Update on GI Malignancies focus on upper GI tract

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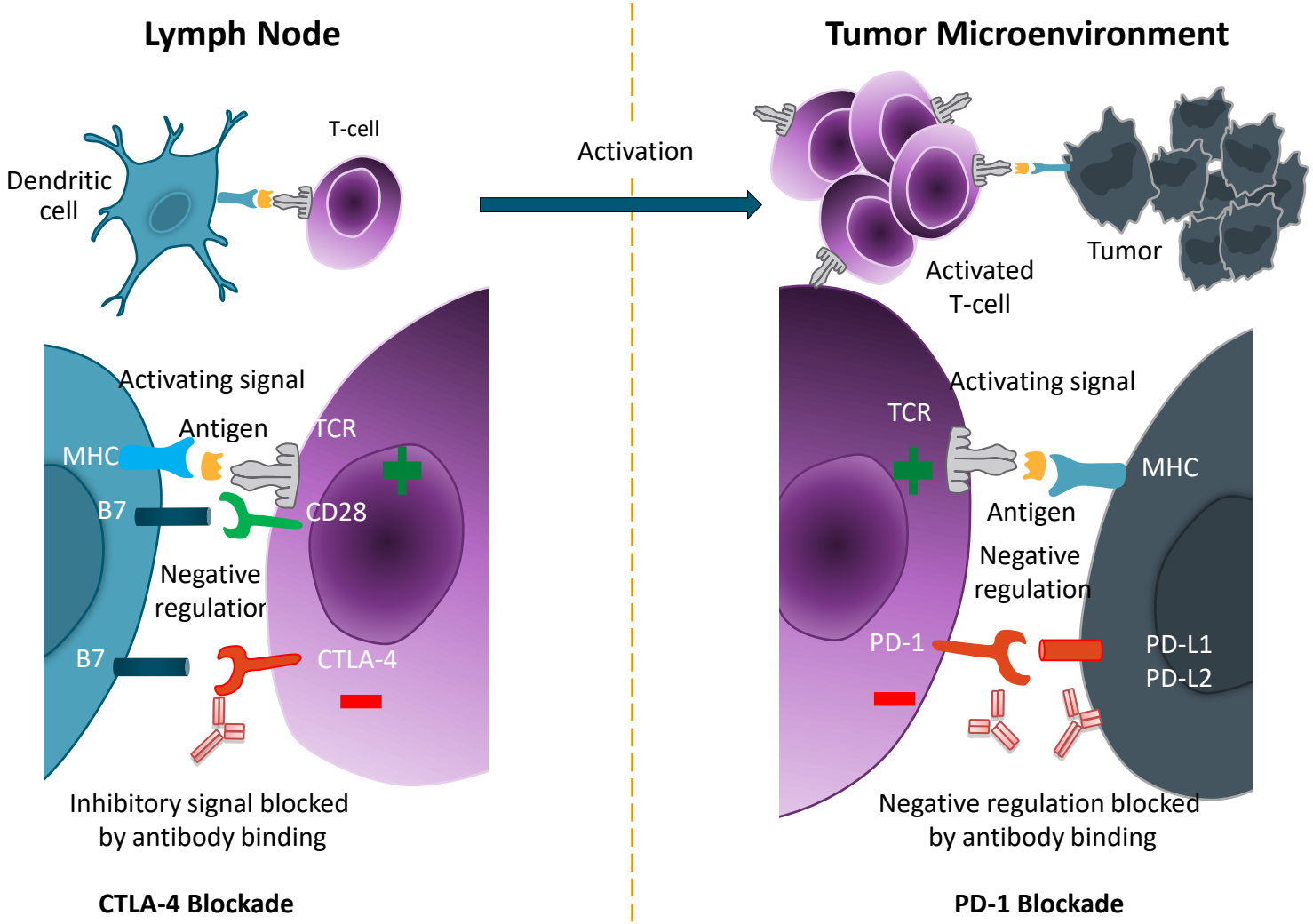
Biologic Rationale for Immune Checkpoint Inhibition as Cancer Therapy



Adapted from Ribas. NEJM. 2012;366:2517.

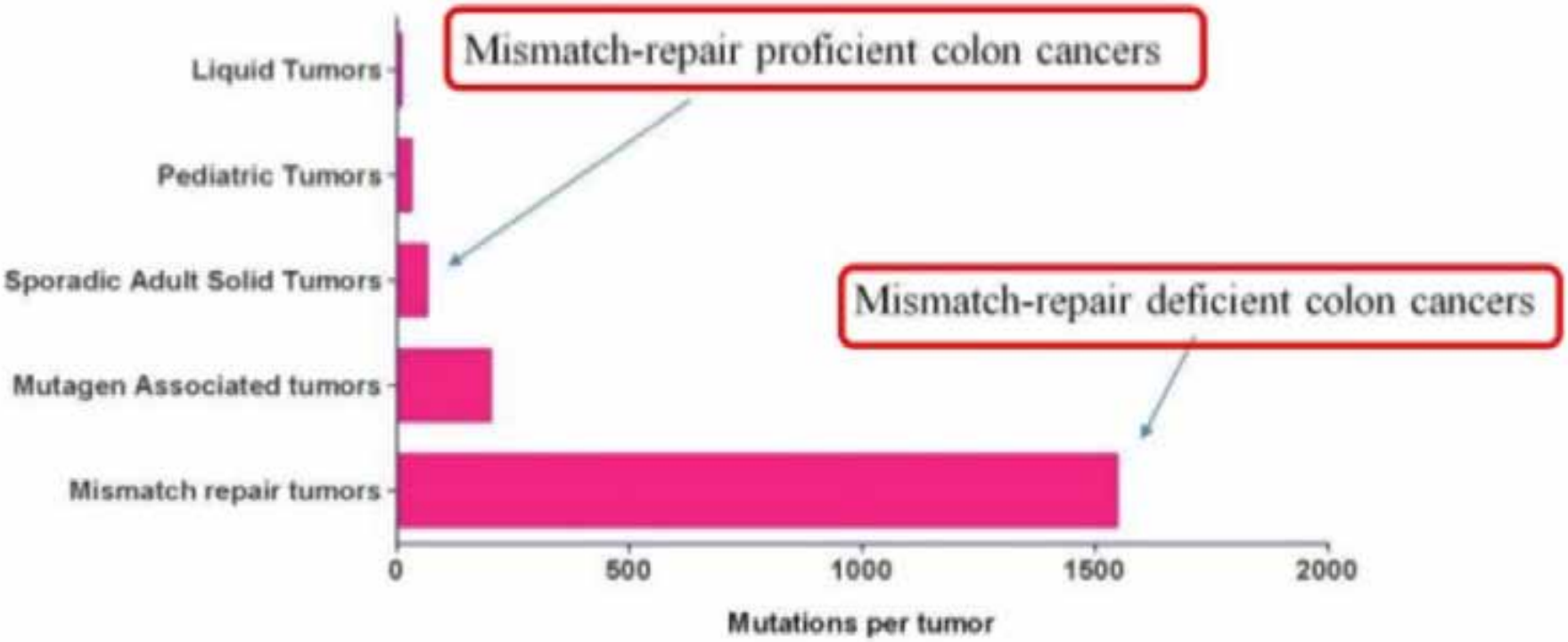
Slide credit: clinicaloptions.com

Basic Unites of Tumorigenesis:

- Microsatellites: Repetitive genetic units (Bases) → Maintained by MMR system (5 Genes).
- Deficient MMR → MSI → Genomic Instability → Tumor formation.
- MSI:
  - H: instability in > 30% of microsatellite loci.
  - L: instability in < 30% of microsatellite loci.

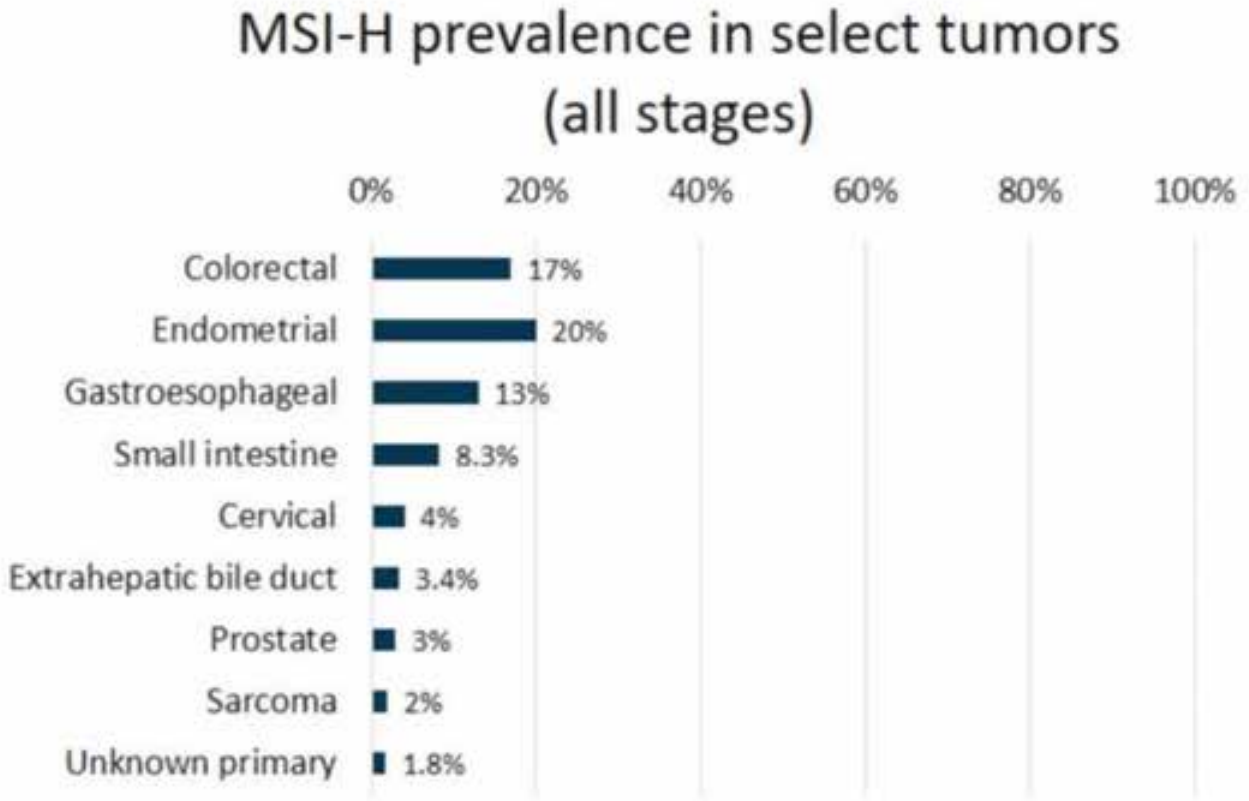
E. Vilar, J. Tabernero, Molecular dissection of microsatellite instable colorectal cancer, Cancer Discov. 3 (5) (2013) 502e511.

Mutational Load Differences



As Presented by Luis Diaz M.D. in 2017 ASCO Gastrointestinal Cancers Symposium.

Microsatellite Instability in Cancer



Luchini C, et al. *Ann Oncol.* 2019. [Epub ahead of print]

Keynote-016: Study Cohorts

Colorectal Cancers

Non-Colorectal Cancers

Cohort A
Deficient in Mismatch Repair (n=28)

Cohort B
Proficient in Mismatch Repair (n=25)

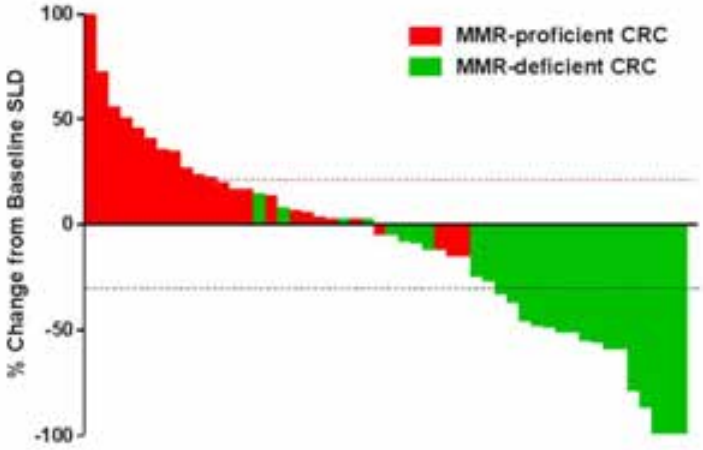
Cohort C
Deficient in Mismatch Repair (n=30)

- Anti-PD1 (Pembrolizumab) – 10 mg/kg every 2 weeks

Le, D, et al. ASCO 2016, Abstract 103.
Diaz LA, et al. ASCO 2016. Abstract 3003.

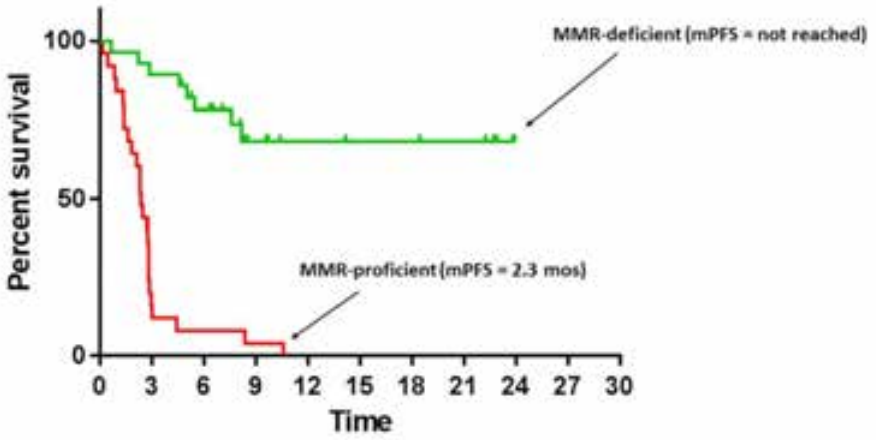
D Le ASCO 2016

Best Radiographic Response



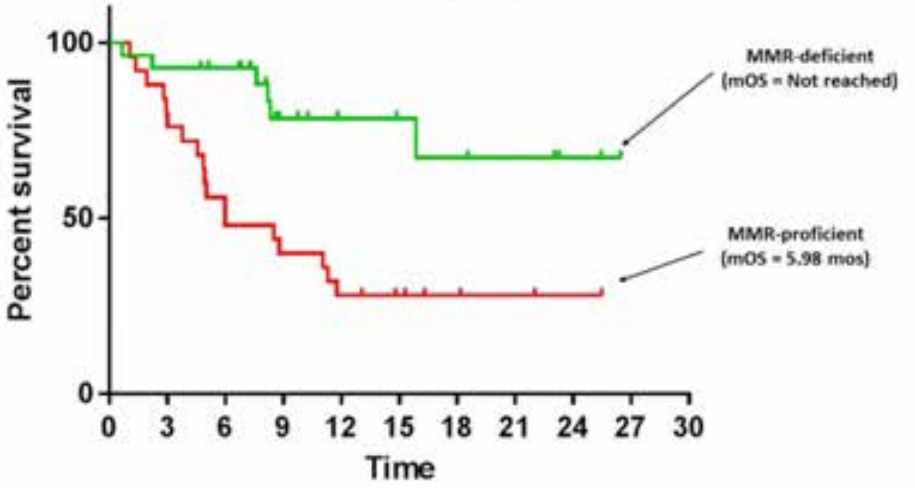
D Le ASCO 2016

Progression-free Survival



D Le ASCO 2016

Overall Survival



Response by Tumor Type: Keynote-016

Ampulary	Cholangio	CRC	Endom	Gastric/ Eso	NET	Pancreas	Prostate	Small Intestine
N=4	N=11	N=40	N=15	N=5	N=1	N=8	N=2	N=5
25%	27%	52%	53%	60%	100%	62%	50%	80%

