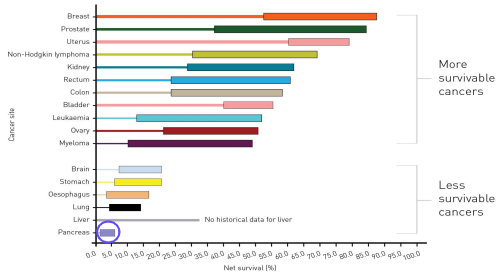
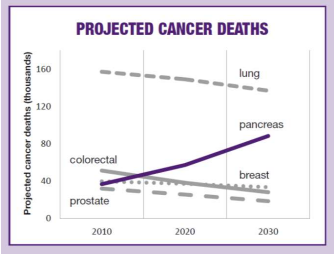
Pancreatic Cancer: A Dismal Prognosis

- 3rd leading cause of cancer death in the US
- The worst survival of any solid tumor
- Only ~10% of all PC patients are cured
- In 2021 it is estimated that there will be:
  - 60,430 new cases
  - 48,220 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 United States



Who Gets Pancreatic Cancer?

Incidence by gender in 2021:
- 31,950 men
- 28,480 women

Deaths by gender in 2021:
- 25,270 men
- 22,950 women

Age:
- Most patients are between 65 and 80 at diagnosis

Race:
- African-Americans are more likely to develop PC than Caucasians

Risk Factors for Pancreatic Cancer

Tobacco smoking
- >30% of PC are due to smoking

Pancreatitis (5%)
- 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[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

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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

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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

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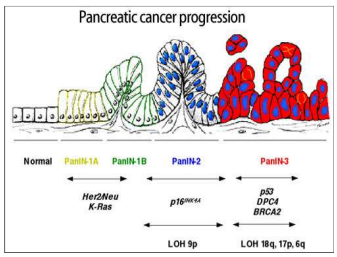
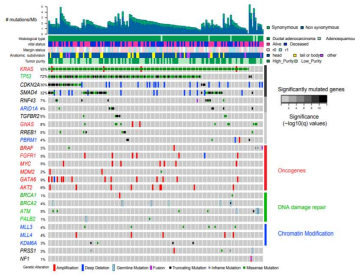
- In pancreatic cancer, as in colorectal cancer, the accumulation of genetic mutations is linked to specific stages of cancer development
- Pancreatic cancer arises from pancreatic ductal epithelial cells via a series of precursor lesions known as Pancreatic Intraepithelial Neoplasias (PanIN 1-3)



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 patients referred

1082 received a report

282 (26%) had actionable mutations

189 had outcome measurements

46 received a matched therapy

143 received a non-matched therapy

	#	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

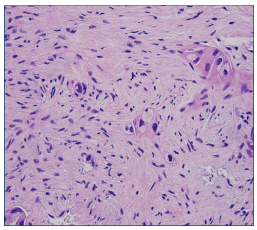
Actionable mutations with matched therapies in KYT			
AKT1	ALK	ATM	BRAF
BRCA1	BRCA2	CDK4	HER2
IDH1	MSI-H	NTRK1	PALB2
RET	ROS1	STK11	

Pishvaian, *Lancet Oncol* 2020

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

GW 13

Clinical Presentation

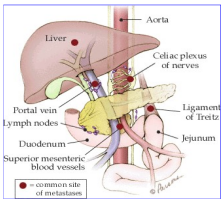
- Pain
- Jaundice
- Weight Loss
- Anorexia
- Depression
- Nausea/vomiting
- Thrombophlebitis
- Pruritus
- Fatigue
- New onset diabetes

GW 14

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

GW

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 months
- Metallic stents: remain patent for ≥ 6 months
- Preferred stent:
  - Metal: if life expectancy ≥ 6 months
  - Plastic or short metal: if surgery is anticipated
- In a patient 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

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

GW 19

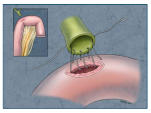
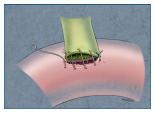
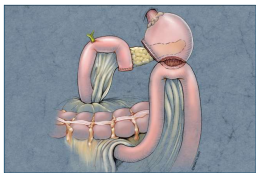
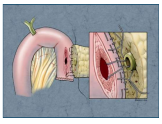
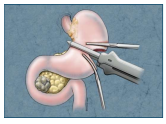
Real World Staging

