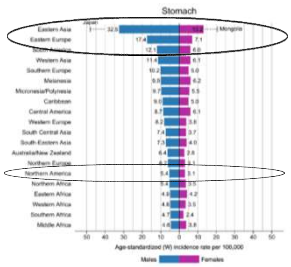
Disclosure

Consulting

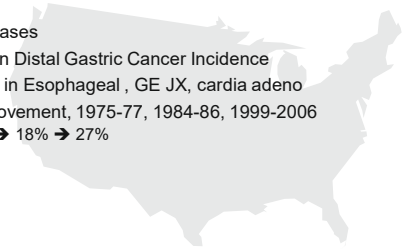
- AMGEN
- Bayer
- Lilly
- Pieris
- Roche Genentech
- Astra Zeneca
- Bristol Myers Squibb
- Astellas
- Merck
- Taiho

Gastric Cancer: Global Incidence: 2021



- 5th leading cause of cancer
- 3rd leading cause of cancer related death
- Uncommon in the U.S. and Europe
- +Esophageal, 2nd leading cause of cancer death

Gastric Carcinoma US Incidence in 2021



- 26,560 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%

Gastric and Esophageal Cancer: AJCC 7th Edition Staging

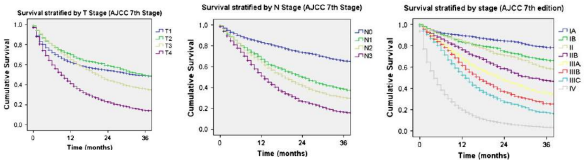
Gastric

- 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

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Genetic 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
- Mutations in CTNNA1

Hopkins *Nature* 392: 402; 1998
Huntsman *NEJM* 344: 1904; 2001

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Genetic 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

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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

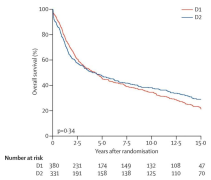
U.S. National Database: Gastric Cancer Surgical Outcome: 1985-1996

- **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

- **Pre and post op chemo**
  - ECF, MAGIC
  - **FLOT, superior to ECF**
- **Post op chemo** (Asia): D2 resection
  - S-1 x 1 year, ACTS-GC Japan
  - Cape-Oxali x 6 months , CLASSIC Korea (NCCN)
  - S-1 + Oxali x 6 months > S1 in node + disease, no benefit for RT, ARTIST 2
  - S-1 + Docetaxel > S-1 Stage III, JACCRO GC-07 Japan
- **Post op RT + chemo** (U.S.), less than a D1-2 resection
  - 5FU-LV + RT, INT 116

Macdonald NEJM 345:725; 2001 Cunningham *NEJM* 355: 11; 2006 Sasako *JCO* 29: 4387; 2011; Noh *Lancet Oncol* 15: 1389; 2014

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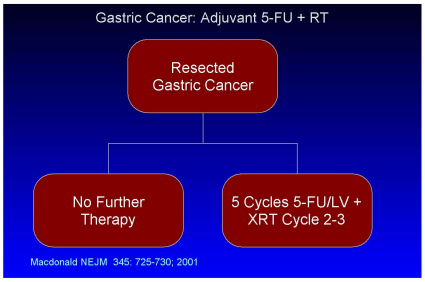
US Intergroup 116 (SWOG 9008)



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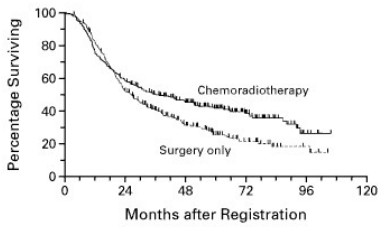
Overall Survival: INT 116



Macdonald *NEJM* 345: 725-730; 2001

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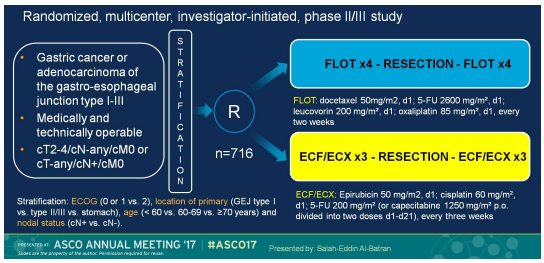
INT 116: Gastric Cancer Conclusions

- **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**

FLOT4 Study Design



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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§	ypT-stage	ECF/ECX (360)	FLOT (356)	P-value§
≤T1	53 (15%)	88 (25%)	0.001	N0	146 (41%)	174 (49%)	0.029
T2	44 (12%)	44 (12%)		N1	44 (12%)	55 (16%)	
T3	175 (49%)	165 (46%)		N2	54 (15%)	47 (13%)	
T4	47 (13%)	37 (10%)		N3	73 (20%)	57 (16%)	
NA*	41 (11%)	22 (6.2%)		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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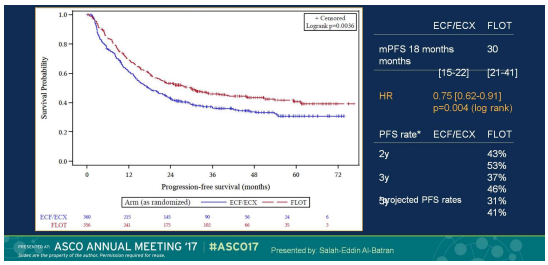
FLOT4: Progression-Free Survival



	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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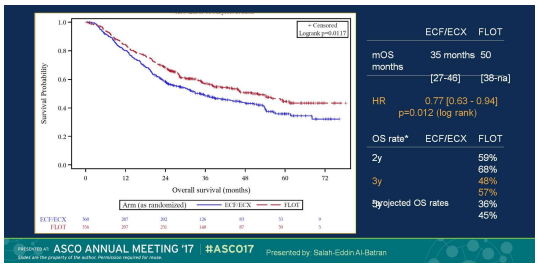
FLOT4: Overall Survival