CRC:
RR 52%
2-yr OS 72%

Non-CRC:
RR 54%
2-yr OS 57%

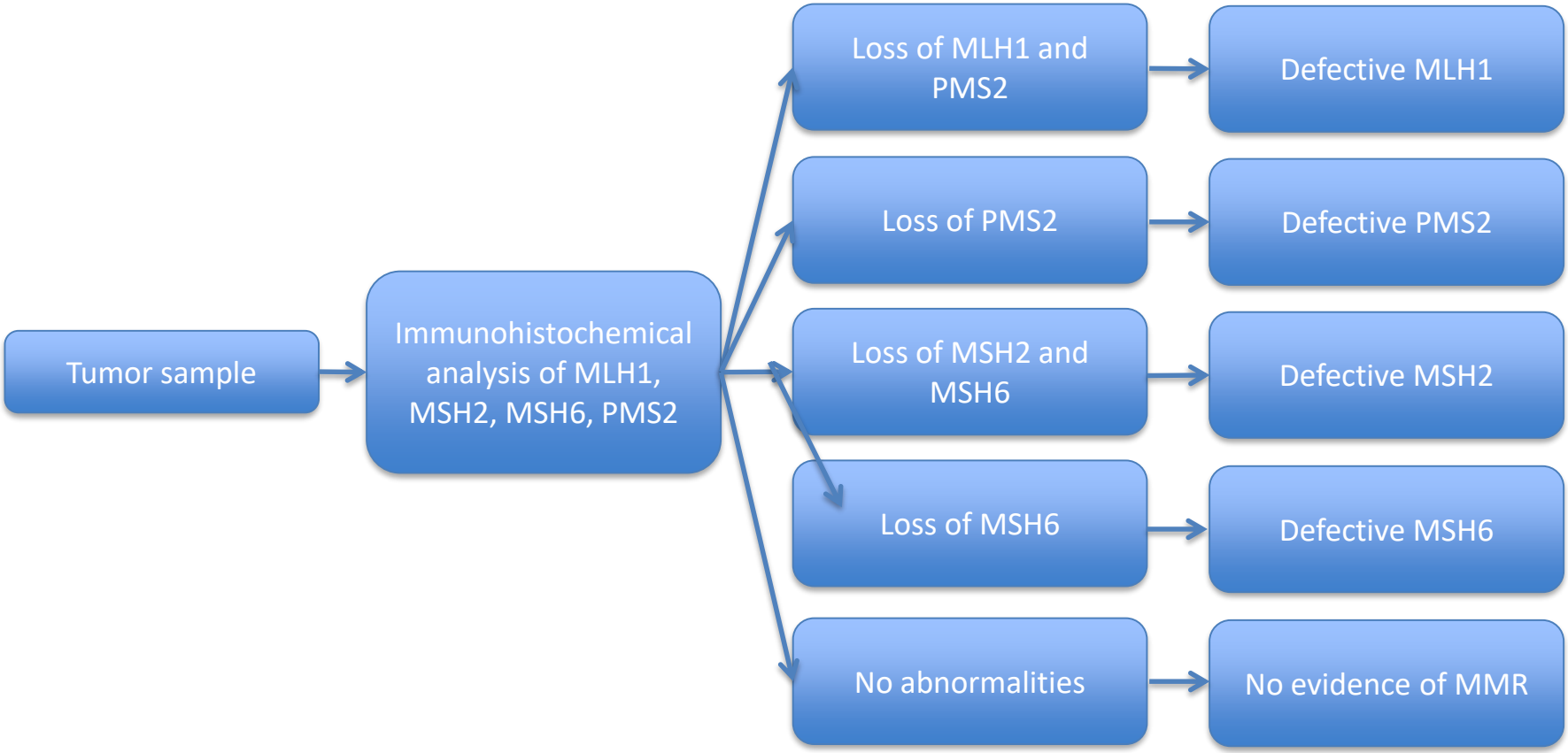
Le DT, et al. *Science*. 2017;357(6349):409-413.

FDA grants accelerated approval to pembrolizumab for first tissue/site agnostic indication

Listen to the FDA D.I.S.C.O. podcast about this approval

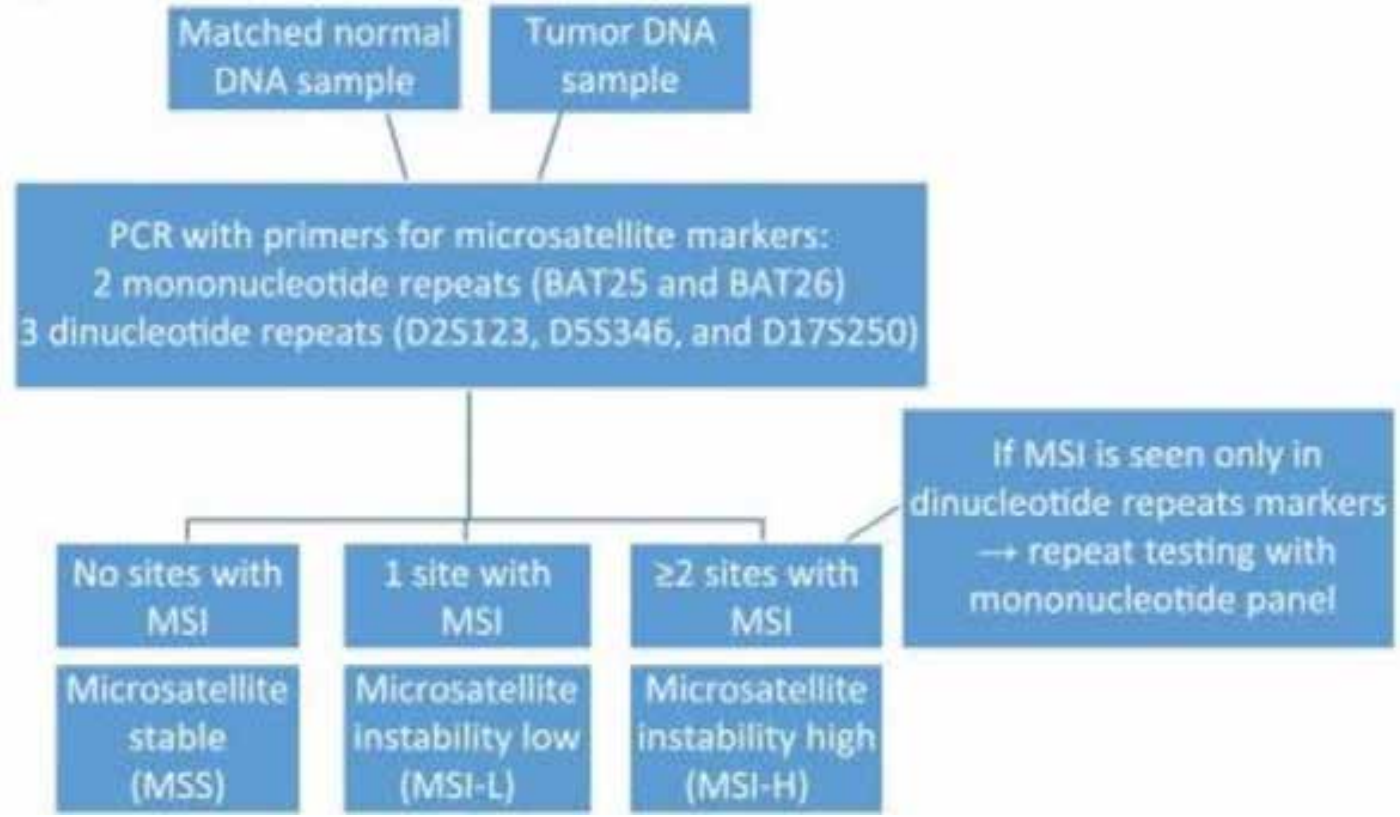
On May 23, 2017, the U.S. Food and Drug Administration granted accelerated approval to pembrolizumab (KEYTRUDA, Merck & Co.) for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Test schemes for MMR-Deficiency by IHC



Valerie Lee et al. The Oncologist 2016;21:1200-1211

Test for MSI with PCR per NCI guideline



Valerie Lee et al. The Oncologist 2016;21:1200-1211

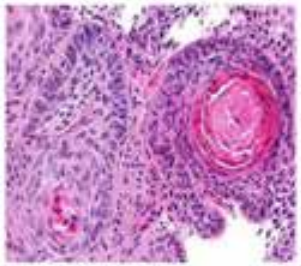
ESOPHAGUS CANCER

ESMO
GOOD SCIENCE
BETTER MEDICINE
BEST PRACTICE
European Society for Medical Oncology

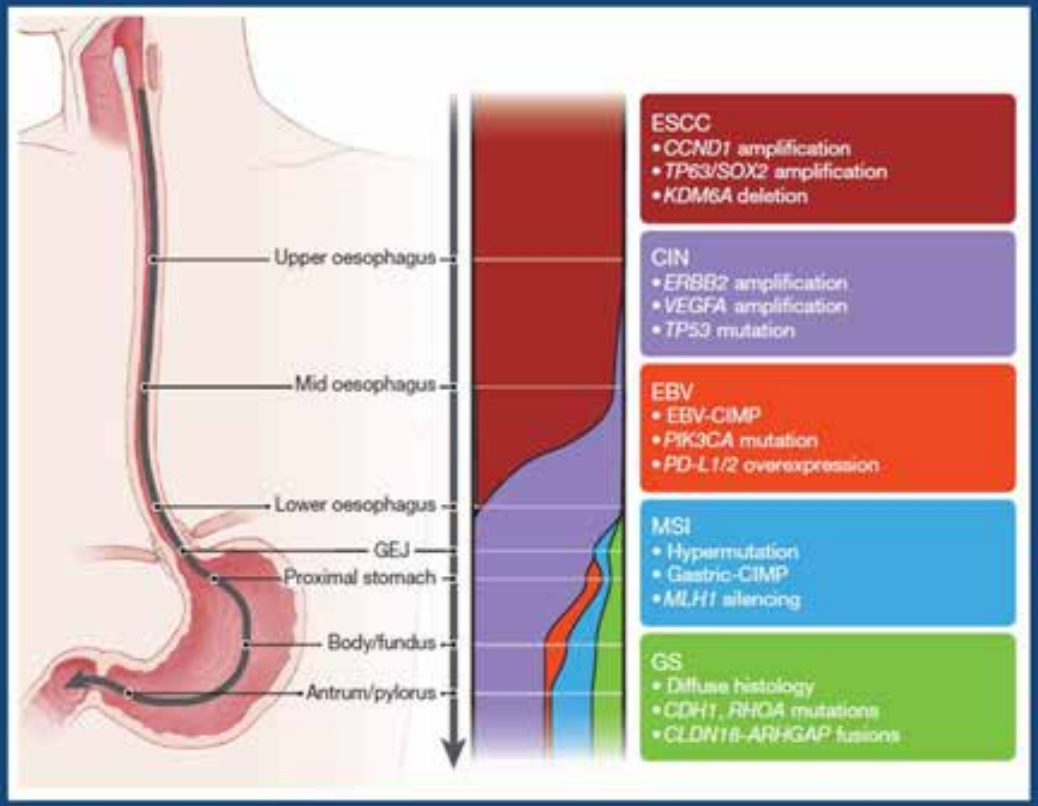
ESOPHAGUEAL CANCERS

5 YEAR SURVIVAL IN WESTERN COUNTRIES: 10-12%

- Squamous cell carcinomas
  - Upper and mid-esophagus location
  - Smoking and alcohol related in Western countries
  - More prevalent in developing countries
- Adenocarcinomas
  - Lower third and junctional location
  - Related to obesity, smoking, gastric reflux and Barret's esophagus
  - Increasing incidence in Western countries (x4.6 US)



Esophago-Gastric Cancer Subclasses



ESCC - Similarities with Head-Neck Cancer

CIN - Immunogenic ??? HER2 / VEGF amplications

EBV - Immunogenic Immune infiltrates, PD-L1 high

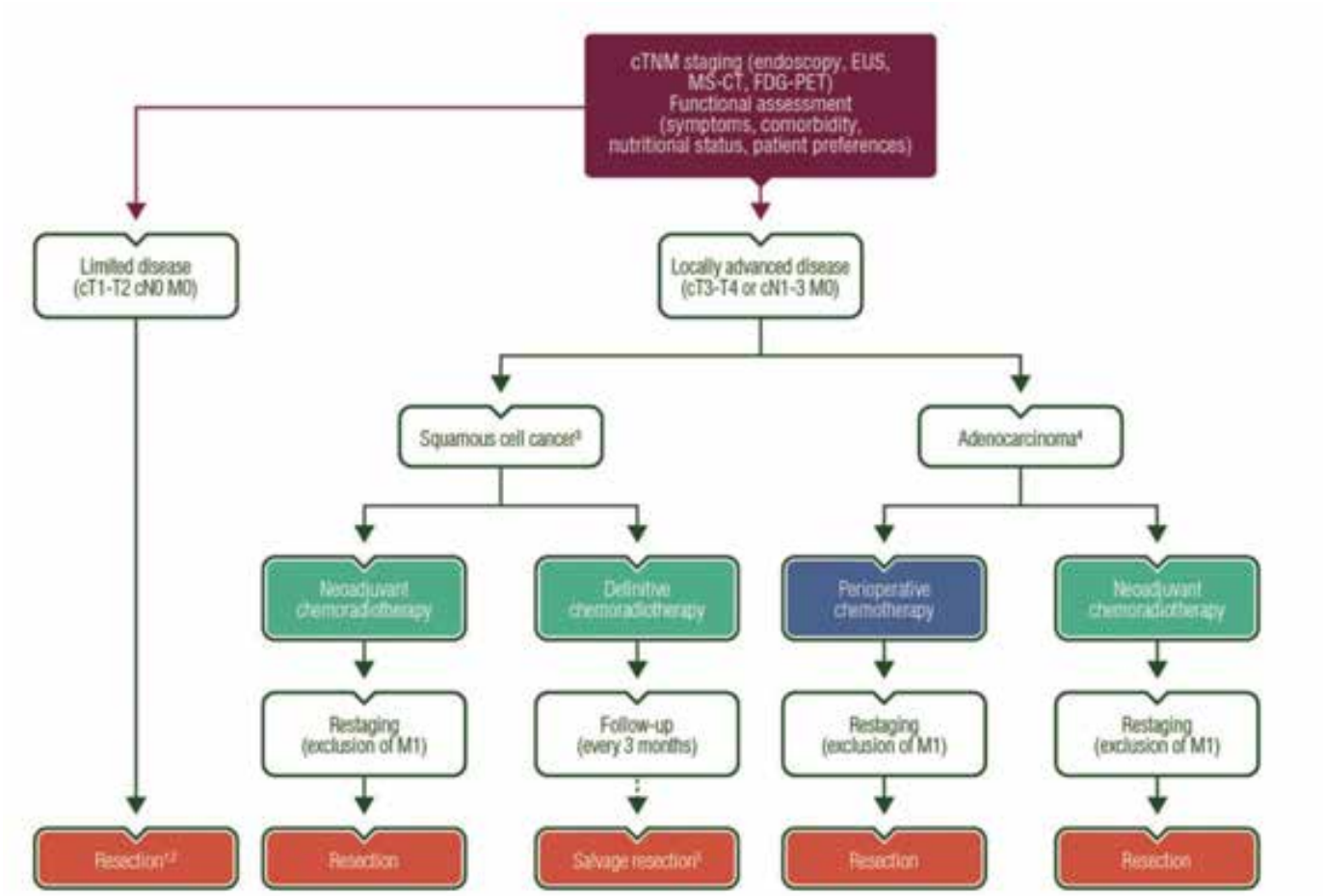
MSI - Immunogenic High mutational burden