- Resectable
- Borderline resectable
- Locally advanced, unresectable
- Metastatic

- Location
  - Head: 80% (more likely to be resectable)
  - Other: 20%

GW 20

"Whipple procedure": Pancreatico-duodenectomy

Surgery for Pancreatic Cancer

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

GW 22

The Surgeon Really 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%

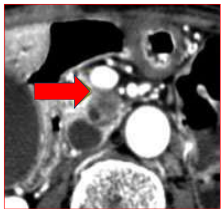
GW 23

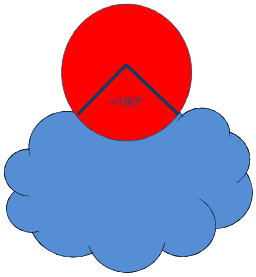
Criteria for Resectability

- 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

GW 24

Resectable



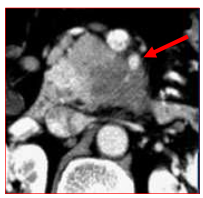


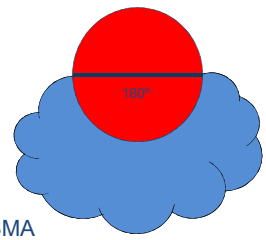
Tumor abuts SMV <180°, not SMA

Borderline Resectable Pancreatic Cancer

- 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



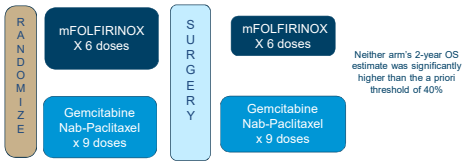


Tumor partially encases SMA

Rationale for Neo-adjuvant Chemotherapy for Resectable and Borderline Resectable PC

- 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: Randomized phase II trial of perioperative mFOLFIRINOX vs. Gemcitabine/nab-Paclitaxel in resectable PC



Neither arm's 2-year OS estimate was significantly higher than the a priori threshold of 40%

Arm	N	2-yr OS	Median OS	Median DFS after resection
mFOLFIRINOX	55	47%	23.2 months	10.9 months
Gem-nab-P	47	48%	23.6 months	14.2 months

Sohal, *JAMA Onco*l 2021

PREOPANC: Phase III trial of immediate surgery vs. pre-operative gemcitabine/RT in resectable and borderline resectable pancreatic cancer

	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

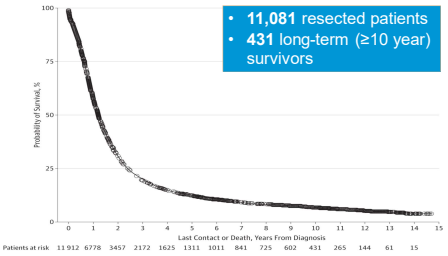
ESPAC-5F: Randomized phase II trial of immediate surgery, neoadjuvant GEMCAP, FOLFIRINOX or chemoRT in borderline resectable PC

	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*

GW 31

Even after "curative" resection, survival is limited



- **11,081** resected patients
- **431** long-term (≥10 year) survivors

Paniccia, *JAMA Surgery 2015*

GW 32

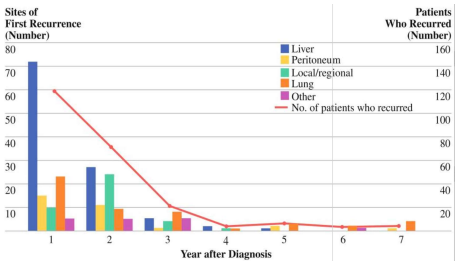
Predictors of long-term survival in resected pancreatic cancer, listed in order of importance