	ECF/ECX	FLOT
mOS months	35 months [27-46]	50 [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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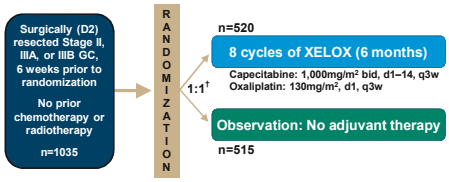
CLASSIC: Surgery vs XELOX after D2



- 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

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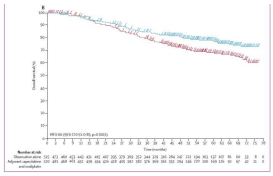
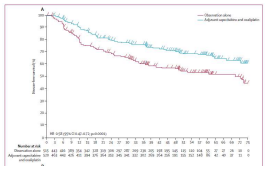
CLASSIC: Surgery vs XELOX after D2



5 yr OS: 78% vs 69%,
HR 0.66, P = 0.0015

5 yr DFS: 68% vs 53%,
HR 0.58, P < 0.001



Noh et al *Lancet Oncol* 15: 1389-1396; 2014

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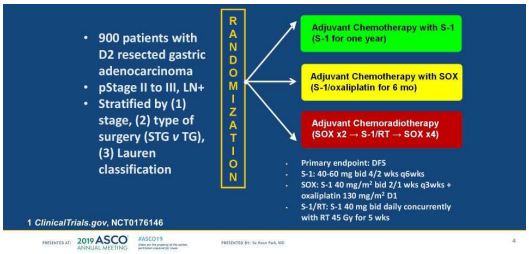
Adjuvant chemoRadioTherapy In Stomach Tumor 2



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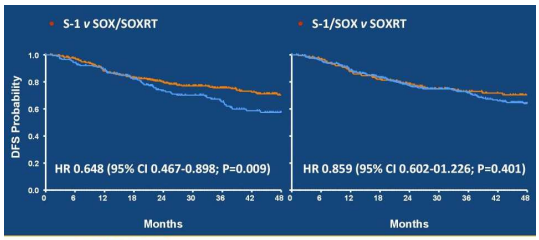
ARTIST 2 Subgroup Analysis of DFS



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A Multicenter Randomized Phase III Trial of Neo-adjuvant Chemotherapy Followed by Surgery and Chemotherapy or by Surgery and Chemoradiotherapy in Resectable Gastric Cancer

First results from the CRITICS study

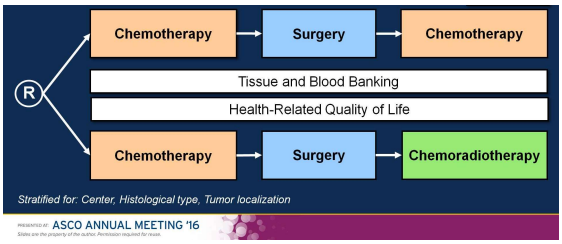
Marcel Verheij[1], EPM Jansen[1], A Cats[1], NCT van Grieken[2], H Boot[1], PA Lind[3], E Meershoek-Klein Kranenbarg[4], M Nordsmark[5], HH Hartgrink[4], H Putter[4], AK Trip[1], JW van Sandick[1], K Sikorska[1], H van Tinteren[1], YHM Claassen[4], CJH van de Velde[4], on behalf of the CRITICS Investigators

[1]Netherlands Cancer Institute, [2]VU University Medical Center, [3]Karolinska University Hospital, [4]Leiden University Medical Center, [5]Århus University Hospital

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented By Marcel Verheij at 2016 ASCO Annual Meeting

Trial Design



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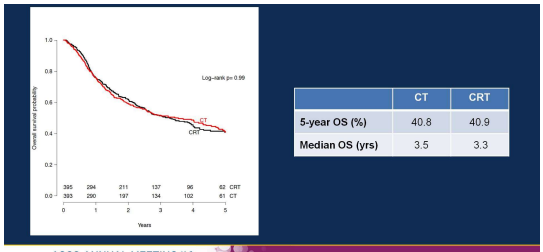
Results: Overall Survival



	CT	CRT
5-year OS (%)	40.8	40.9
Median OS (yrs)	3.5	3.3

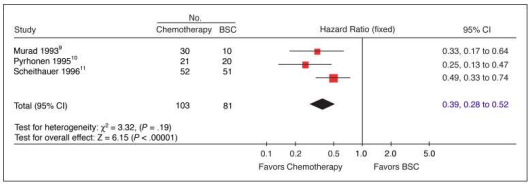
PRESENTED AT ASCO ANNUAL MEETING '16

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 chemo (FLOT)
  - Post op Chemo (CAPEOX)
  - Without RT after D2 resection

Metastatic Disease: Best Supportive Care vs Chemotherapy



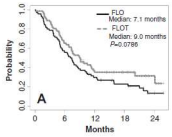
Wagner *J Clin Oncol* 24: 2903; 2006

Metastatic Disease: NCCN Endorsed Chemo

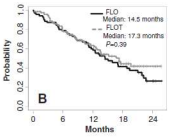
- 2 drug regimens are preferred
  - FOLFOX, CAPE-OX, FOLFIRI; S-1-Cisplatin or Oxaliplatin Asia
- 3 drug regimens adding docetaxel (DCF, mDCF, FLOT) not recommended
  - No survival benefit in patients 65 or older: FLOT65
  - No survival benefit for Doc + S-1/Cisplatin: JCOG 1013
  - No benefit for Epirubicin: NCCN does not endorse its use
- Add trastuzumab in HER2+, add pembrolizumab
- Add nivolumab to FOLFOX First Line
- Add pembrolizumab to FU/Cis First Line

FLO = FLOT: Patients 65 and older (FLOT 65 Trial)