Genomic stable (silent) Lower mutational burden

The Cancer Genome Atlas Research Network. *Nature.* 2017;541:169-175

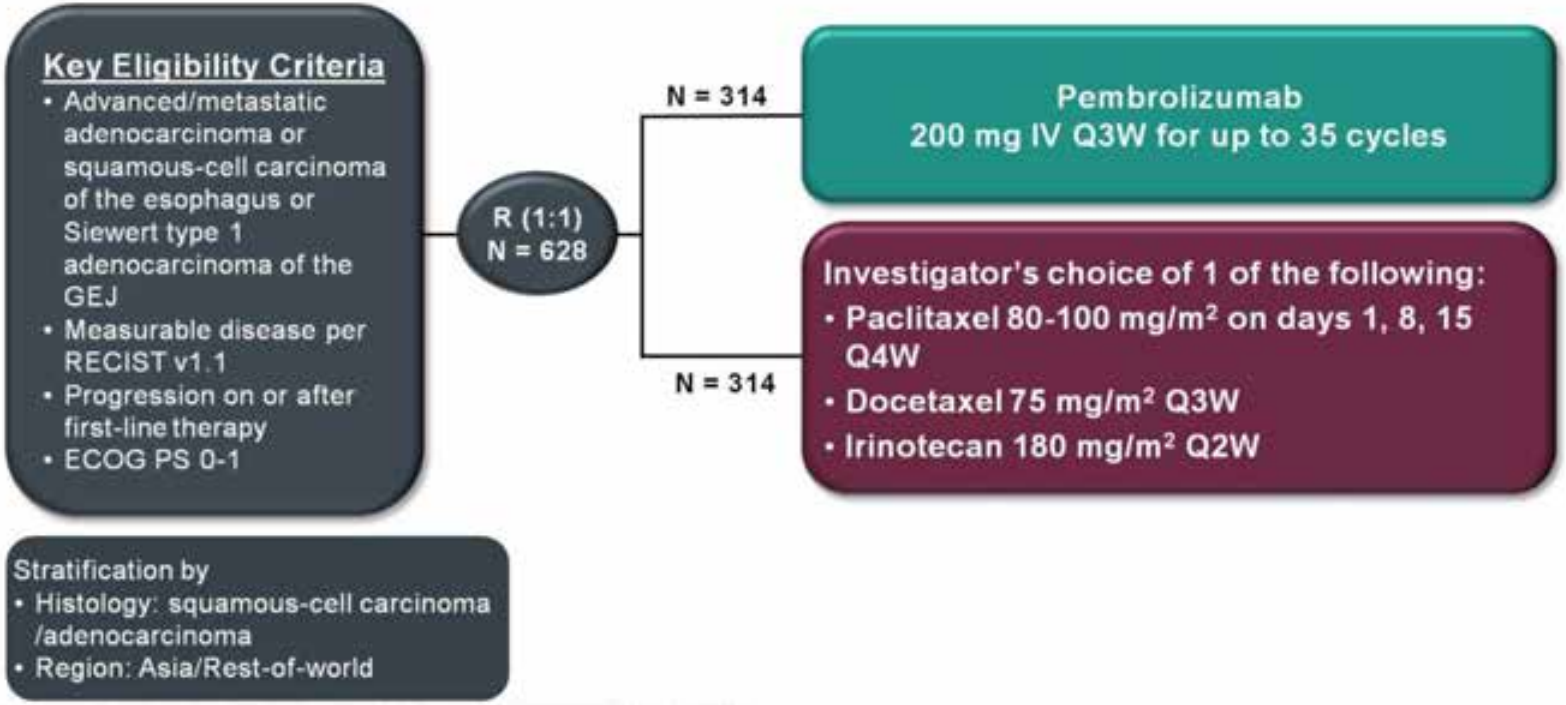
Presented By Florian Lordick at 2019 ASCO Annual Meeting

Treatment algorithm of Esophageal and EGJ Cancer



Annals of Oncology 27 (Supplement 5): v50–v57, 2016

Phase 3 KEYNOTE-181 Study (NCT02564263)



Presented By Takashi Kojima at 2019 Gastrointestinal Cancer Symposium

Analysis Populations and Endpoints

- Analysis populations
  - Efficacy: assessed in patients with PD-L1 CPS ≥10, SCC, and ITT
  - Safety: assessed in all patients who received ≥1 dose of study drug
- 3 primary endpoints
  - Overall survival in
    1. Patients with PD-L1 CPS ≥10
    2. Patients with SCC
    3. All patients (ITT)
- Secondary endpoints
  - Progression-free survival
  - Objective response
  - Safety

SCC, squamous cell carcinoma; ITT, intent-to-treat; PD-L1 CPS: defined as number of PD-L1 positive cells (tumor cells, macrophages, lymphocytes)/total number of tumor cells x 100.

Assessments and Statistical Considerations

- Assessments
  - Response: assessed at week 9 and then every 9 weeks (RECIST, v1.1, BICR)
  - Survival follow-up every 9 weeks
- Statistical considerations
  - **Planned** enrollment: 600; Actual: 628
  - Overall alpha for study: one-sided alpha of 2.5%
    1. α 0.9% ($P \leq 0.0085$) for superiority of OS in PD-L1 CPS ≥10
    2. α 0.8% ($P \leq 0.0077$) for superiority of OS in SCC
    3. α 0.8% ($P \leq 0.0077$[a]) for superiority of OS in ITT
  - Stratified log-rank test used to assess differences between treatment groups for OS and PFS (CPS ≥10, SCC)
  - Stratified maximum weighted log-rank test used to assess differences between treatment groups for OS and PFS (ITT)

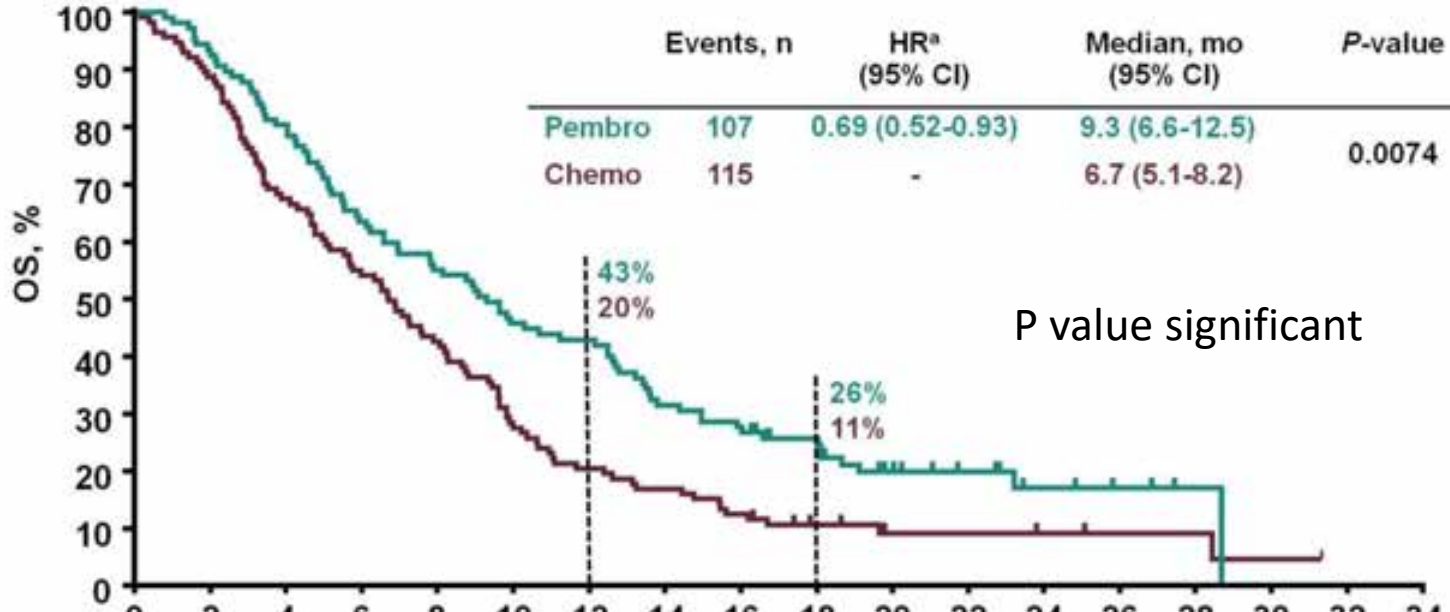
[a]Actual boundary is 0.0162 after alpha passing from OS in PD-L1 CPS ≥10 to OS in ITT (all patients) due to rejected OS in PD-L1 CPS ≥10 hypothesis.
BICR, blinded independent central review; PD-L1 CPS: defined as number of PD-L1 positive cells (tumor cells, macrophages, lymphocytes)/total number of tumor cells x 100.

Baseline Characteristics (ITT)

Characteristic, n	Pembrolizumab N = 314	Chemotherapy N = 314
Median age, years (range)	63 (23-84)	62 (24-84)
≥65 years	139 (44.3)	133 (42.4)
Male	273 (86.9)	271 (86.3)
Asia	121 (38.5)	122 (38.9)
Rest of World	193 (61.5)	192 (61.1)
ECOG PS 1	187 (59.6)	197 (62.7)
Squamous-cell carcinoma	198 (63.1)	203 (64.6)
Adenocarcinoma	116 (36.9)	111 (35.4)
PD-L1 CPS ≥10[a]	107 (34.1)	115 (36.6)
Metastatic disease	290 (92.4)	286 (91.1)
0-1[b] prior therapies	305 (97.1)	310 (98.7)
≥2 prior therapies	9 (2.9)	4 (1.3)

[a]6 patients in pembrolizumab and 3 in chemotherapy group were not evaluable; [b]2 patients in pembrolizumab group had 0 prior therapies; Data cutoff: October 15, 2018.

Overall Survival (PD-L1 CPS ≥10)



	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	107	0.69 (0.52-0.93)	9.3 (6.6-12.5)	0.0074
Chemo	115	-	6.7 (5.1-8.2)	

P value significant

No. at risk																		
Pembrolizumab	107	100	86	68	59	49	45	33	29	23	13	9	5	3	1	0	0	0
Chemotherapy	115	102	76	61	48	31	23	19	14	8	4	4	3	2	2	1	0	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

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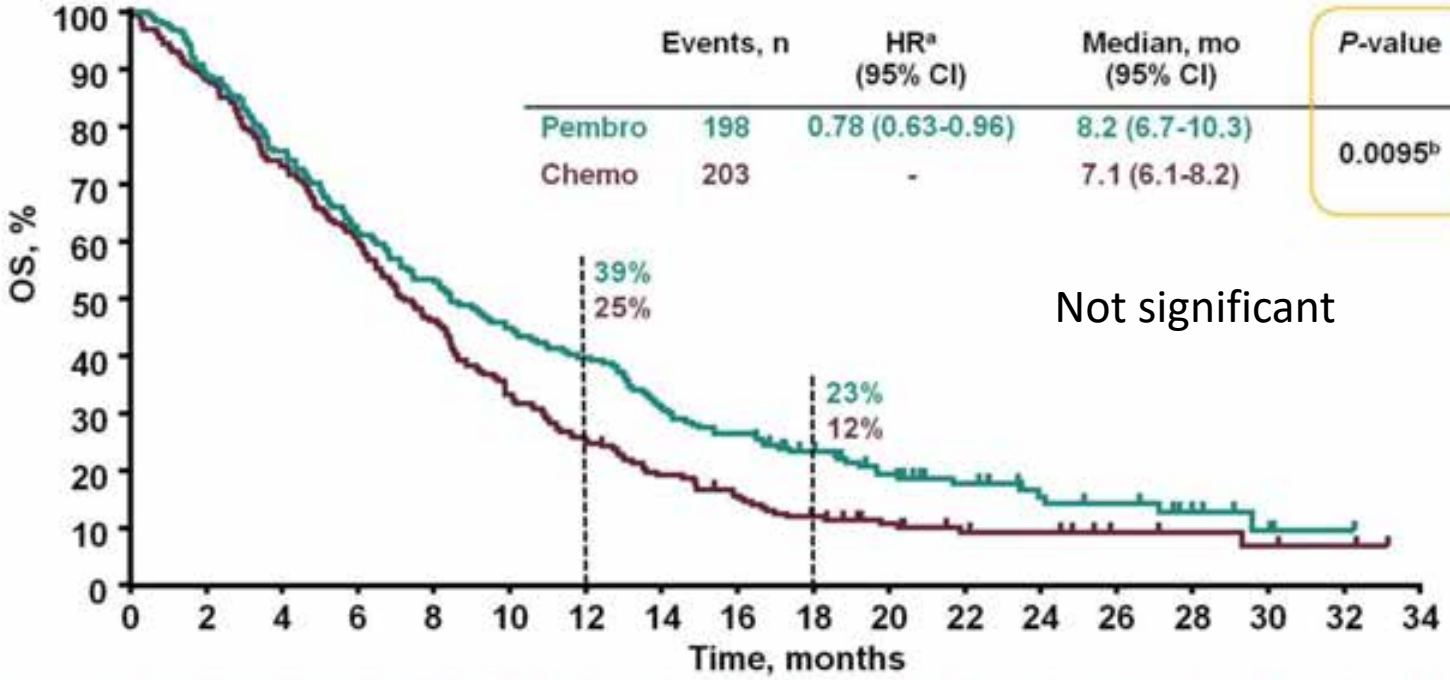
Overall Survival (SCC)



	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	198	0.78 (0.63-0.96)	8.2 (6.7-10.3)	0.0095[b]
Chemo	203	-	7.1 (6.1-8.2)	

Not significant

No. at risk																		
Pembrolizumab	198	177	150	121	103	86	77	57	52	38	24	17	12	10	5	1	0	0
Chemotherapy	203	179	147	118	91	64	50	38	27	20	13	10	8	5	4	2	1	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology; [b]Not significant based on pre-specified statistical boundaries of $P \leq 0.0077$ for superiority of OS in SCC; Data cutoff: October 15, 2018.

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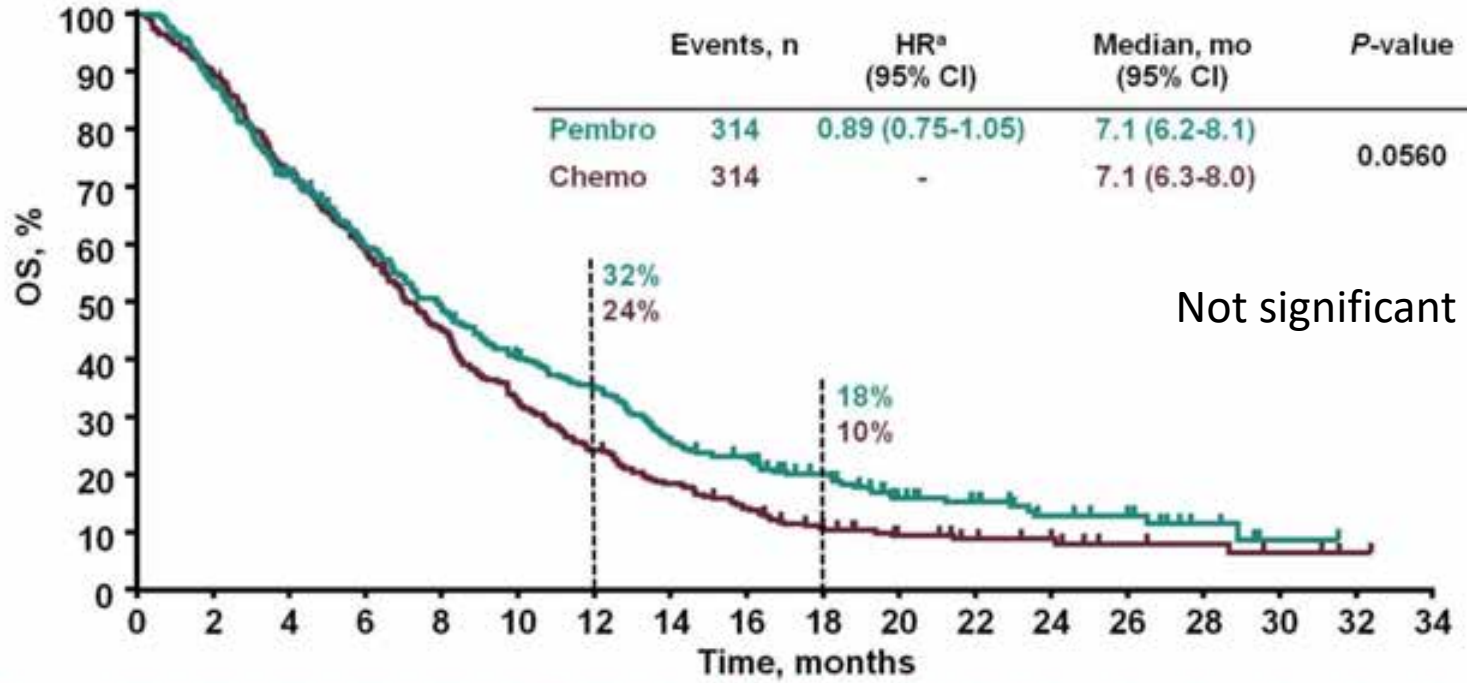
Overall Survival (ITT)



	Events, n	HR[a] (95% CI)	Median, mo (95% CI)	*P*-value
Pembro	314	0.89 (0.75-1.05)	7.1 (6.2-8.1)	0.0560
Chemo	314	-	7.1 (6.3-8.0)	

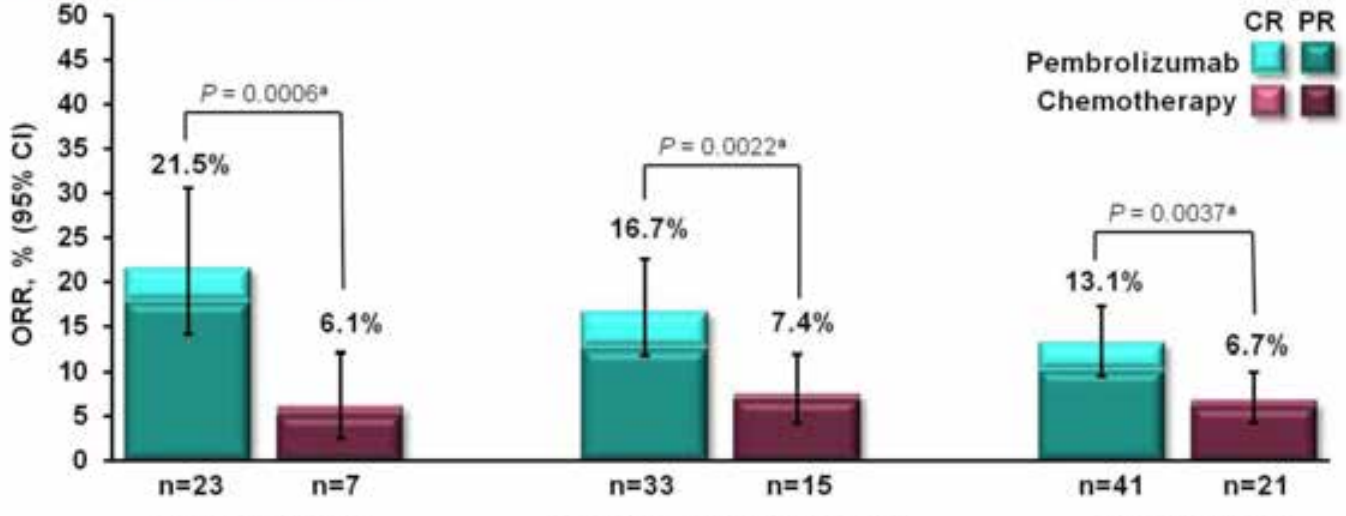
Not significant

No. at risk																		
Pembrolizumab	314	275	224	176	143	116	100	73	63	46	28	20	14	10	5	1	0	0
Chemotherapy	314	280	226	181	139	98	75	56	41	26	18	13	9	6	5	3	1	0

[a]Based on Cox regression model with treatment as a covariate stratified by region and histology.
Data cutoff: October 15, 2018.