		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*

GW 33

Patterns of Recurrence after Resection



Katz, *Ann Surg Oncol* 2009

CONKO-001

Resected pancreatic cancer
N=368

Gemcitabine for 6 months

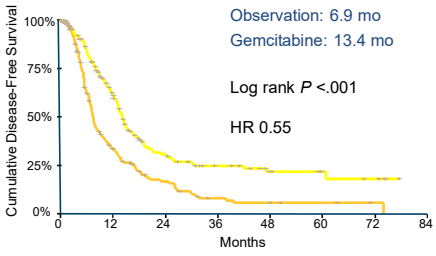
Observation for 6 months

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



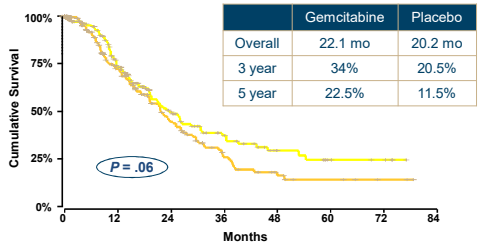
Observation: 6.9 mo
Gemcitabine: 13.4 mo

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

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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

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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

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Adjuvant data from ESPAC Trials

	# Patients	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 had equivalent efficacy, but gemcitabine was less toxic

ESPAC-4

730 patients

Gemcitabine 1000 mg/m^2
Days 1, 8, 15
x 6 cycles

Gemcitabine 1000 mg/m^2
Days 1, 8, 15
Capecitabine 1660 mg/m^2/day
Days 1-21 Q28 days
x 6 cycles

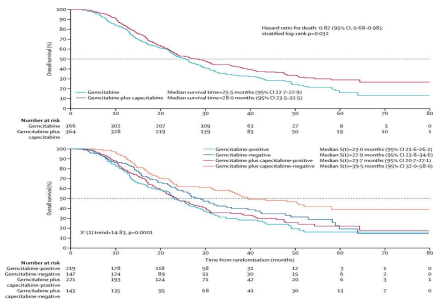
Primary endpoint: Overall survival

Neoptolemos, *Lancet* 2017

ESPAC-4: OS

Overall survival by treatment group

Overall survival by margin status and treatment group



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%	

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ESPAC-4: Predictors of survival on multivariate analysis

		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

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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 months, 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 months, HR 0.86
- **Author's conclusions: ESPAC-4 supports adjuvant gemcitabine-capecitabine as a new standard of care**

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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

GW 46

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

GW 47

PRODIGE 24: Efficacy

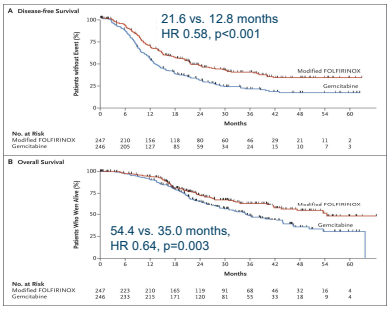
	mFFX	G	HR	P
Relative dose intensity >70%	48.7%	91.4%		<0.001
Median disease-free survival	**21.6** months	**12.8** months	**0.58** 95% CI: 0.46-0.73	<0.0001
3-year disease-free survival	39.7%	21.4%		
Metastasis free survival	30.4 months	17.7 months	0.59 95% CI: 0.46-0.75	<0.0001
Overall survival	**54.4** months	**35.0** months	**0.64** 95% CI: 0.48-0.86	<0.003
3-year overall survival	63.4%	48.6%		

GW 48

PRODIGE 24

Disease-free survival

Overall survival



Prognostic factors for disease-free survival on multivariate analysis in 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 Gemcitabine, 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

52

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

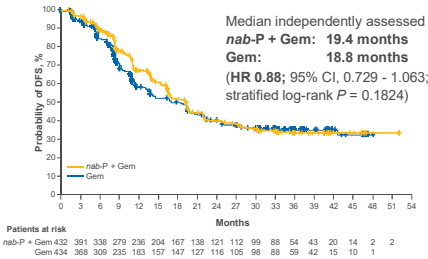
Primary endpoint:
Independently-assessed
Disease-free survival

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

53

APACT Primary endpoint: Independently assessed DFS (ITT population)



Median independently assessed DFS
***nab*-P + Gem: 19.4 months**
Gem: 18.8 months
(**HR 0.88;** 95% CI, 0.729 - 1.063;
stratified log-rank *P* = 0.1824)

