCTB contains osteoclast-like giant cells and precursors that express RANK and mononuclear cells that express RANKL, which mediates osteoclast activation.
- RANK and RANKL are involved in the pathophysiology of GCTB

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Giant cell tumor of bone (GCTB)

- In the United States, GCTB accounts for approximately 3 to 5 percent of all primary bone tumors and 15 to 20 percent of all benign bone tumors.
- In approximately 2 to 3 percent of cases of extremity giant cell tumors, metastases develop, most frequently to the lungs.
- In rare cases, true spontaneous malignant transformation of GCTB is reported.
- For patients with potentially resectable GCTB for whom initial surgery would be associated with unacceptable functional compromise or significant morbidity, treatment with denosumab rather than initial resection is a reasonable approach.

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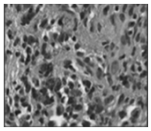
Tenosynovial Giant Cell Tumor (Pigmented Villonodular Synovitis)

- Vascular, proliferative, inflammatory synovium
  - Multinucleated giant cells, macrophages, and hemosiderin
- Localized or diffuse-type growth pattern
- Intra- or extra articular locations
- Translocations (1p13)/alterations involving CSF1
- ↑ CSF1 expression → macrophage recruitment to tumor site → CSF1/CSF1R autocrine/ paracrine loop of neoplastic/ non-neoplastic cells



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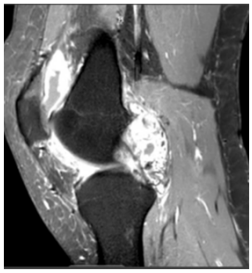
Tenosynovial Giant Cell Tumor Therapies

- Localized
  - Surgical- subtotal/ total resection, synovectomy to arthroplasty
  - Radiation/ radio-synovectomy
- Systemic → anti-CSF1R therapies



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Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial

William D Tap, Hans Gelderblom, Emanuela Palmerini, Jayesh Desai, Sebastian Bauer, Jean-Yves Blay, Thierry Alcindor, Kristen Ganjoo, Javier Martin-Broto, Christopher W Ryan, David M Thomas, Charles Peterfy, John H Healey, Michiel van de Sande, Heather L Gelhorn, Dale E Shuster, Qiang Wang, Antoine Yver, Henry H Hsu, Paul S Lin, Sandra Tong-Starksen, Silvia Stacchiotti, Andrew J Wagner*, on behalf of the ENLIVEN investigators†*

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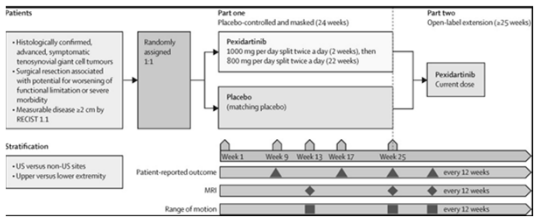
Study Design



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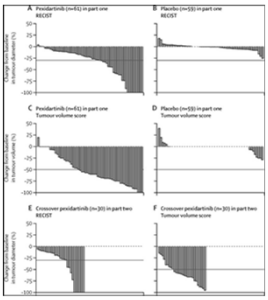
Maximum change in tumor size according to RECIST and tumor volume score



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Adverse Reactions

WARNING: HEPATOTOXICITY
- **TURALIO can cause serious and potentially fatal liver injury.**
- **Monitor liver tests prior to initiation of TURALIO and at specified intervals during treatment. Withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity.**
- **TURALIO is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program.**

- Serious ARs were reported in 13% leading to permanent discontinuation- the most frequent ARs included increased ALT (4.9%), increased AST (4.9%), and hepatotoxicity (3.3%).
- Dose reductions or interruptions occurred in 38% of patients 2ndary to increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%).

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- On August 2, 2019, the FDA approved pexidartinib capsules for adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery.
- Pexidartinib is the first systemic therapy approved for patients with TGCT.
- The approval was based on durable ORR.
- After 25 weeks of treatment, the ORR was 38% (95% confidence interval: 27, 50), with a 15% complete response rate and a 23% partial response rate.
- No patients receiving placebo had a response (p<0.0001).
- 22 of 23 patients who responded and had been followed for a minimum of 6 months after the initial response maintained the response for ≥6 months.

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