Presented By Takashi Kojima at 2019 Gastrointestinal Cancer Symposium

Response Rate and Duration
(RECIST v1.1, BICR)



Duration	Median, mo (range)	≥ 6 mo, %
Pembro	9.3 (2.1+ to 22.6+)	77
Chemo	7.7 (4.3 to 16.8+)	57

Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.5 (2.1+ to 25.8+)	68
Chemo	10.7 (2.1+ to 16.8+)	75

Duration	Median, mo (range)	≥ 6 mo, %
Pembro	8.5 (2.1+ to 25.8+)	72
Chemo	10.7 (1.8+ to 16.8+)	62

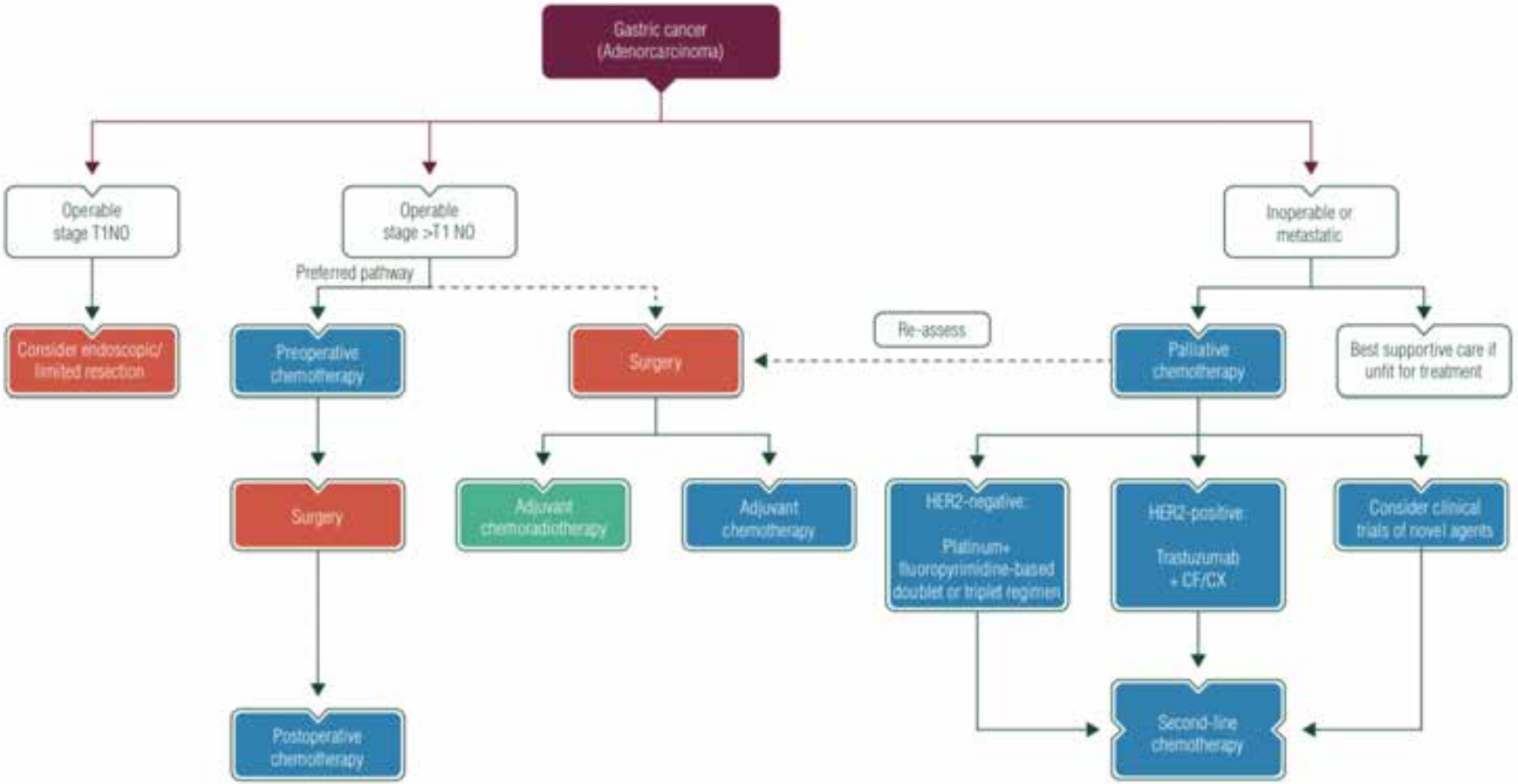
aNominal; one-sided.
Data cutoff: October 15, 2018.

Summary and Conclusions

- Pembrolizumab significantly improved OS in patients with metastatic esophageal cancer and PD-L1 CPS ≥10 that progressed after 1 prior therapy versus chemotherapy
  - Superior OS in patients with PD-L1 CPS ≥10 metastatic esophageal cancer who had progressed after 1 prior therapy (HR 0.69, 95% CI 0.52-0.93)
  - Clinically meaningful increase in OS in patients with SCC (HR 0.78, 95% CI 0.63-0.96)
  - Similar OS in ITT (HR 0.89 95% CI 0.75-1.05)
- ORR higher with pembrolizumab versus chemotherapy
  - 21.5% vs 6.1% (CPS ≥10); 16.7% vs 7.4% (SCC); 13.1% vs 6.7% (ITT)
- More favorable safety profile with pembrolizumab compared with chemotherapy
  - Lower frequency of grade 3-5 treatment-related adverse events with pembrolizumab versus chemotherapy (18.2% vs 40.9%)
  - No new safety signals were observed
- Data suggest that pembrolizumab should be considered a new standard-of-care in the second-line for patients with metastatic esophageal cancer and PD-L1 CPS ≥10

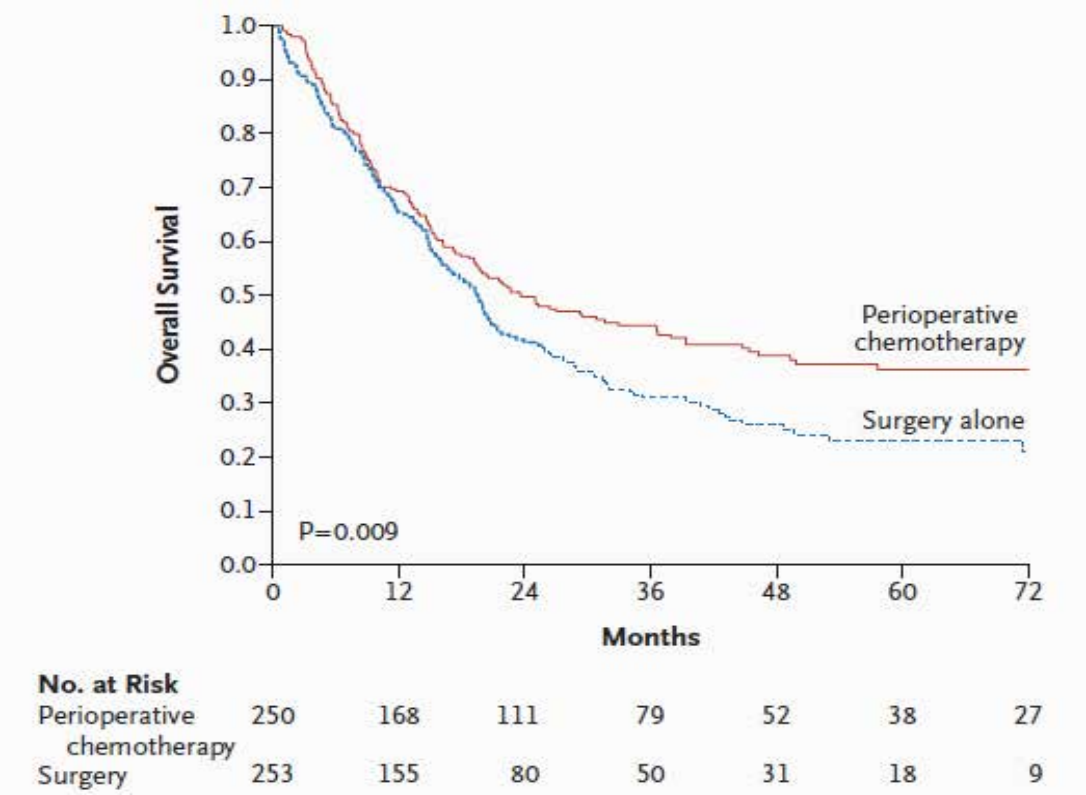
GASTRIC CANCER

ESMO guideline algorithm



Annals of Oncology 27 (Supplement 5): v38–v49, 2016

MAGIC trial



- Gastric / GEJ adenoca, n=503
- 3 cycles ECF pre-op, 3 cycles post-op vs. surg only
- 5 yr survival 36% chemo grp (vs. 23% in surg grp) p=0.009
- Only 26% GEJ / esoph ca BUT **no heterogeneity treatment effect based on tumor location**
- 91% pts completed preop chemo, 50% completed postop chemo

N Engl J Med 2006;355:11-20.

LBA27_PR: Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) for resectable esophagogastric cancer: updated results from multicenter, randomized phase 3 FLOT4-AIO trial (German Gastric Group at AIO) – Al-Batran S-E, et al

Study objective

- To provide updated efficacy and safety data from the phase 3 FLOT4-AIO study in patients with oesogastric cancer

Key patient inclusion criteria

- Gastric cancer or adenocarcinoma of the GEJ type I–III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

(n=716)

R 1:1

FLOT* x 4, resection, then FLOT* x 4 (n=356) → PD

Stratification

- ECOG PS (0 or 1 vs. 2)
- Primary location (GEJ type I vs. type II/III vs. stomach)
- Age (<60 vs. 60–69 vs. ≥70 years)
- Nodal status (cN+ vs. cN-)

ECF/ECX† x 3, resection, then ECF/ECX† x 3 (n=360) → PD

PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

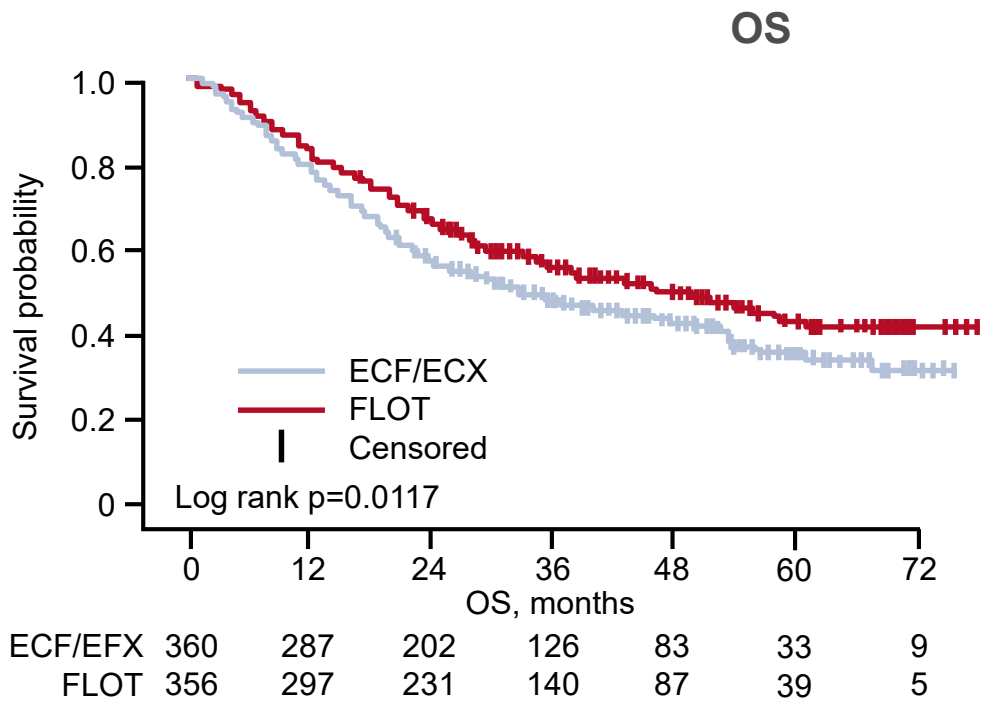
- PFS, safety

*Docetaxel 50 mg/m^2 D1 + 5FU 2600 mg/m^2 D1 + leucovorin 200 mg/m^2 D1 + oxaliplatin 85 mg/m^2 D1 q2w; †Epirubicin 50 mg/m^2 D1 + cisplatin 60 mg/m^2 D1 + 5FU 200 mg/m^2 (or capecitabine 1250 mg/m^2 po divided into two doses D1–21) q3w

Al-Batran S-E, et al. Lancet 2019; 393: 1984-1957

LBA27_PR: Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) for resectable esophagogastric cancer: updated results from multicenter, randomized phase 3 FLOT4-AIO trial (German Gastric Group at AIO) – Al-Batran S-E, et al

Key results



	ECF/ECX	FLOT
mOS, months (95%CI)	35 (27, 46)	50 (38, NE)
HR (95%CI)	0.77 (0.63, 0.94)	
Log-rank p-value	0.012	