54

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

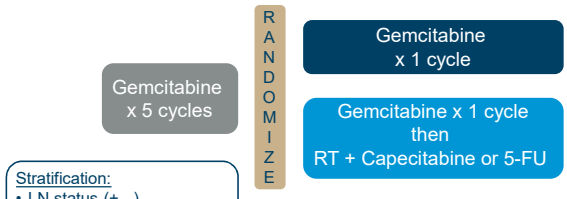
- **This was a negative trial which did not meet its DFS primary endpoint**
  - Target HR of 0.73 was not achieved via either independent or investigator-assessed DFS
- OS data is immature, correlative studies are pending
- This trial demonstrates the importance of performing a randomized trial rather 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

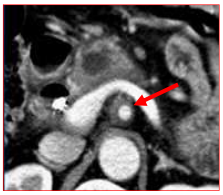
RTOG 0848

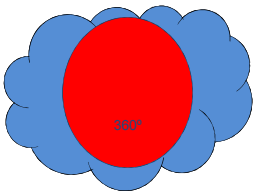


Summary: Adjuvant Therapy for PC

- 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

GW 61

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**

GW 62

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

GW 63

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

Investigator's 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

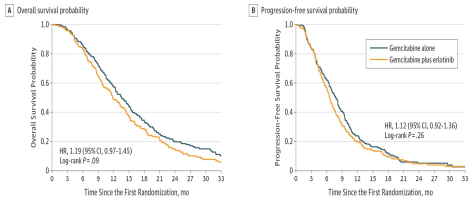
- Gemcitabine x 4 months
- Gemcitabine + Erlotinib x 4 months

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

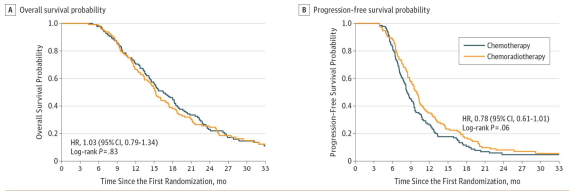
Futility boundary for 1^0 hypothesis crossed after 442 pts randomized

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

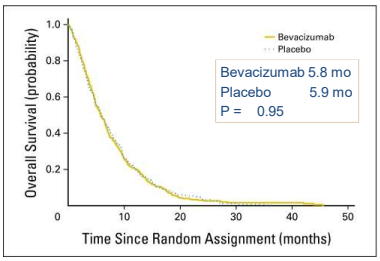
In LAPC patients whose tumor is controlled after 4 months of gemcitabine induction:

- CRT does not increase OS compared with chemotherapy
  - 15.2 vs. 16.5 months
- The increased PFS with CRT (9.9 vs. 8.4 months) 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



GW 70

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

GW 71

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 g*BRCA*m PC

GW 72

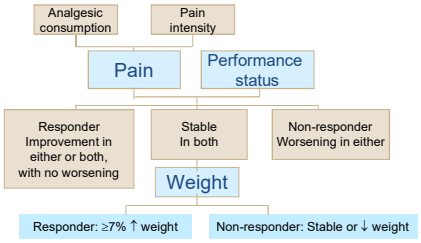
Gemcitabine has a genuine, but modest impact on survival and QOL

	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

GW 73

We administer gemcitabine principally because it produces "clinical benefit"



GW

It was 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

GW 75

The NCIC PA3 trial demonstrated a modest improvement in survival for gemcitabine + erlotinib

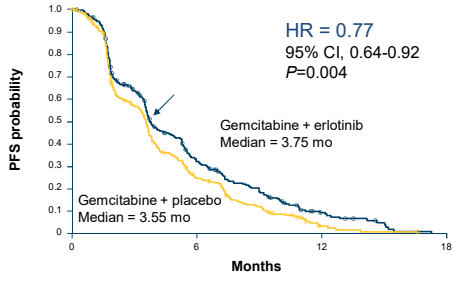
569 patients

- Gemcitabine + Erlotinib: 100 or 150 mg po qd
- Gemcitabine + Placebo

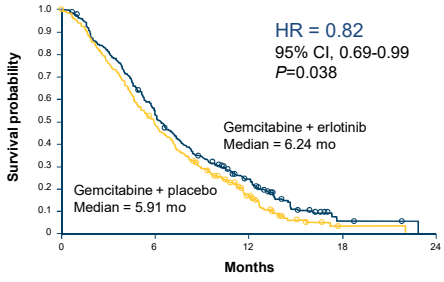
Statistics: 80% power to detect a 33% ↑ survival, α=0.05