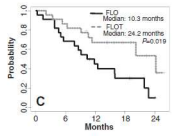
PFS



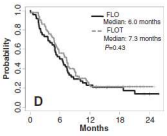
OS



PFS Local Disease



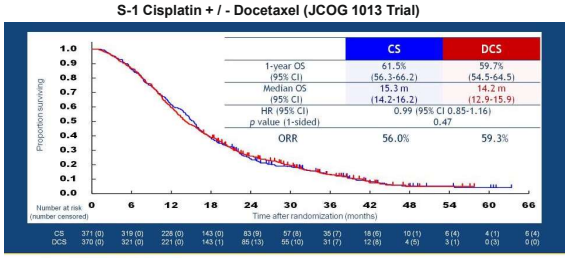
PFS Met Disease



Al Batran *EJC* 49: 835-842; 2013

Primary Endpoint: Overall Survival (OS)

S-1 Cisplatin + / - Docetaxel (JCOG 1013 Trial)



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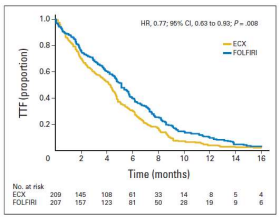
Lancet Gastroenterol Hepatol 4: 501; 2019

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

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Second Line Chemo Gastric Phase III Trials ➔ Taxanes and Irinotecan Improve Survival

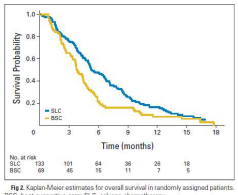

Fig 2. Kaplan-Meier estimates for overall survival in randomly assigned patients. BSC, best supportive care; SLC, salvage chemotherapy.

Docetaxel/Irinotecan vs BSC

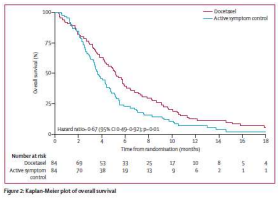

Figure 2: Kaplan-Meier plot of overall survival

Docetaxel vs BSC

Ford H *Lancet Oncol* 15:78; 2014; Kang JH *J Clin Oncol* 30:1513; 2012

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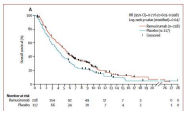
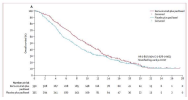
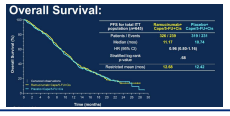
Angiogenesis Agents: Second Line

- Ramucirumab: VEGFR2
- RAM vs BSC: Improved OS, PFS
  - REGARD
- **Paclitaxel/RAM vs Paclitaxel: Improved OS, PFS, RR**
  - **RAINBOW**
- First line: RAM + 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

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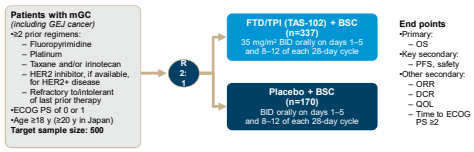
TAGS: TAS-102 Gastric Study[a]



- 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; aNCT02500043

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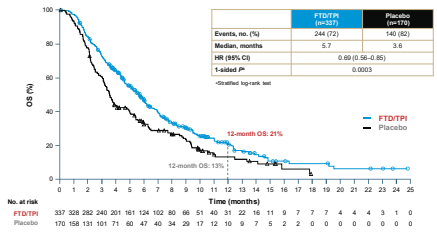
Primary Endpoint – OS



	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

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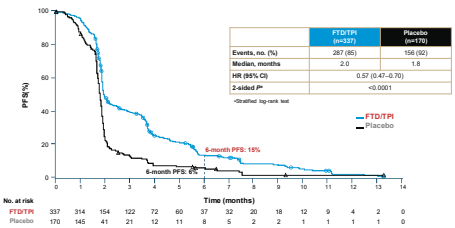
Secondary Endpoint – PFS



	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

ITTA population

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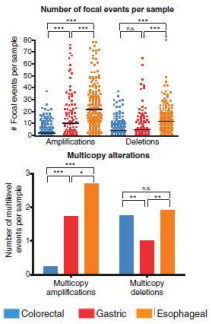
Genome Atlas: Gene Amplification in Esophagogastric Cancer is Common

- 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

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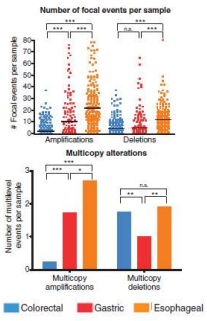
Gene Amplification in Esophagogastric Cancer

- 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

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Genome Atlas in Gastric Cancer: 4 Subsets with Therapeutic Implications

- Genomically unstable (intestinal)
  - RTK amplification
  - RTK directed therapy: HER2 only success
- MSI
  - Immune checkpoint inhibitors: approved for refractory MSI high solid tumors, CPI's superior to chemo earlier line
- Genomically stable (diffuse)
  - Not clearly targetable
- Epstein-Barr virus
  - PIK3CA, immune checkpoint inhibitors

Nature 24: 2903; 2014

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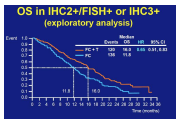
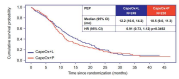
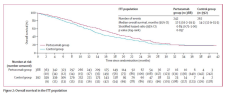
HER2: Esophagogastric Cancer is not Breast Cancer

- 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

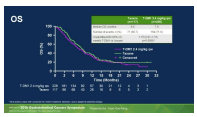


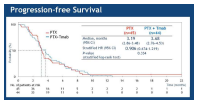


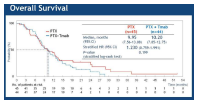
Bang *Lancet* 376: 687; 2010, Hecht *JCO* 34: 443; 2016, Tabernero *Ann Oncol* 28: 2017