OS rate*, %	ECF/ECX	FLOT
2-year	59	68
3-year	48	57
5-year	36	45

Median follow-up for surviving patients: 43 months in both arms

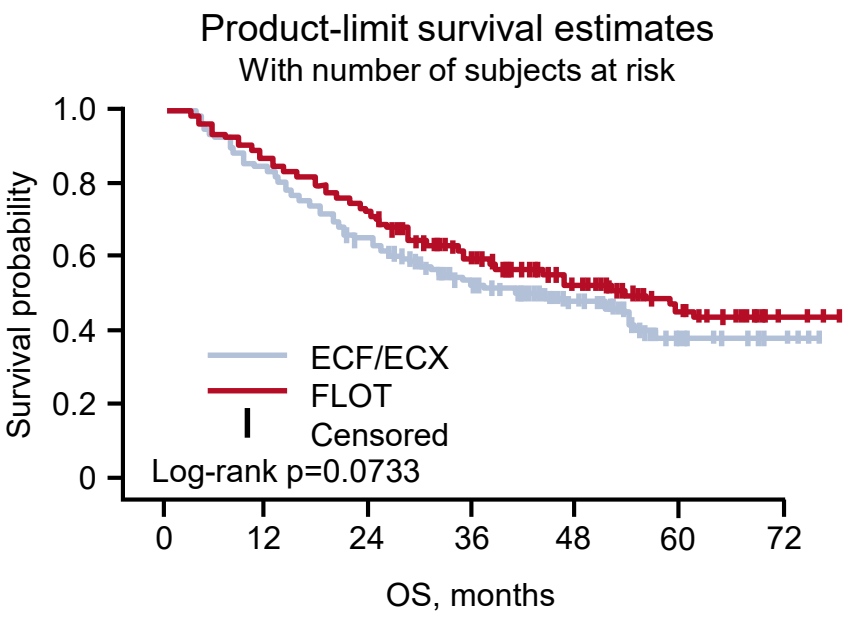
*Projected OS rates

LBA27_PR: Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) for resectable esophagogastric cancer: updated results from multicenter, randomized phase 3 FLOT4-AIO trial (German Gastric Group at AIO) – Al-Batran S-E, et al

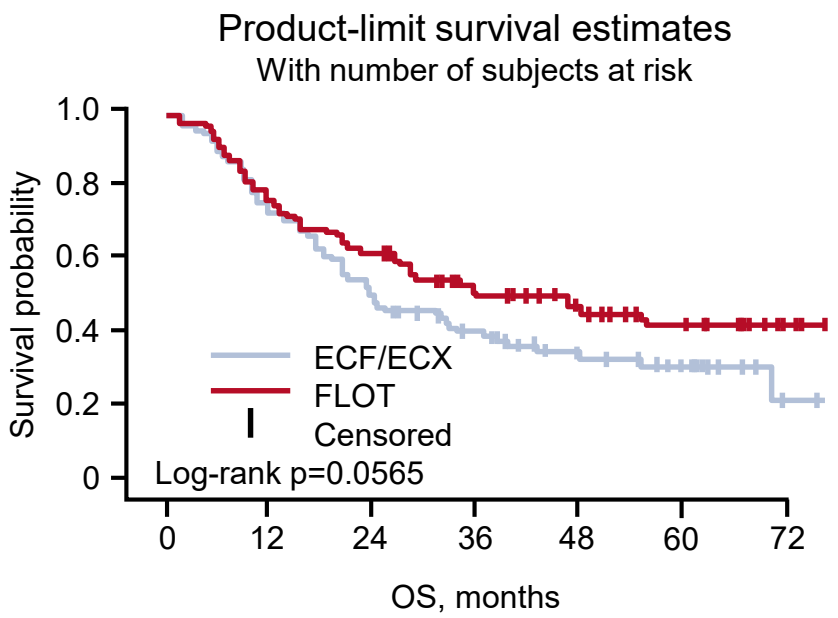
Key results (cont.)

Efficacy by histology: signet cell tumours derive pronounced benefit

OS with ECF/ECX vs. FLOT in patients with no signet cells



OS with ECF/ECX vs. FLOT in patients with signet cells



Al-Batran S-E, et al. Ann Oncol 2017;28(Suppl 5):Abstr LBA27_PR

LBA27_PR: Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) for resectable esophagogastric cancer: updated results from multicenter, randomized phase 3 FLOT4-AIO trial (German Gastric Group at AIO) – Al-Batran S-E, et al

Conclusions

- **In patients with oesogastric cancer, compared with ECF/ECX, FLOT increased rates of curative surgery and prolonged PFS and OS**
- **FLOT demonstrated a consistent relative effect across all subgroups and sensitivity analyses**
- **In perioperative treatment of patients with oesogastric cancer, FLOT may be considered as a new standard of care**

Al-Batran S-E, et al. Lancet 2019; 393: 1984-1957

Adjuvant Therapy In Gastric Cancer Improves OS

- Pre and Post op chemo
  - ECF VS surgery alone, MAGIC trial:
    - 13% 5 yr OS, HR 0.75
  - FLOT VS ECF
    - OS 50 mos VS 35 mos, HR = 0.77
- Post op chemo (Asia) 2 trial, 2000, D2 resection
  - S-1 VS surgery alone, ACTS-GC:
    - 13% 5 yr OS, HR 0.67 (2011 update)
  - Post op CapeOx VS surgery alone, CLASSIC trial:
    - 14% 3yr DFS, HR 0.56
- Post op RT + chemo
  - 5FU-LV + RT VS surgery alone, INT 116: (D1 LN dissection)
    - 10% 5 yr OS, HR 0.65
  - Cape/cisplatin VS CMT+ RT, ARTIST: (D2 LN dissection)
    - No benefit of adding RT to CMT

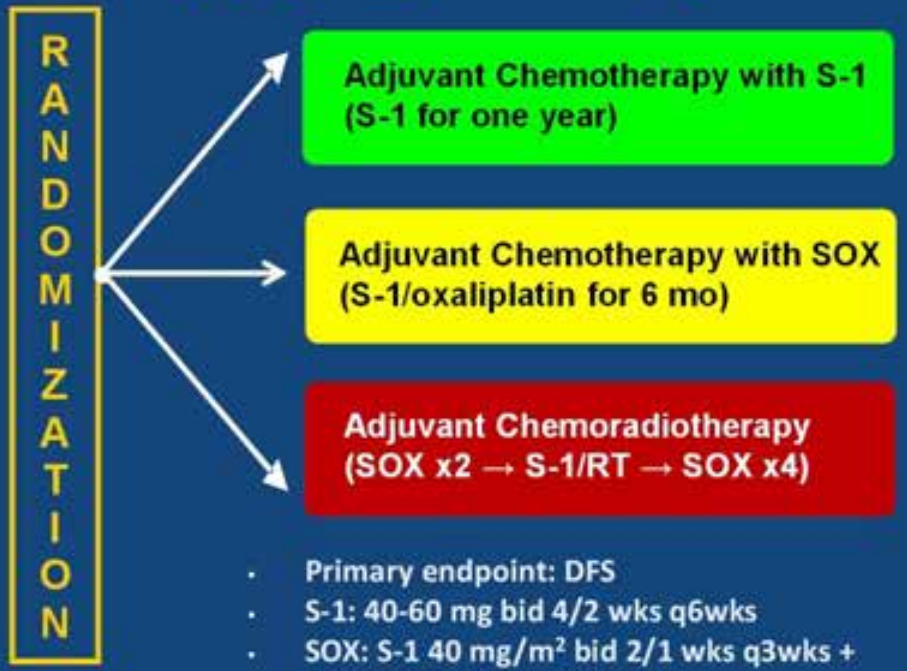
ARTIST 2: Interim results of a phase III trial involving adjuvant chemotherapy and/or chemoradiotherapy after D2-gastrectomy in stage II/III gastric cancer (GC)

Se Hoon Park,[1] Dae Young Zhang,[2] Boram Han,[2] Jun Ho Ji,[3] Tae Gyu Kim,[3] Sung Yong Oh,[4] In Gyu Hwang,[5] Jung Hoon Kim,[6] Dong Bok Shin,[7] Do Hoon Lim,[1] Kyoung Mee Kim,[1] Ji Yeong An,[1] Min-Gew Choi,[1] Jun-Ho Lee,[1] Tae Sung Sohn,[1] Jae-Moon Bae,[1] Sung Kim,[1] Seung Tae Kim,[1] Jeeyun Lee[1] and Won Ki Kang[1]

[1]Sungkyunkwan University, Samsung Medical Center, Seoul, Korea; [2]Hallym University Medical Center, Anyang, Korea; [3]Samsung Changwon Hospital, Changwon, Korea; [4]Dong-A University, Busan, Korea; [5]Chung-Ang University, Seoul, Korea; [6]Gyeongsang National University, Jinju, Korea; [7]Gachon University Gil Hospital, Incheon, Korea.

Adjuvant chemoRadioTherapy In Stomach Tumor 2

- 900 patients with D2 resected gastric adenocarcinoma
- pStage II to III, LN+
- Stratified by (1) stage, (2) type of surgery (STG *v* TG), (3) Lauren classification



- Primary endpoint: DFS
- S-1: 40-60 mg bid 4/2 wks q6wks
- SOX: S-1 40 mg/m^2 bid 2/1 wks q3wks + oxaliplatin 130 mg/m^2 D1
- S-1/RT: S-1 40 mg bid daily concurrently with RT 45 Gy for 5 wks

1 *ClinicalTrials.gov*, NCT0176146

Presented By Se Hoon Park at 2019 ASCO Annual Meeting

ARTIST 2 Secondary Endpoints and Statistics

Secondary endpoints

- Safety
- Overall survival
- Patterns of recurrence
- Quality-of-life
- Biomarker studies

Statistical design

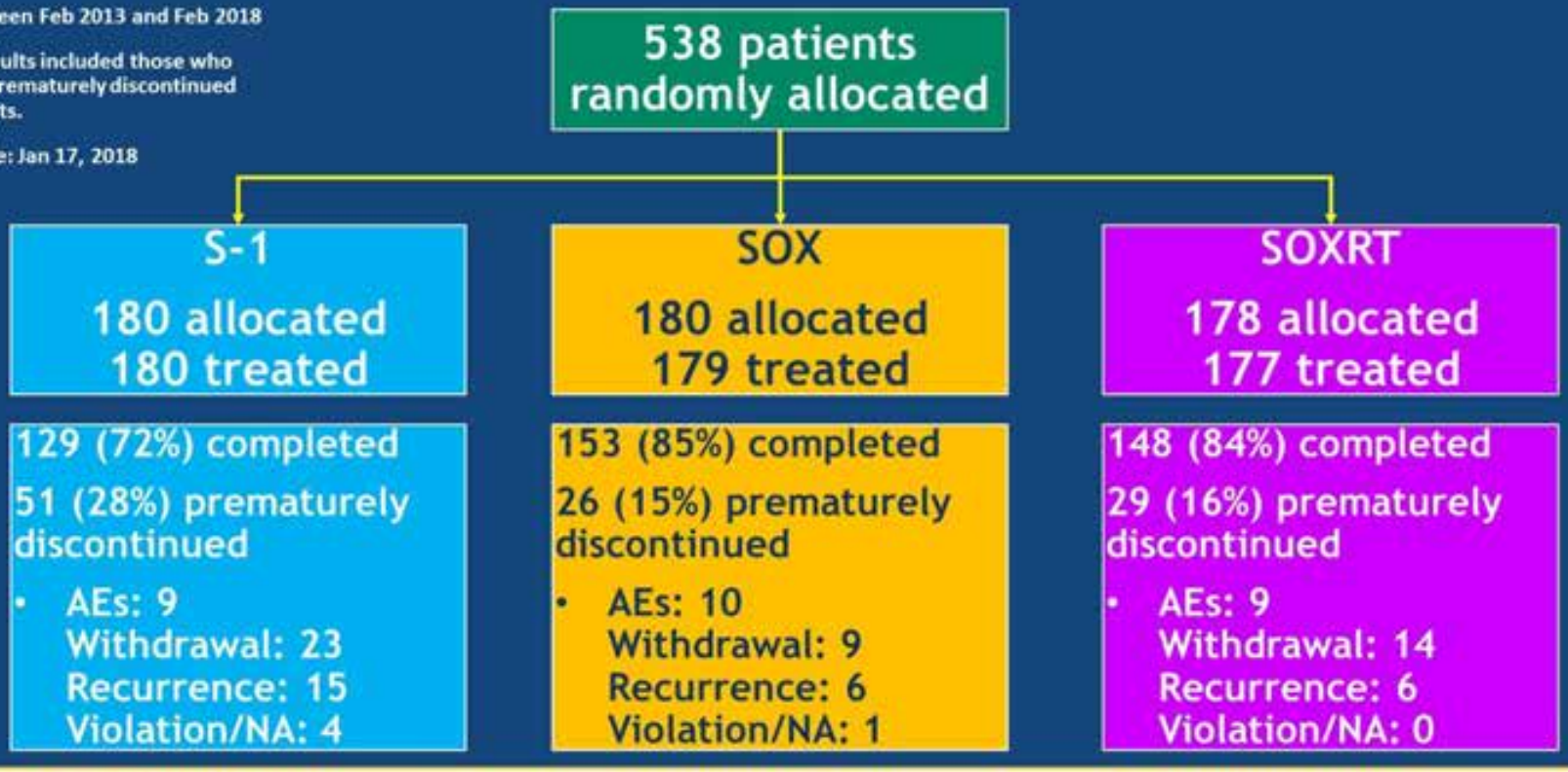
- Target of 226 DFS events (=855 eligible patients) provides 90% power to detect a HR of 0.67, assuming a 3-y DFS of,
  - 72.00% with S-1 arm
  - 80.33% with SOX or SOXRT arms
- Planned interim analyses
  - To test for both superiority and futility
  - By far, 5 interim analyses performed

ARTIST 2 Disposition of Study Treatment

Recruited between Feb 2013 and Feb 2018

This interim results included those who completed or prematurely discontinued study treatments.

Data cutoff date: Jan 17, 2018



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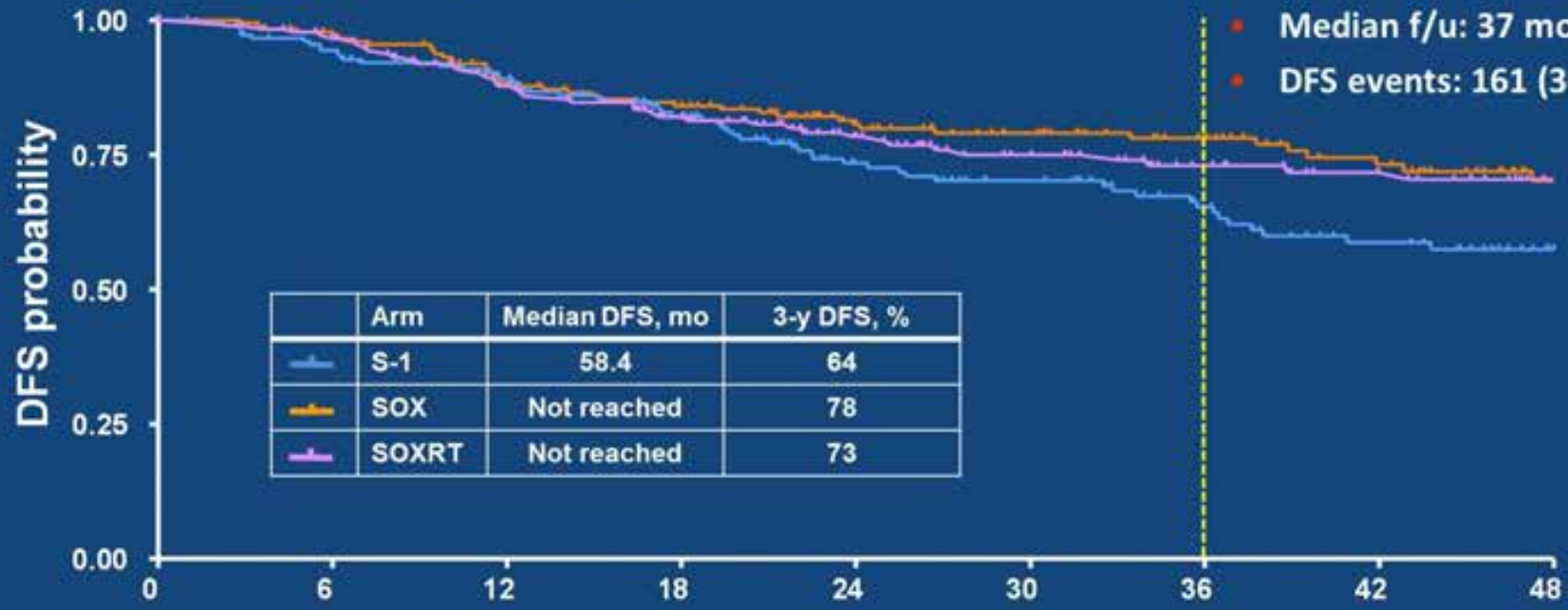
ARTIST 2 Baseline Characteristics: Patient