Moore, JCO 2007

Progression-Free Survival



Overall Survival



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				

GW 79

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

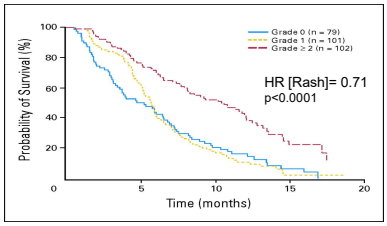
- Rare (<4%)

Molecular subset analysis of PA3 trial

- KRAS status did not predict a survival benefit for gemcitabine + erlotinib

da Cunha Santos, *Cancer* 2010

GW 80



	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%

Severity of rash correlates with survival

GW 81

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

Van Cutsem, 2012

82

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 and toxicity?

Who is the best patient for this regimen?

83

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

84

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

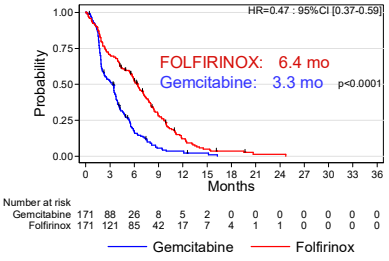
- FOLFIRINOX — Primary endpoint: OS
- Gemcitabine

Stratification:
- Center
- PS: 0 vs. 1
- 1^0 tumor location: head vs. other

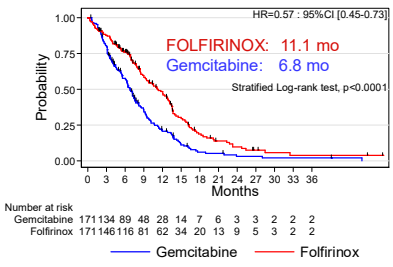
Statistics: 80% power to detect an ↑ in median OS from 7 to 10 mo (HR 0.70, α= 0.05)

Conroy, *ASCO* 2010, *NEJM* 2011

Progression-free Survival



Overall Survival



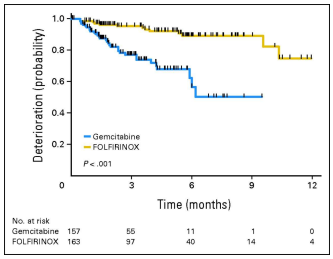
FOLFIRINOX vs. Gemcitabine Efficacy

	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 (months)	11.1	6.8	0.57	<0.0001
1-year survival	48.4%	20.6%		
18-month survival	18.6%	6%		
PFS (months)	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

91

The MPACT Trial

861 patients

- Stage IV
- No prior treatment for metastatic disease
- KPS ≥ 70
- Measurable disease
- Total bilirubin ≤ ULN

Primary endpoint:
Overall survival

151 sites
enrolled 861 patients
on 3 continents
over 3 years

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

- 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

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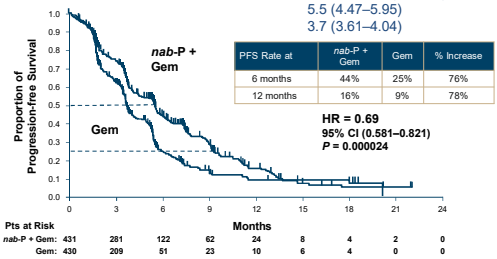
Progression-free Survival

Median PFS, months (95% CI)
5.5 (4.47–5.95)
3.7 (3.61–4.04)

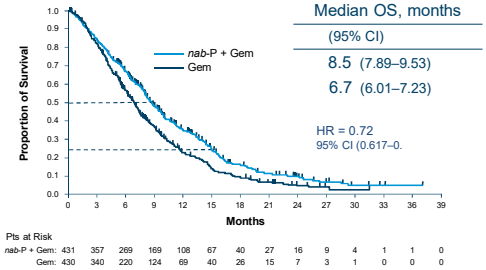


PFS Rate at	*nab*-P + Gem	Gem	% Increase
6 months	44%	25%	76%
12 months	16%	9%	78%

HR = 0.69
95% CI (0.581–0.821)
***P* = 0.000024**

93

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 Gemcitabine 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

FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine: How do these regimens compare?

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%		

FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine: How do these regimens compare?

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%

FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine: How do these regimens compare?

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

FOLFIRINOX vs. *nab*-Paclitaxel-Gemcitabine: How do these regimens compare?