HER2 Targeted Agents: Second Line

- Second line: trastuzumab emtansine (TDM-1) no better than a taxane
- T-ACT: phase II trastuzumab continuation 2nd line
  - First line Tras
  - Paclitaxel + / - Tras
  - No difference PFS, OS
- De novo and acquired HER2 resistance are likely
  - Loss of HER2 overexpression







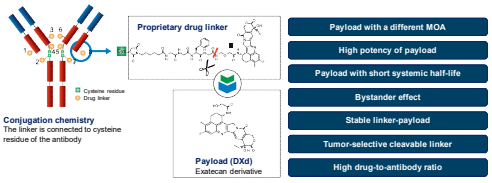
Bang *Lancet* 376: 1302; 2010, Makiyama *J Clin Oncol* 38: 2018 (suppl, Abst 4011)

Bi Specific, Other Monoclonal Antibodies

- Trastuzumab Deruxtecan: HER2
  - Trastuzumab conjugated to a topo-I inhibitor
  - 43% response in 23 pts in phase I/II
  - + Phase 2 vs chemotherapy: DESTINY: FDA approval
- Margetuximab: HER2
  - Anti HER-2 with optimized Fc domain to increase activation of CD16A receptors on NK cells
  - Phase I / II + Pembrolizumab: 18% response rate second line, higher in PDL-1+ or HER2 3+
  - Phase III first line: MAHOGANY
- Zanidatamab: Targets 2 epitopes on HER2

Doi *Lancet Oncol* 11: 1512; 2017, Catenacci *Lancet Oncol* 21: 1066; 2020

Trastuzumab Deruxtecan Structure and Mechanism of Action1



- 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

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

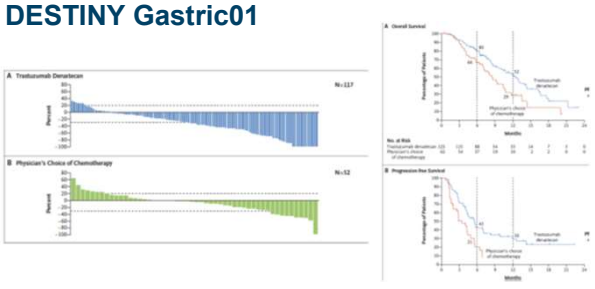
N = ~220

- **Experimental**: Trastuzumab deruxtecan (IV infusion every 3 weeks)
- **Active comparator:** Physician's choice of irinotecan 150 mg/m² biweekly or paclitaxel 80 mg/m² 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

DESTINY Gastric01



Shitara NEJM 2020

Phase III: EGFr Trials Negative

- 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

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FIGHT The FIGHT Clinical Trial — Targeting the FGF Receptor

A double-blind randomized study of bemarituzumab (bema) plus mFOLFOX6 versus placebo plus mFOLFOX6 as first-line treatment for advanced gastric/gastroesophageal junction cancer (FIGHT)

Zev A Wainberg, Peter Enzinger, Yoon-Koo Kang, Kensai Yamaguchi, Shukui Qin, Keun-Wook Lee, Sang Cheul Oh, Jin Li, Haci Mehmet Turk, Alexandra Teixeira, Giovanni Gerardo Cardellino, Rachel Guardeno Sanchez, Siddhartha Mitra, Yingsi Yang, Helen Collins, Daniel V Catenacci

[1]University of California, Los Angeles, USA, [2]Dana Farber Cancer Institute, Boston, USA, [3]Asan Medical Center, Seoul, South Korea, [4]The Cancer Institute Hospital of JFCR, Koto-Ku, Tokyo, Japan, [5]1 Hospital Nanjing University of Chinese Medicine, Nanjing, China, [6]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Gyeonggi-do, S.Korea, [7]Korea University Guro Hospital, Seoul, South Korea, [8]Shanghai East Hospital, Shanghai, China, [9]Bezmialem Vakif Universitesi Tip Fakultesi Hastanesi, Fatih, Turkey, [10]Hospital Senhora Da Oliveira, Guimaraes, Portugal, [11]Dipartimento di Oncologia, Azienda Ospedaliero Universitaria, Udine, Italy, [12]Institut Catala d Oncologia Girona, Spain, [13]Five Prime Therapeutics, South San Francisco, USA, [14]University of Chicago, Chicago, USA

Late Breaking Abstract (LBA160)

ASCO Gastrointestinal Cancer Symposium 2021

UCLA Jonsson Comprehensive Cancer Center

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium

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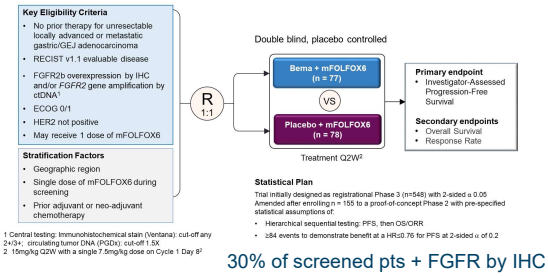
FIGHT Trial Design



30% of screened pts + FGFR by IHC

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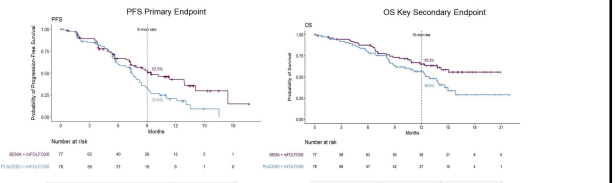
Progression-Free Survival and Overall Survival: Intent to Treat



	Bema N = 77	Placebo N = 78
Median PFS, mo (95% CI)	9.5 (7.3, 12.9)	7.4 (5.6, 8.4)
	P=0.0727	
HR (95% CI)	0.68 (0.44, 1.04)	