	Total (*n*=538)	S-1 (*n*=180)	SOX (*n*=180)	SOXRT (*n*=178)
Median age, years (range)	61 (27-85)	63 (32-85)	60 (31-79)	62 (27-77)
Male gender	350 (65%)	121 (67%)	112 (62%)	117 (66%)
ECOG performance status				
0	295 (55%)	93 (52%)	93 (52%)	109 (61%)
1	241 (45%)	86 (48%)	85 (48%)	68 (39%)
2	2 (0%)	1 (0%)	1 (0%)	0 (0%)
Type of surgery				
Total gastrectomy	194 (36%)	65 (36%)	62 (34%)	67 (38%)
Subtotal gastrectomy	344 (64%)	115 (64%)	117 (66%)	110 (62%)
Stage				
II	161 (30%)	55 (31%)	51 (28%)	55 (31%)
III	377 (70%)	125 (69%)	128 (72%)	122 (69%)

ARTIST 2 Baseline Characteristics: Tumor

	Total (*n*=538)	S-1 (*n*=180)	SOX (*n*=180)	SOXRT (*n*=178)
Intestinal type disease	162 (30%)	52 (29%)	58 (32%)	52(29%)
pT				
1	42 (8%)	14 (8%)	13 (7%)	15 (8%)
2	90 (17%)	32 (18%)	29 (16%)	29 (16%)
3	214 (39%)	79 (44%)	60 (33%)	73 (41%)
4	192 (36%)	55 (31%)	77 (43%)	60 (34%)
pN, median (range)				
Dissected no. of LNs	43 (12-101)	42 (16-99)	45 (12-95)	43 (20-101)
Positive no. of LNs	5 (1-66)	6 (1-33)	4 (1-42)	6 (1-66)
LN ratio	0.13 (0.01-0.91)	0.13 (0.01-0.91)	0.10 (0.02-0.83)	0.15 (0.01-0.71)
Lymphovascular invasion	409 (76%)	130 (72%)	145 (81%)	134 (75%)
Perineural invasion	329 (61%)	110 (61%)	110 (61%)	109 (61%)
HER2+ (2+/ISH+ or 3+)	30 (6%)	9 (5%)	8 (4%)	13 (7%)

ARTIST 2 Primary Endpoint



	Arm	Median DFS, mo	3-y DFS, %
	S-1	58.4	64
	SOX	Not reached	78
	SOXRT	Not reached	73

Pts at risk									
	S-1	180	170	161	149	137	130	124	118	116
	SOX	180	175	159	151	145	142	140	135	133
	SOXRT	178	172	156	146	140	137	135	134	132

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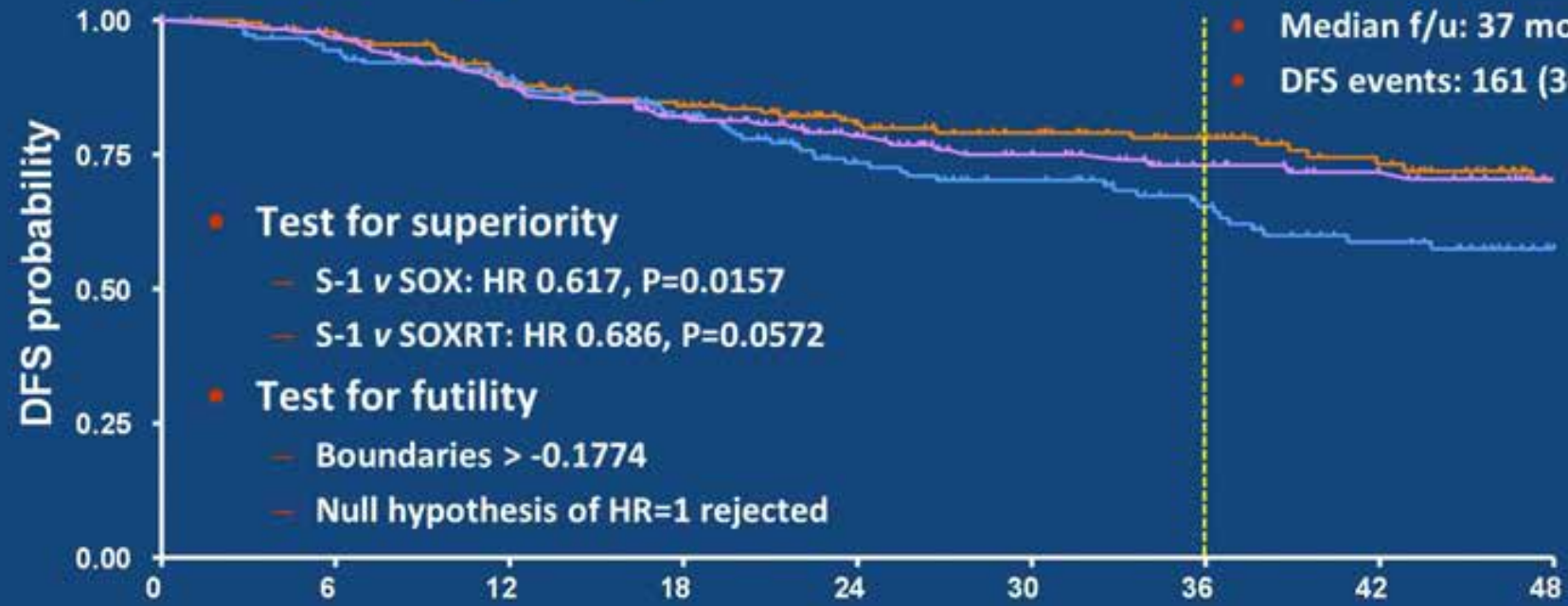
ARTIST 2 Primary Endpoint



Pts at risk									
	S-1	180	170	161	149	137	130	124	118	116
	SOX	180	175	159	151	145	142	140	135	133
	SOXRT	178	172	156	146	140	137	135	134	132

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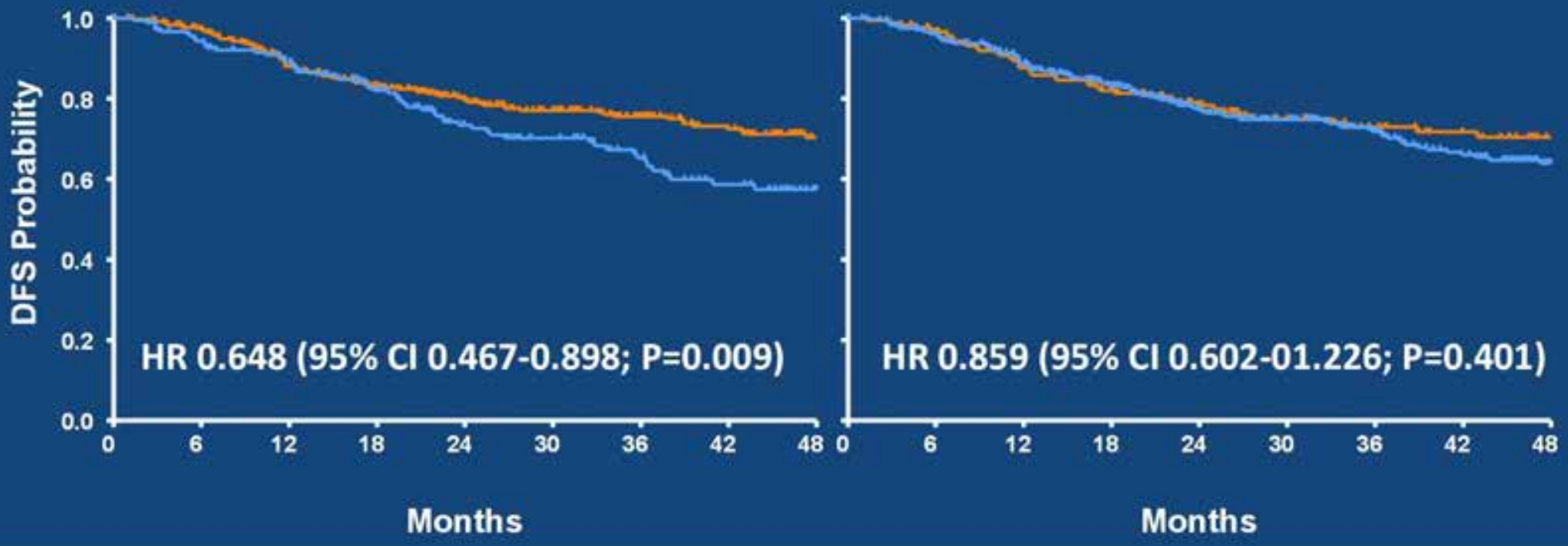
ARTIST 2 Subgroup Analysis of DFS

- S-1 *v* SOX/SOXRT
- S-1/SOX *v* SOXRT



Conclusions

- In patients with curatively D2-resected, stage 2 or 3, node-positive GC, adjuvant SOX or SOXRT was effective in prolonging DFS, when compared to S-1 monotherapy.
  - Adjuvant S-1, SOX and SOXRT were well tolerated
  - No additional benefit with chemoradiotherapy
- Although the boundaries for stopping trial were not reached, the IDMC considered the results from this efficacy interim analysis sufficient to meet the endpoints of the ARTIST 2 trial.
  - As of Jan 2019, a total of 547 patients enrolled onto the ARTIST 2 trial
  - IDMC recommended stopping the trial
  - Prolonged follow-up data and secondary endpoints will be reported in the future.

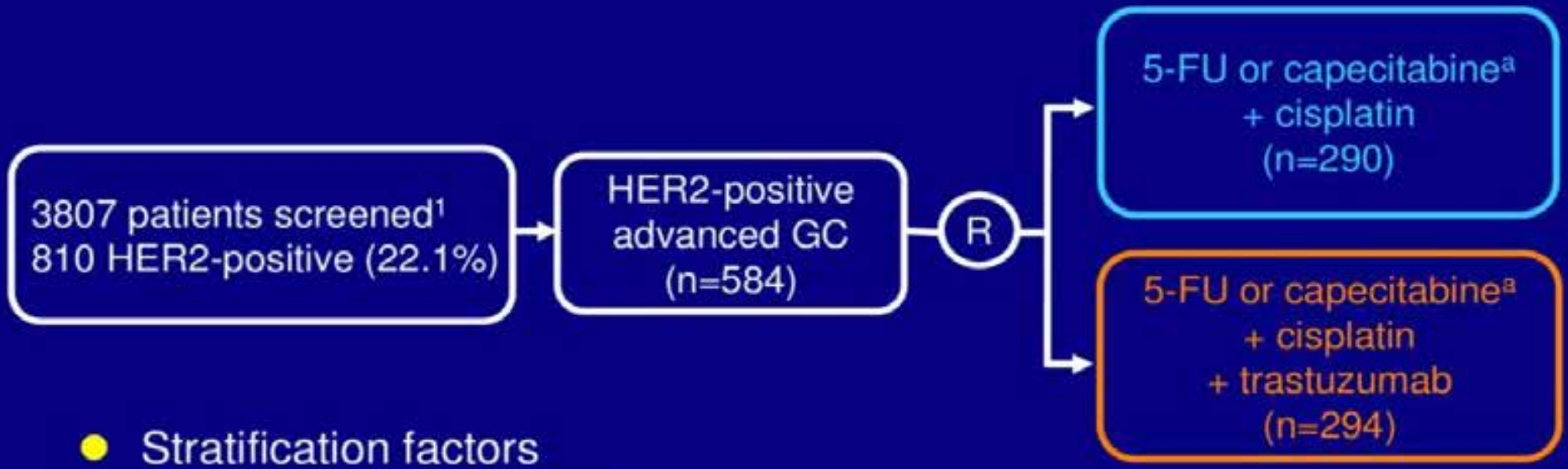
Systemic Treatment for Metastatic Disease

First line

- Preferred regimens: fluoropyrimidine (5-FU or capecitabine) combined with either oxaliplatin or cisplatin
- Trastuzumab combined in HER-2 positive mGC