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

Standard-of-care FOLFIRINOX or gemcitabine + nab-paclitaxel
Median PFS ~6 months
Median OS 8–12 months

<50% of patients receive 2nd-line treatment

No targeted treatments for a biomarker-selected population validated by Phase III trial

4–7% harbor a germline *BRCA1* and/or *BRCA2* mutation (gBRCAm) → Increased benefit from platinum-based chemotherapy → Maintenance treatments aim to delay disease progression following chemotherapy without compromising health-related quality of life (HRQoL)

Golan, *NEJM* 2019

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POLO Study Design

Screen for gBRCAm

- Metastatic pancreatic cancer
- Deleterious germline BRCA1 or BRCA2 mutation
- ≥ 16 weeks of first-line platinum-based chemotherapy, with no limit to duration, without progression (CR, PR, SD)

RANDOMIZE

3:2

N=145

Olaparib
tablets
300 mg po bid

Placebo

Primary endpoint:
PFS by blinded independent central review

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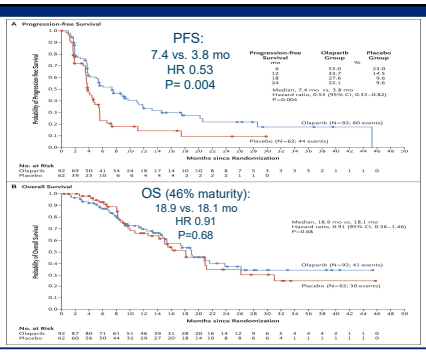
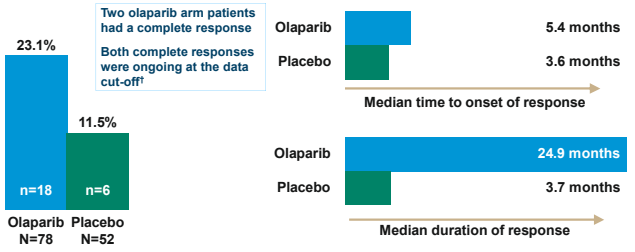
POLO: PFS and OS



Golan, *NEJM* 2019

105

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 *gBRCA*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 gBRCAm testing in this setting
- Maintenance olaparib was FDA-approved for *gBRCA*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 pancreatic cancer, 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

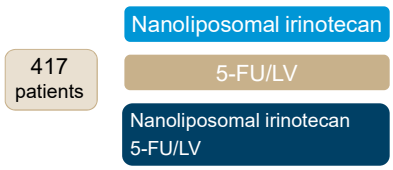
Second-line treatment options in PC

Depending on the front-line regimen, options include:

- Gemcitabine
- Gemcitabine-nab-paclitaxel
- FOLFOX, FOLFIRI
- FOLFIRINOX
- 5-FU/LV-nanoliposomal irinotecan

GW 109

Nanoliposomal irinotecan in PC patients previously-treated with gemcitabine: NAPOLI-1



Wang-Gillam, *Lancet* 2016

GW 110

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		

GW 111

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

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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)

113

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

114

Supportive care: Celiac Plexus Neurolysis (CPN)

3 equivalent approaches:
- Percutaneous
- Endoscopic
- Surgical

In a 98 patient 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

GW 115

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

GW 116

Many symptoms affect the nutritional status of pancreatic cancer 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 patients
- Small bowel obstruction
- Ascites
- Pancreatic endocrine insufficiency
  - >50% of PC patients are diagnosed with DM or impaired glucose tolerance in the preceding 24 months

Wiebe, Oncology 2009

GW 117

Pancreatic Exocrine Insufficiency:
A poorly recognized cause of malnutrition in PC patients

- 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

GW 118

Pancreatic Exocrine Insufficiency: Management

- Empiric pancreatic enzyme replacement:
  - Start with 40-50K IU lipase per meal, half that with snacks
  - Low fat diet is not necessary
    - Results in insufficient intake of fat soluble vitamins
- Gastric acid inactivates lipase:
  - Don't take on an empty stomach
    - Take with, not before meals!
  - Use with PPI or H2 blockade

Wiebe, ASCO Ed Book 2012; Dominguez-Munoz, Gastroenterol & Hepatol 2011

GW 119

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

GW 120