	Bema N = 77	Placebo N = 78
Median OS, mo (95% CI)	NR (13.8, NR)	12.9 (9.1, 15.0)
	P=0.0266	
HR (95% CI)	0.58 (0.35, 0.95)	

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium

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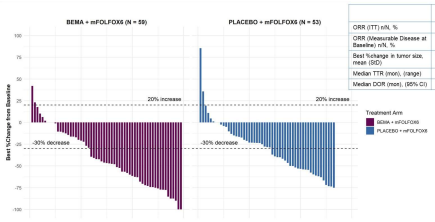
Best % Change in Target Lesions from Baseline



	Bema + mFOLFOX6	Placebo + mFOLFOX6
ORR (ITT) n/N, %	36/77, 47%	26/78, 33%
ORR (Measurable Disease at Baseline) n/N, %	35/66, 53%	24/60, 40%
Best %change in tumor size, mean (SD)	-41.7 (33.76)	-29.9 (30.49)
Median TTR (mon), (range)	1.84 (1.7, 7.6)	1.87 (1.6, 7.3)
Median DOR (mos), (95% CI)	12.2 (5.5,15.6)	7.1 (4.3,11.7)

Only subjects with measurable disease at baseline and at least 1 evaluable scan postbaseline are included in the waterfall plot.
DOR = Duration of response; TTR = Time to response
*: estimated among subjects with measurable disease at baseline

Presented By Zev Wainberg at 2021 Gastrointestinal Cancers Symposium

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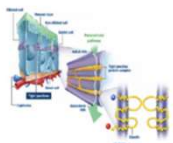
IMAB362: Zolbetuximab- Targets Claudin 18.2

CLDN18.2 IS EXPRESSED IN SEVERAL CANCER TYPES



- Member of the claudin family
- Major structural component of tight junctions
  - Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except for stomach mucosa, with limited accessibility to the antibody
- Broadly expressed in various cancer types

Immunohistological CLDN18.2 Labeling		
Source of tissue	CLDN18.2 + samples	[%]
Gastric adenocarcinomas	958/1182	81
Diffuse	203/342	59
Intestinal	238/338	70
Mixed	49/63	78
Not specified	368/439	84
Gastric cancer metastases	291/377	77
Lymph node	168/219	77
Ovarian	42/48	88
Peritoneum	29/36	81
Liver	12/20	60
Other	40/54	74
Esophageal adenocarcinomas	72/96	75
Pancreatic cancers	166/286	58
Ductal adenocarcinomas	103/174	59
Neuroendocrine carcinomas	5/25	20
Acinar cell carcinoma	1/3	33
Lymph node metastasis	34/49	69
Liver metastasis	23/35	66

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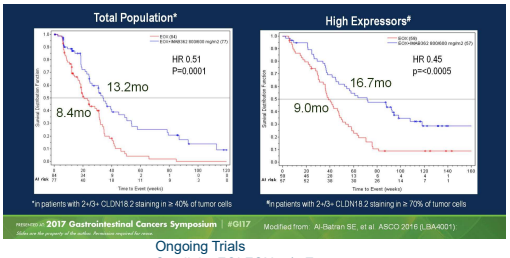
FAST - Overall Survival



Ongoing Trials
Spotlight: FOLFOX + / - Z
Glow: CapeOx + / - Z

Presented By Peter Enzinger at 2017 Gastrointestinal Cancers Symposium

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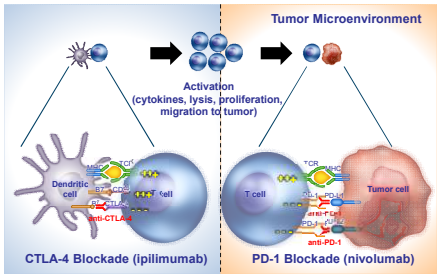
Blocking CTLA-4 and PD-1



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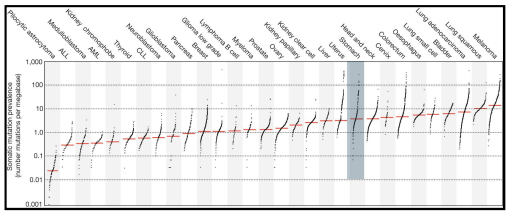
Somatic Mutation Prevalence



LB Alexandrov et al. *Nature* 000, 1-7 (2013) doi:10.1038/nature12477

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Immunotherapy in Esophagogastric Cancer: Older Studies leading to approval

- Refractory GEJ and gastric adeno
  - **KEYNOTE 59: Phase 2 Pembrolizumab, led to approval for MSI high and CPS > = 1%**
  - **Attraction 2: Led to approval for Nivolumab in Japan irrespective of PDL-1**

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Immunotherapy in Esophagogastric Cancer: Highlighted Trials leading to first line approval

- First line use of immunotherapy
- JAVELIN-100: Maintenance Avelumab no better than chemo
- KEYNOTE 62: Pembro + FU/Cisplatin in gastric/GEJ (CPS +)
- ***KEYNOTE 590: Pembrolizumab Eso GEJ AC/SCC (FU/Cisplatin)**
- ***Checkmate 649: Nivolumab Gastric/GEJ (FOLFOX or CAPE-OX)**
- ***KEYNOTE 811: HER2 +, Pembro + Tras / Chemo (Response rate)**
- ***US FDA approval irrespective of PDL-1 status**

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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 Sklodowska-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]Sheba Medical Center, Ramat Gan, Israel; [16]Merck & Co., Inc., Kenilworth, NJ, USA; [17]National Cancer Center Hospital East, Kashiwa, Japan

Presented By Kohei Shitara at 2018 ASCO Annual Meeting

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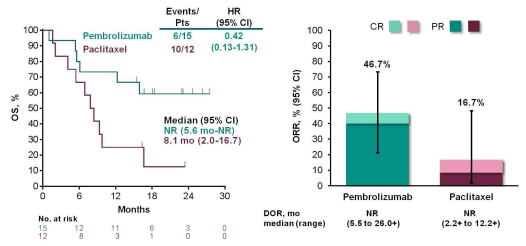
OS, ORR, and DOR for MSI-H Tumorsa



aPost-hoc subgroup analysis. Data cutoff date: Oct 26, 2017.