ToGA trial design

Phase III, randomized, open-label, international, multicenter study

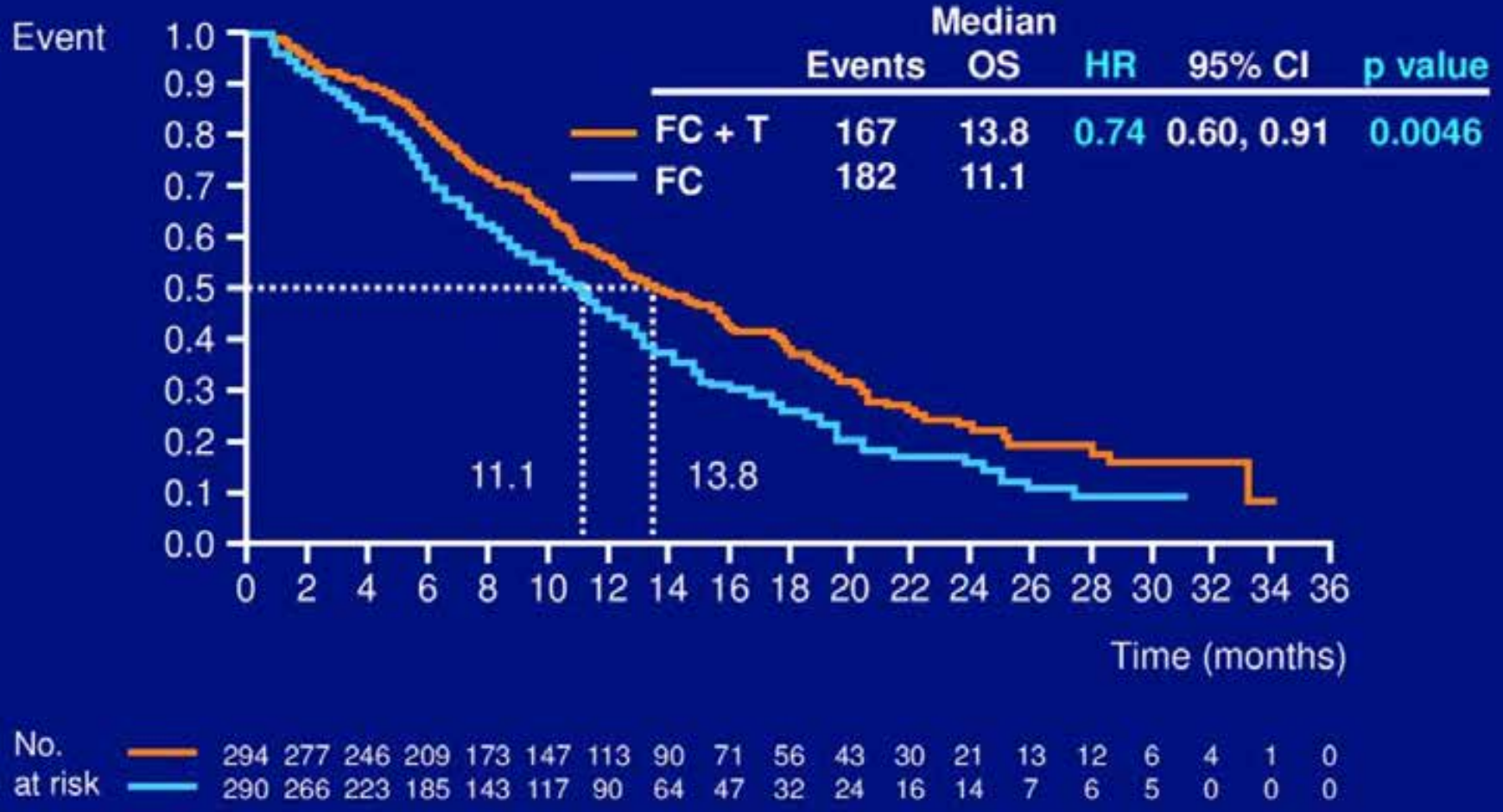


- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

[a]Chosen at investigator's discretion
GEJ, gastroesophageal junction

[1]Bang et al; Abstract 4556, ASCO 2009

Primary end point: OS

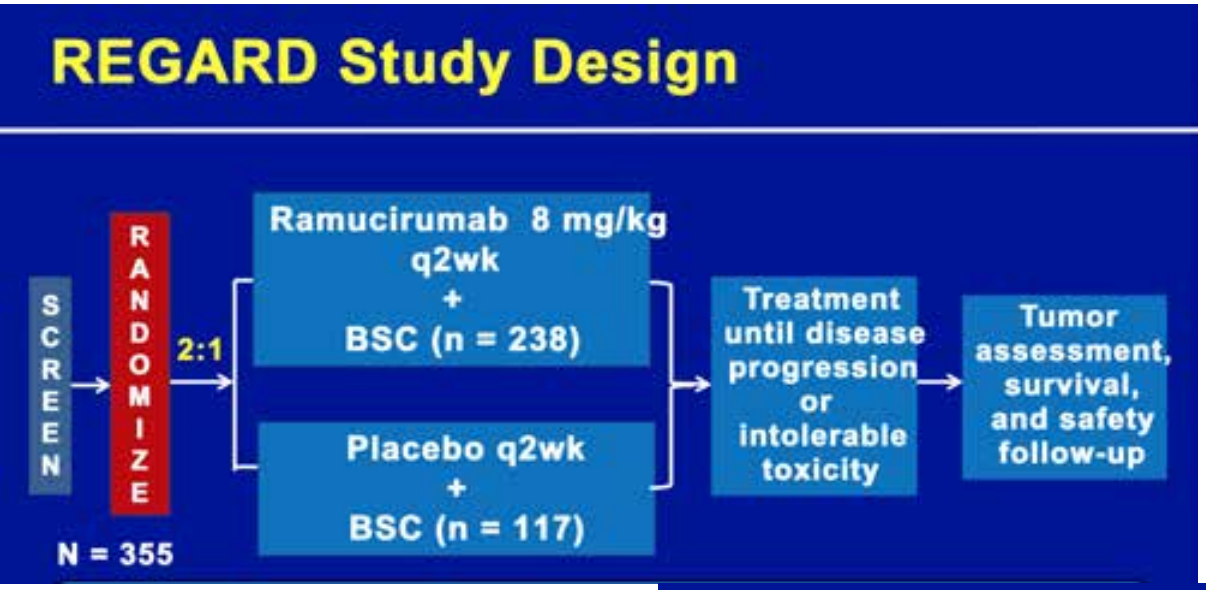


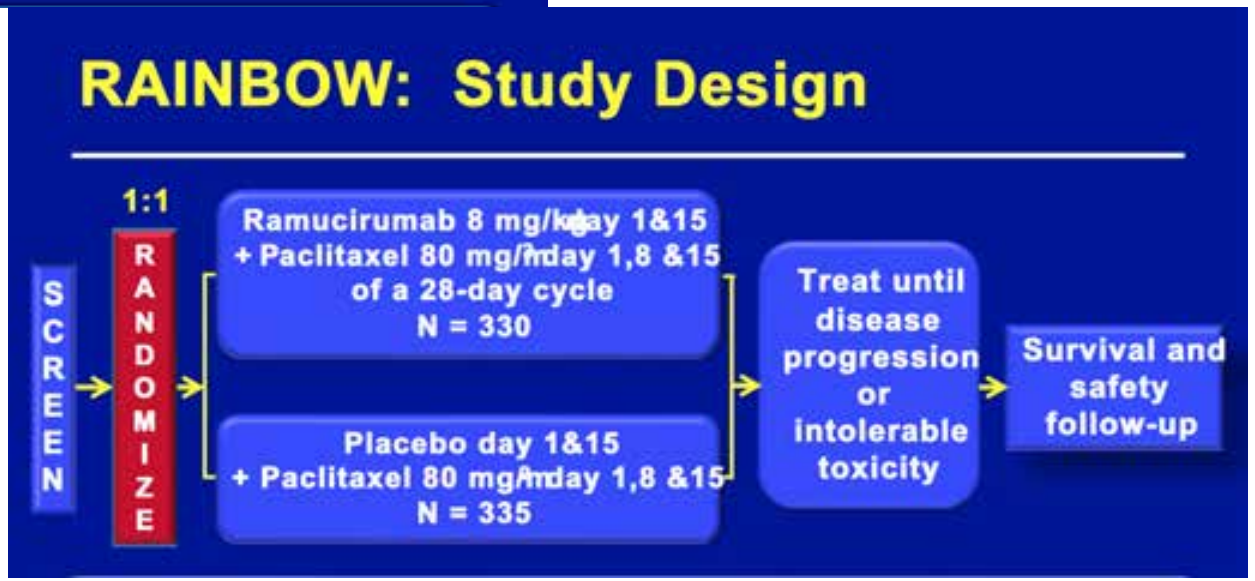
T, trastuzumab

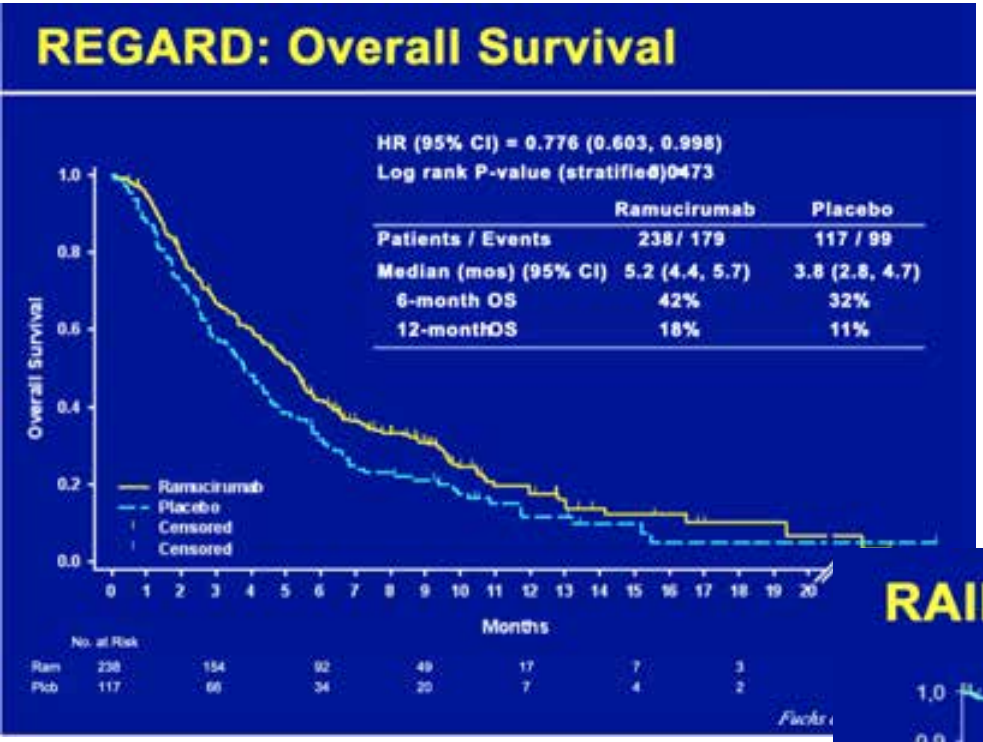
Choices of Later-line Treatment

- Chemotherapy
  - Paclitaxel
  - Docetaxel
  - Irinotecan
  - trifluridine and tipiracil (TAS-102) (3rd line)
- Targeted therapy
  - Ramucirumab (single or combination with paclitaxel)
- Immunotherapy
  - Pembrolizumab (MSI-H or positive PD-L1)
  - Nivolumab

Ramucirumab in second-line Treatment



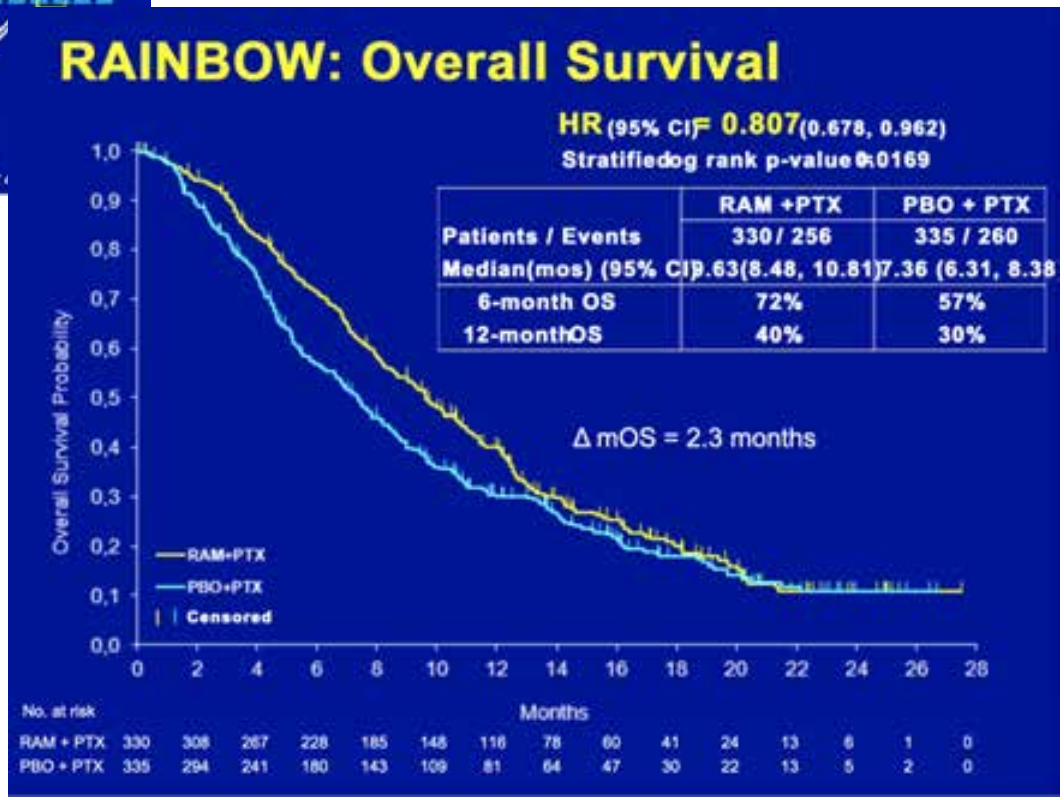




REGARD

OS: Ramu 5.2 mos VS Plb 3.8 mos

HR 0.77



RAINBOW

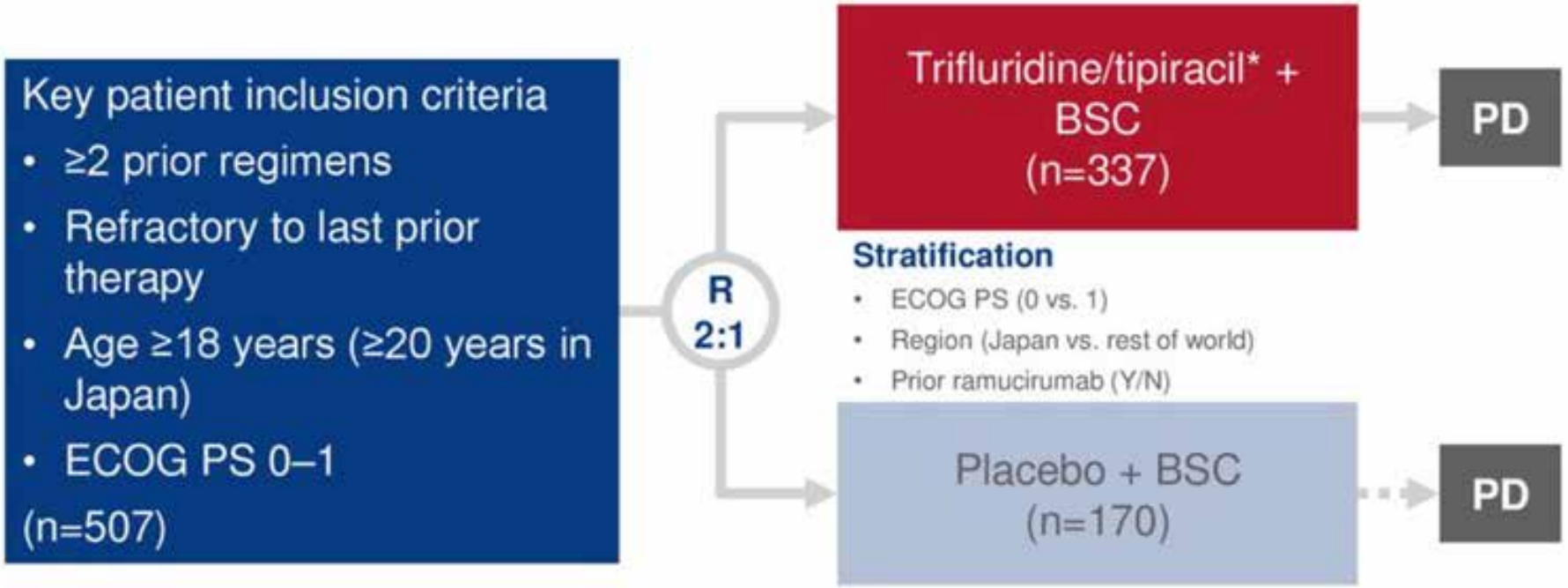
OS: Ramu+Pac 9.63mos VS Plb 7.36 mos

HR 0.80

LBA-002: Overall survival results from a phase III trial of trifluridine/tipiracil vs. placebo in patients with metastatic gastric cancer refractory to standard therapies (TAGS) – Tabernero J, et al

Study objective

- To assess the efficacy and safety of trifluridine/tipiracil vs. placebo in patients with metastatic gastric cancer refractory to standard therapies (TAS-102 trial)



PRIMARY ENDPOINT

- OS

SECONDARY ENDPOINTS

- PFS, ORR, DCR, QoL, time to ECOG PS ≥2, safety

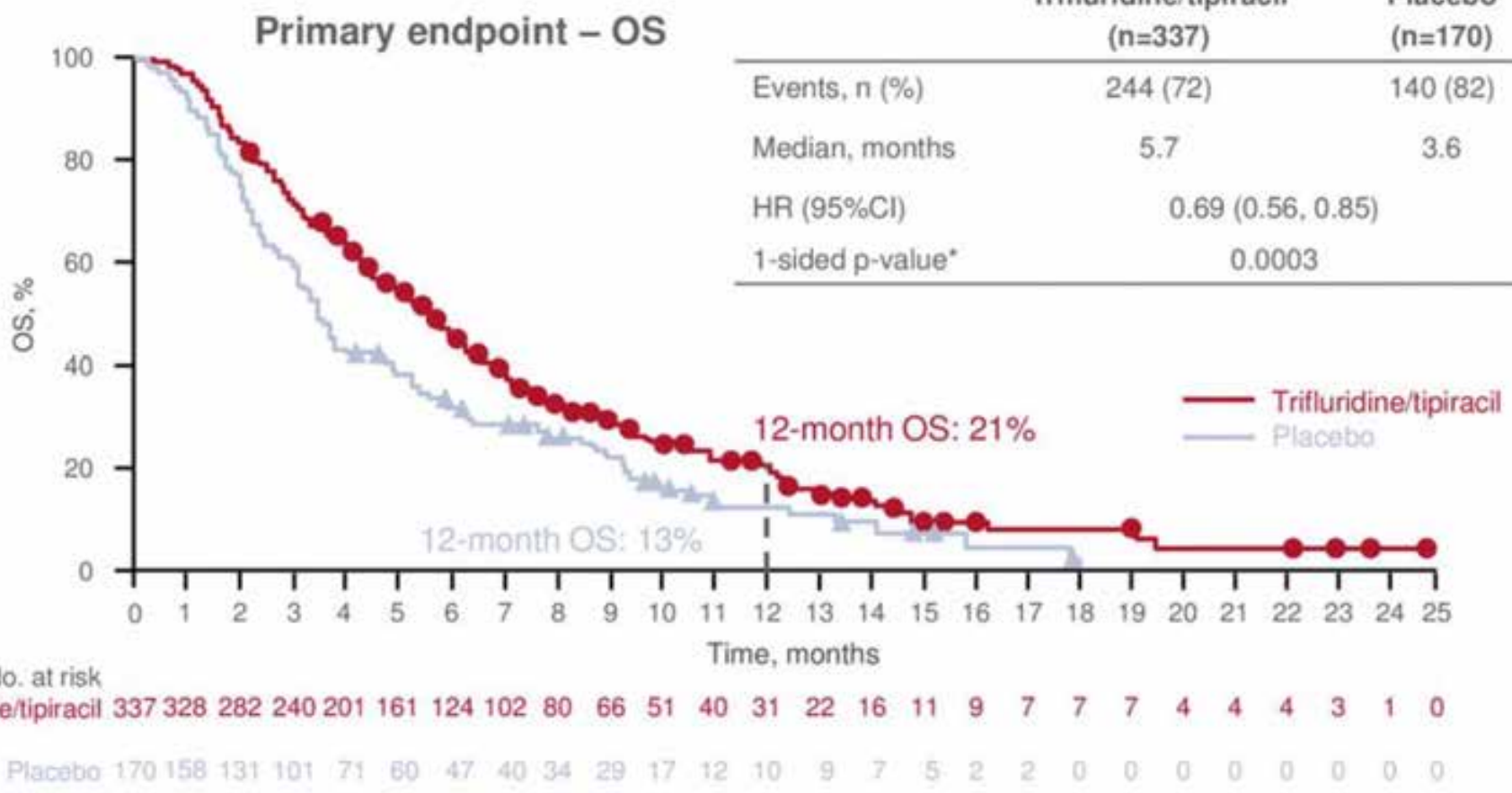
*35 mg/m^2 bid orally D1–5, 8–12 of each 28-day cycle