Presented By Kohei Shitara at 2018 ASCO Annual Meeting

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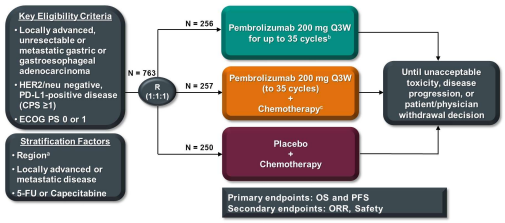
KEYNOTE-062 Study Design (NCT02494583)



[a]EU/North America/Australia, Asia (South Korea, Hong Kong, Taiwan, Japan), Rest of World (including South America).
[b]Administration of pembrolizumab monotherapy was not blinded.
[c]Chemotherapy: Cisplatin 80 mg/m² Q3W + 5-FU 800 mg/m²/d for 5 days Q3W or capecitabine BID d1-14 Q3W (Cisplatin may be capped at 6 cycles as per country guidelines).

Presented By Josep Tabernero at 2019 ASCO Annual Meeting

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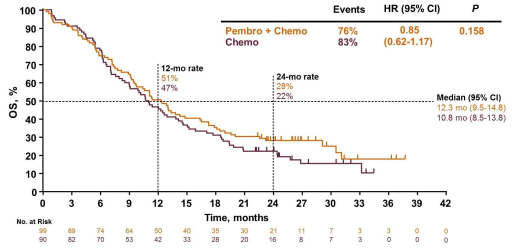
Overall Survival: P+C vs C (CPS ≥10)



Data cutoff: March 26, 2019.

Presented By Josep Tabernero at 2019 ASCO Annual Meeting

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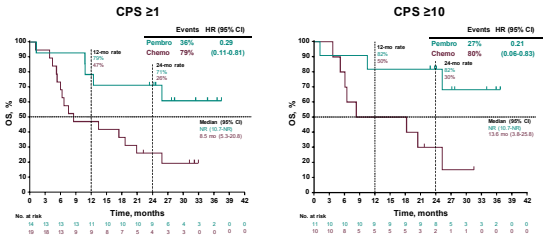
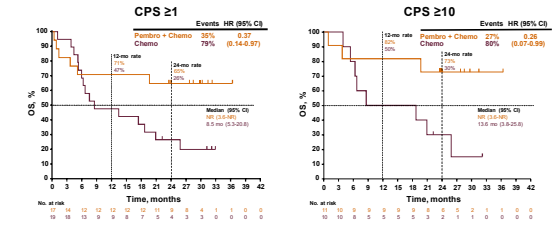
Pembro vs Chemo: OS in MSI-H Group



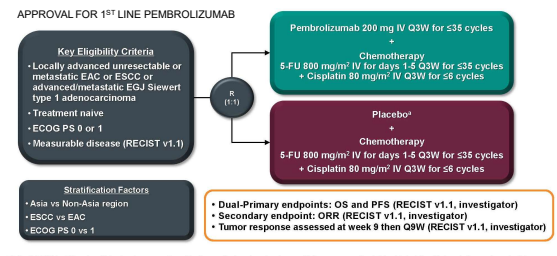
Data cutoff: March 26, 2019.

Pembro + Chemo vs Chemo: OS in MSI-H Group



Data cutoff: March 26, 2019.

KEYNOTE-590 Study Design (NCT03189719)



[a]Saline IV Q3W for ≤35 cycles. All treatments were continued for the specified number of cycles or until disease progression, intolerable toxicity, withdrawal of consent, or physician decision; EAC, esophageal adenocarcinoma; EGJ, esophagogastric junction; ESCC, esophageal squamous cell carcinoma.

Baseline Characteristics (ITT)

Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally-advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10[a]	186 (49.9)	197 (52.4)

[a]PD-L1 status was not evaluable or missing in 12 patients in the pembro + chemo group and 7 patients in the chemo group.
Data cut-off: July 2, 2020.

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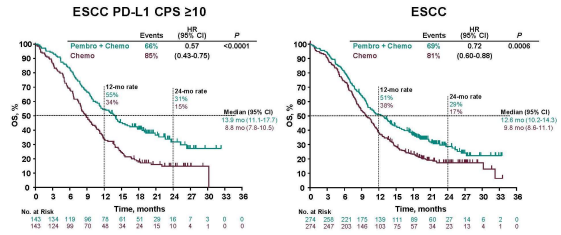
Overall Survival



Data cut-off: July 2, 2020.

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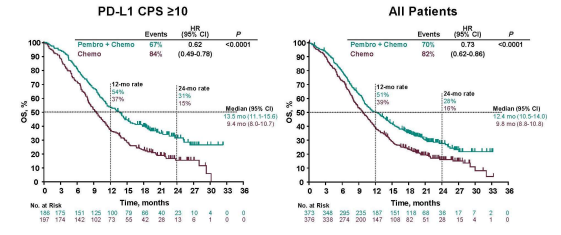
Overall Survival



Data cut-off: July 2, 2020.

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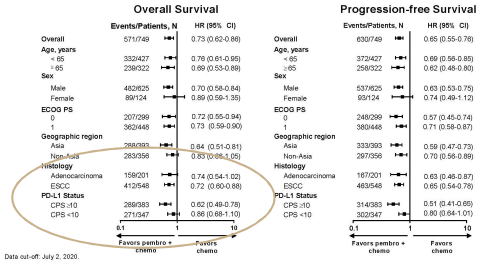
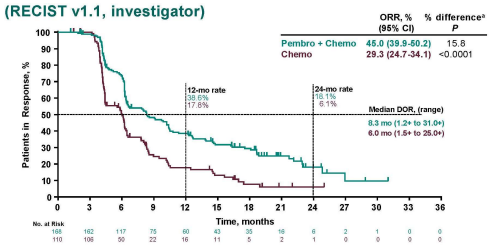
Survival in Key Subgroups: All Patients



Data cut-off: July 2, 2020.

Response Rate and Duration: All Patients



[a]Estimate based on Miettinen & Nurminen method stratified by geographic region, histology, and ECOG performance status; Data cut-off: July 2, 2020.

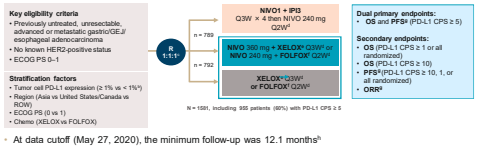
CheckMate 649 Study Design

Gastric and GEJ Adenocarcinoma

HIGHLY CONFIDENTIAL

APPROVAL FOR FIRST LINE NIVOLUMAB

- CheckMate 649 is a randomized, open-label, phase 3 studya



- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 monthsh

a ClinicalTrials.gov number, NCT02872116; b< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); c After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; d Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; e Oxaliplatin 130 mg/m2 IV (day 1) and capecitabine 1000 mg/m2 orally twice daily (days 1–14); f Oxaliplatin 85 mg/m², leucovorin 400 mg/m², and FU 400 mg/m2 IV (day 1) and FU 1200 mg/m2 IV daily (days 1–2); gBICR assessed; hTime from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

Baseline Characteristics

HIGHLY CONFIDENTIAL

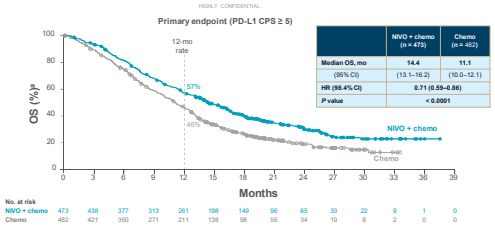
	PD-L1 CPS ≥ 5	
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median age (range), years	63 (18-88)	62 (23-90)
Male, %	70	72
Non-Asian/Asian, %	75/25	76/24
ECOG PS 1, %	59	58
Primary tumor location, %		
GC	70	69
GEJC	18	18
EAC	12	13
Metastatic disease, %	96	96
Liver metastases, %	40	45
Signet ring cell carcinoma, %	15	14
MSI status,[a] %		
MSS	89	88
MSI-high	4	3
FOLFOX/XELOX received on study,[b] %	51/49	52/48

- **The distribution of baseline characteristics was consistent with that of all randomized patients**

[a]MSI status was not reported or invalid for 75 patients; [b]All treated patients with PD-L1 CPS ≥ 5: NIVO + chemo, n = 468 and chemo, n = 465.

Overall Survival

HIGHLY CONFIDENTIAL



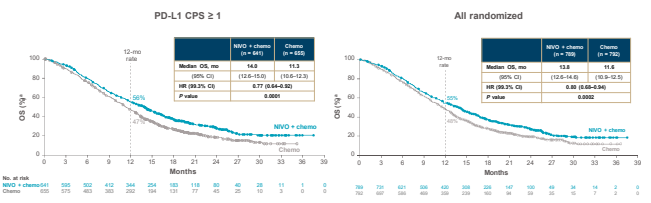
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1–16.2)	(10.0–12.1)
HR (98.4% CI)	0.71 (0.59–0.86)	
***P* value**	< 0.0001	

- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

[a] Minimum follow-up 12.1 months.

Overall Survival

HIGHLY CONFIDENTIAL



	NIVO + chemo (n = 541)	Chemo (n = 535)
Median OS, mo	14.0	11.3
(95% CI)	(12.6–15.0)	(10.6–12.3)
HR (99.3% CI)	0.77 (0.64–0.92)	
***P* value**	0.0001	

	NIVO + chemo (n = 789)	Chemo (n = 782)
Median OS, mo	12.9	11.6
(95% CI)	(12.6–14.6)	(10.9–12.5)
HR (99.3% CI)	0.80 (0.68–0.94)	
***P* value**	0.0002	

- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

[a] Minimum follow-up 12.1 months.

Efficacy Subgroup Analysis by PD-L1 CPS in all Randomized Patients

Survival

PD-L1 CPS[a]	Number of patients, n	Median, months: NIVO + chemo	Median, months: Chemo	Unstratified HR[b]	Unstratified HR (95% CI)
Overall survival					
Overall (N = 1581)		13.8	11.6	0.79	
≥ 1	265	13.1	12.5	0.92	
≥ 1	1296	14.0	11.3	0.76	
≥ 5	606	12.4	12.3	0.94	
≥ 5	955	14.4	11.1	0.70	
Progression-free survival					
Overall (N = 1581)		7.7	6.9	0.77	
≥ 1	265	8.7	8.1	0.93	
≥ 1	1296	7.5	6.9	0.75	
≥ 5	606	7.5	8.2	0.93	
≥ 5	955	7.7	6.1	0.69	

OS and PFS Benefits limited to CPS > = 5%

Objective response rate

PD-L1 CPS[a]	Number of patients, n	Objective response rate, %: NIVO + chemo	Objective response rate, %: Chemo	Unweighted ORR difference,[c] %	Unweighted ORR difference,[c] % (95% CI)
Overall (N = 1211)		58	46	12	
≥ 1	178	51	41	9	
≥ 1	1019	60	46	13	
≥ 5	428	55	46	9	
≥ 5	769	60	45	15	

- OS and PFS benefit with NIVO + chemo was enriched at higher PD-L1 CPS cutoffs, and higher ORR was observed across all cutoffs vs chemo, including CPS < 1 and CPS < 5

[a]PD-L1 CPS expression indeterminate/unevaluable/not available, n = 23; [b]Unstratified HR for death (OS) or unstratified HR for progression or death (PFS); [c]Randomized patients who had target lesion measurements at baseline, per BICR assessment. PD-L1 CPS expression indeterminate/not available, n = 16. *Percentages may not reflect an exact difference due to rounding.

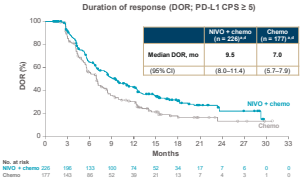
PFS and OS benefits > = CPS 5%

Response and Duration of Response

	PD-L1 CPS ≥ 5	
	NIVO + chemo (n = 378)[a]	Chemo (n = 391)[a]
ORR, %	60	45
95% CI	55–65	40–50
P value[b]	< 0.0001	
Best overall response,[c] %		
Complete response	12	7
Partial response	48	38
Stable disease	28	34
Progressive disease	7	11
Not evaluable	6	10
Median TTR (range), months	1.5 (0.8–10.2)	1.5 (1.0–7.1)

Duration of response (DOR; PD-L1 CPS ≥ 5)

	NIVO + chemo (n = 226)[a,d]	Chemo (n = 177)[a,d]
Median DOR, mo	9.5	7.0
(95% CI)	(8.0–11.4)	(5.7–7.9)



No. at risk
NIVO + chemo 226 196 133 100 74 52 34 17 7 6 0 0
Chemo 177 143 86 52 39 21 13 7 4 3 1 0

[a]Randomized patients who had target lesion measurements at baseline per BICR assessment; [b]ORR was not formally tested, the pre-specified *P* value is descriptive; [c]Percentages may not add up to 100% due to rounding; [d]Number of responders.

ORR was higher with NIVO + chemo versus chemo, and responses were more durable

KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study

APPROVAL FOR FIRST LINE PEMBROLIZUMAB

HER2 +

Key Eligibility Criteria
- Unresectable or metastatic gastric or GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2-positive tumor by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

R 1:1
N = 692

Pembrolizumab 200 mg IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W
+
Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Stratification Factors
- Geographic region (Australia/Europe/Israel/North America vs Asia vs ROW)
- PD-L1 CPS (≥1 vs <1)
- Chemotherapy choice (FP vs CAPOX)

End Points
- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

Confirmed Response at IA1, Efficacy Population

ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	**74.4% (66.2-81.6)**	**51.9% (43.0-60.7)**
ORR difference[a]	**22.7% (11.2-33.7) *P* = 0.00006**	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

DOR[b]	Pembro Arm (N = 99)	Placebo Arm (N = 68)
Median (range)	10.6 mo (1.1+ to 16.5+)	9.5 mo (1.4+ to 15.4+)
≥6-mo duration	70%	61%
≥9-mo duration	58%	51%

Best Response, n (%)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
CR	**15 (11%)**	**4 (3%)**
PR	**84 (63%)**	**64 (49%)**
SD	29 (22%)	49 (37%)
PD	5 (4%)	7 (5%)
Not evaluable	0	2 (2%)
Not assessed	0	5 (4%)

[a]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [b]Calculated in participants with best response of CR or PR; medians and ≥6-mo and ≥9-mo durations estimated using the Kaplan-Meier method. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

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Gastroesophageal adenocarcinoma: First Line approval for all patients with esophageal/gastric AC

- Pembrolizumab first line + Chemo in Esophageal / GEJ AC and SCC
  - OS 12.4 months
  - Benefit greater, limited to CPS > = 10%
- Nivolumab first line + Chemo Gastric/GEJ adeno
  - OS 13.8 months
  - Benefit greater and limited to CPS > = 5% (no benefit in 38% CPS < 5%)
- HER2 +: Pembro approved in first line based on response rate

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Immunotherapy Neoadjuvant/Adjuvant Trials

- KEYNOTE 585: Periop Pembro + Cape/5-FU cisplatin
- Matterhorn: Periop Durvalumab + FLOT
- ONO-4538: Post op Nivolumab + S-1 or CAPE-OX
- Pilots: combining anti PD-1 or PDL-1 agents with chemo + RT
  - ECOG: CROSS + /- Nivolumab ➔ Surgery ➔ Nivolumab vs Ipi/Nivo
  - EORTC: post op Ipi/Nivo vs Chemo in high risk
  - FLOT-A: UK, FLOT + Avelumab
  - AIO: FLOT + / - Atezolizumab

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Gastric Cancer: Summary

- Poor survival with Surgery Alone (20-30%)
- Adjuvant Therapy for Gastric Cancer:
  - Pre and Post Op Chemo with ECF
    - Post op RT added no benefit
    - FLOT superior to ECF
  - Adjuvant chemo alone after D2 resection
    - CAPE-OX
    - RT adds no benefit
  - Surgery followed by 5-FU + RT (less than a D1-2 resection)

Gastric Cancer: Summary

- Metastatic Disease
  - Platinum + FU +/ - third drug
    - ECF, DCF, FLOT
    - Epirubicin may not add benefit
  - Two drugs (FOLFOX, FOLFIRI, Cape-Cis or Oxali) preferred
  - Trastuzumab improves outcome in HER2+ esophagogastric ca first line
  - Second Line: taxane or irinotecan
    - Ramucirumab alone or with Paclitaxel improves outcomes second line
  - TAS102: Third or later line
- Immunotherapy
  - Pembrolizumab: approved for MSI-H
  - Pembrolizumab approved first line for Eso/GEJ AC and SCC, and for HER2+
  - Nivolumab approved fist line for Gastric/GEJ cancers
  - Pembrolizumab approved for refractory PDL-1+ disease