Tabernero J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-002

LBA-002: Overall survival results from a phase III trial of trifluridine/tipiracil vs. placebo in patients with metastatic gastric cancer refractory to standard therapies (TAGS) – Tabernero J, et al

Key results

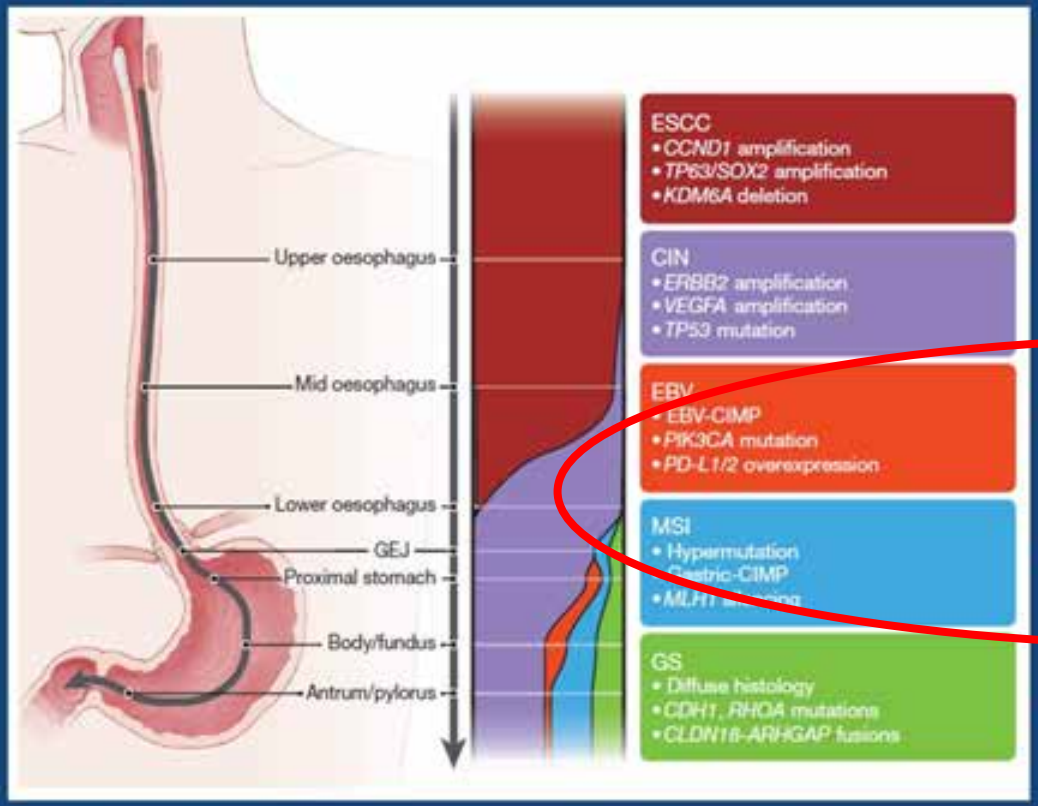
	Trifluridine/tipiracil (n=337)	Placebo (n=170)
Events, n (%)	244 (72)	140 (82)
Median, months	5.7	3.6
HR (95%CI)	0.69 (0.56, 0.85)	
1-sided p-value*	0.0003	



*Stratified log-rank test

Tabernero J, et al. Ann Oncol 2018;29(suppl 5):abstr LBA-002

Esophago-Gastric Cancer Subclasses



ESCC - Similarities with Head-Neck Cancer

CIN - Immunogenic ??? HER2 / VEGF amplications

EBV - Immunogenic Immune infiltrates, PD-L1 high

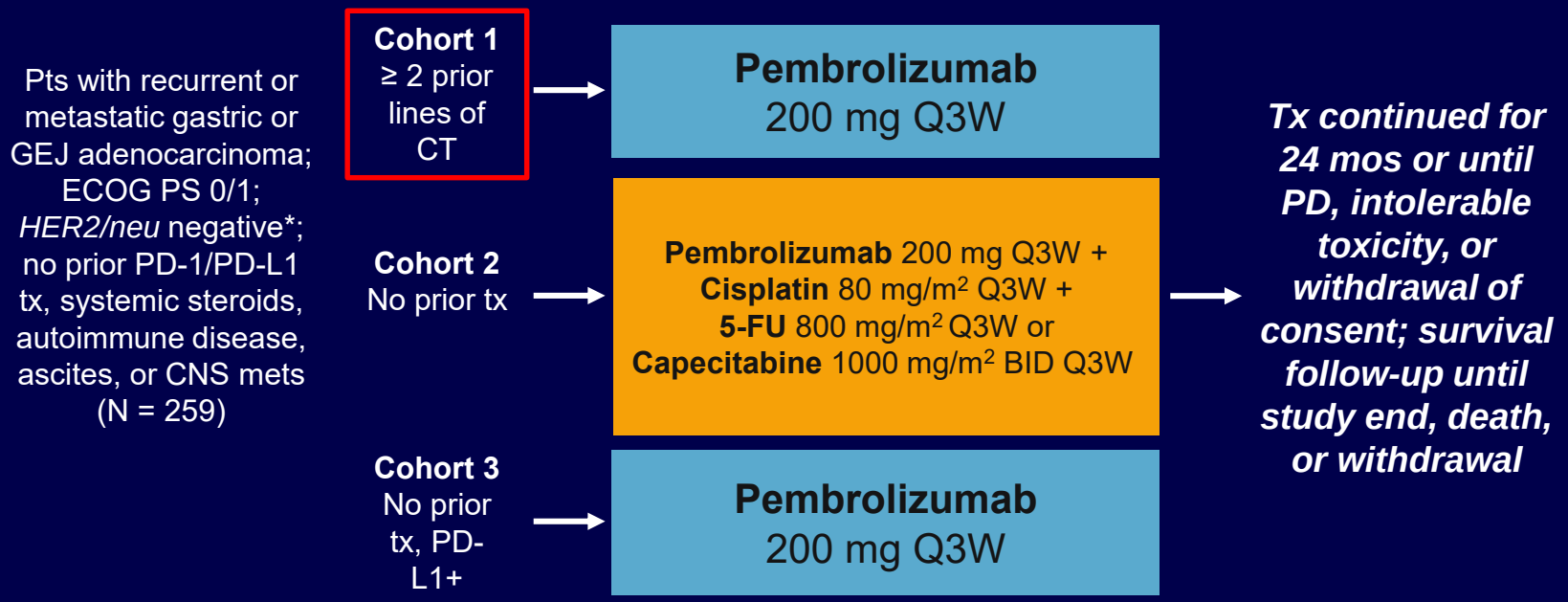
MSI - Immunogenic High mutational burden

Genomic stable (silent) Lower mutational burden

The Cancer Genome Atlas Research Network. *Nature*. 2017;541:169-175

KEYNOTE-059: Study Design

- Open-label, multicohort phase II study



**HER2/neu* positive allowed in cohort 1 if prior trastuzumab administered.

- **Primary endpoints:** ORR, safety; **secondary endpoints:** DoR, PFS, OS
- Exploratory biomarker endpoints: efficacy by MSI, GEP

Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

KEYNOTE-059 (Cohort 1): Baseline Characteristics

Characteristic	All Pts (N = 259)
Median age, yrs (range)	62 (24-89)
Male, n (%)	198 (76.4)
Geographic region, n (%)	
▪ United States	124 (47.9)
▪ East Asia	34 (13.1)
▪ Other	101 (39.0)
ECOG PS, n (%)	
▪ 0	107 (41.3)
▪ 1	151 (58.3)
Primary tumor location, n (%)	
▪ Gastric	125 (48.3)
▪ GEJ	133 (51.4)

Characteristic, n (%)	All Pts (N = 259)
Prior therapies	
▪2	134 (51.7)
▪3	75 (29.0)
▪≥ 4	50 (19.3)
Prior surgery for gastric cancer	66 (25.5)
HER2 positive	63 (24.3)
PD-L1 expression	
▪Positive*	148 (57.1)
▪Negative	109 (42.1)

*CPS ≥ 1% where CPS is (PD-L1 staining cells/total tumor cells) x 100

Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

KEYNOTE-059 (Cohort 1): Response

Confirmed Response, % (95% CI)	All Pts (N = 259)
ORR	**11.6 (8.0-16.1)**
CR	2.3 (0.9-5.0)
PR	9.3 (6.0-13.5)
SD	16.2 (11.9-21.3)
PD	56.0 (49.7-62.1)
DCR*	27.0 (21.7-32.9)

- Median follow-up: 5.8 mos (range: 0.5-21.6 mos)

*CR + PR + SD ≥ 2 mos.

Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

KEYNOTE-059 (Cohort 1): Safety

TRAE Occurring in > 5% of Pts, %	All Pts (N = 259)	
	Any Grade	Grade 3/4
Fatigue	18.9	2.3
Pruritus	8.9	0
Rash	8.5	0.8
Hypothyroidism	7.7	0.4
Decreased appetite	7.3	0
Anemia	6.9	2.7
Nausea	6.9	0.8
Diarrhea	6.6	1.2
Arthralgia	5.8	0 .4

D/c for TRAEs: abnormal hepatic function, bile duct stenosis, n = 1 each.
Grade 5 TRAEs: acute kidney injury, pleural effusion, n = 1 each.

irAE Occurring in > 1% of Pts, %	All Pts (N = 259)	
	Any Grade	Grade 3/4
Any	17.8	4.6
Hypothyroidism	8.9	0.4
Hyperthyroidism	3.5	0
Colitis	2.3	1.2
Pneumonitis	1.9	0.8
Thyroiditis	1.5	0.4
Infusion reaction	1.5	0
Severe skin reaction*	1.5	1.5

*Includes erythema multiforme, jaundice, rash, maculopapular rash.
Systemic corticosteroids for irAEs: n = 13.
Treatment interruption due to irAEs: n = 10.

Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

KEYNOTE-059 (Cohort 1): Response by PD-L1 Expression and Line of Therapy

Confirmed Response, % (95% CI)	PD-L1		Line of Therapy		PD-L1 and Third Line of Therapy	
	Positive (n = 148)	Negative (n = 109)	Third (n = 134)	≥ Fourth (n = 125)	Positive (n = 75)	Negative (n = 58)
ORR	**15.5** (10.1-22.4)	**6.4** (2.6-12.8)	**16.4** (10.6-23.8)	**6.4** (2.8-12.2)	**22.7** (13.8-33.8)	**8.6** (2.9-19.0)
CR	2.0 (0.4-5.8)	2.8 (0.6-7.8)	3.0 (0.8-7.5)	1.6 (0.2-5.7)	2.7 (0.3-9.3)	3.4 (0.4-11.9)
PR	13.5 (8.5-20.1)	3.7 (1.0-9.1)	13.4 (8.2-20.4)	4.8 (1.8-10.2)	20.0 (11.6-30.8)	5.2 (1.1-14.4)
DCR*	33.1 (25.6-41.3)	19.3 (12.3-27.9)	31.3 (23.6-39.9)	22.4 (15.4-30.7)	38.7 (27.6-50.6)	22.4 (12.5-35.3)

Outcome	All Pts*	PD-L1+	PD-L1-
Median DoR, mos (95% CI)	**8.4** (1.6+† to 17.3+)	**16.3** (1.6+ to 17.3+)	**6.9** (2.4 to 7.0+)

Fuchs CS, et al. ASCO 2017. Abstract 4003.

Slide credit: clinicaloptions.com

KEYNOTE-061: Study Design

- Final analysis of international, randomized, open-label phase III trial
  - Analysis planned after ≥ 290 deaths in CPS ≥ 1 population or ~ 15 mos after last randomization, whichever was later (data cutoff after median f/u of 7.9 mos: October 26, 2017; deaths in CPS ≥ 1 population, n = 326)

Stratified by region (Europe/Israel/N. America/Australia vs Asia vs rest of world), ECOG PS (0 vs 1), TTP on first-line tx (< 6 vs ≥ 6 mos), PD-L1 CPS (< 1 vs ≥ 1)*

Unresectable metastatic or locally advanced adenocarcinoma of the stomach or GEJ, PD following first-line platinum- and fluoropyrimidine-based tx, ECOG PS 0/1, any PD-L1 CPS in first 489 patients and PD-L1 CPS ≥ 1 in final 103 patients† (N = 592)

→ **Pembrolizumab** 200 mg Q3W for up to 35 cycles (n = 296)

→ **Paclitaxel** 80 mg/m^2 on Days 1, 8, and 15 of 4-wk cycles (n = 296)

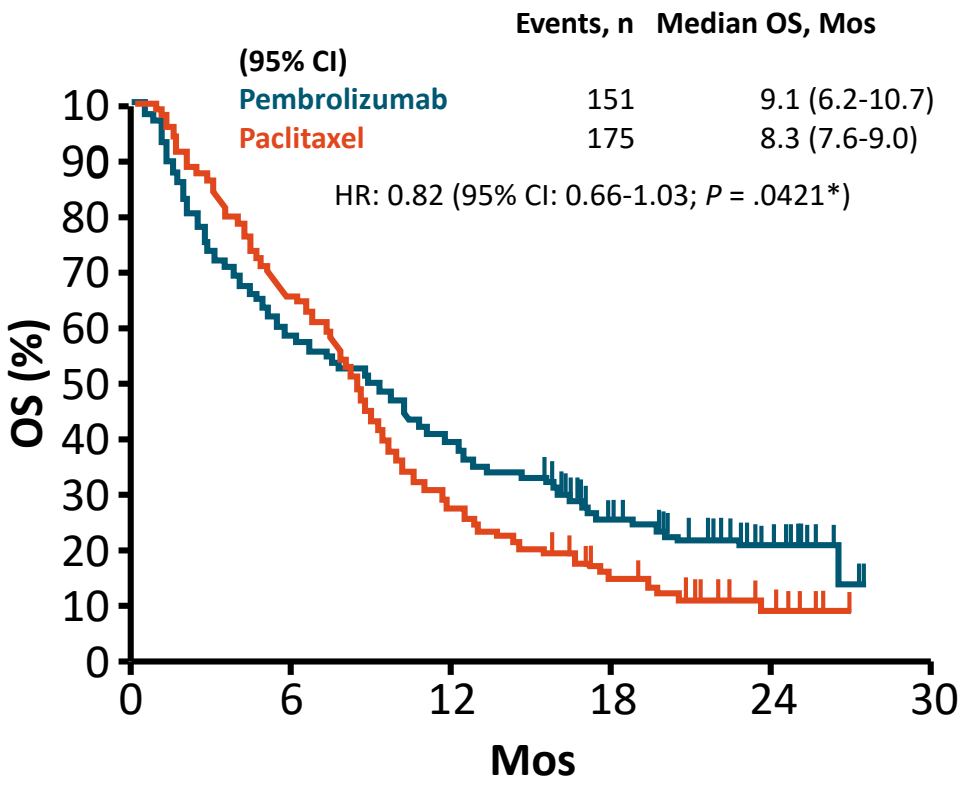
→ ***Until confirmed PD, unacceptable toxicity, withdrawal, or investigator decision***

- Primary endpoints: OS and PFS in CPS ≥ 1 population
  - 91% power with 1-sided α = 0.0215 if HR = 0.67 and 290 OS events observed in CPS ≥ 1 population
- Secondary endpoints: ORR and DoR in CPS ≥ 1 population, safety in all treated patients

*Only first 125 patients. †PD-L1 CPS determined with PD-L1 IHC 22C3 pharmDx assay, where CPS = number of PD-L1–positive tumor cells, lymphocytes, and macrophages out of total tumor cells x 100.

Fuchs CS, et al. ASCO 2018. Abstract 4062. Shitara K, et al. Lancet. 2018;[Epub ahead of print].

KEYNOTE-061: OS in PD-L1 CPS ≥ 1 Population



*OS significantly different in CPS PD-L1 ≥ 1 population when 1-sided *P* = .0135.

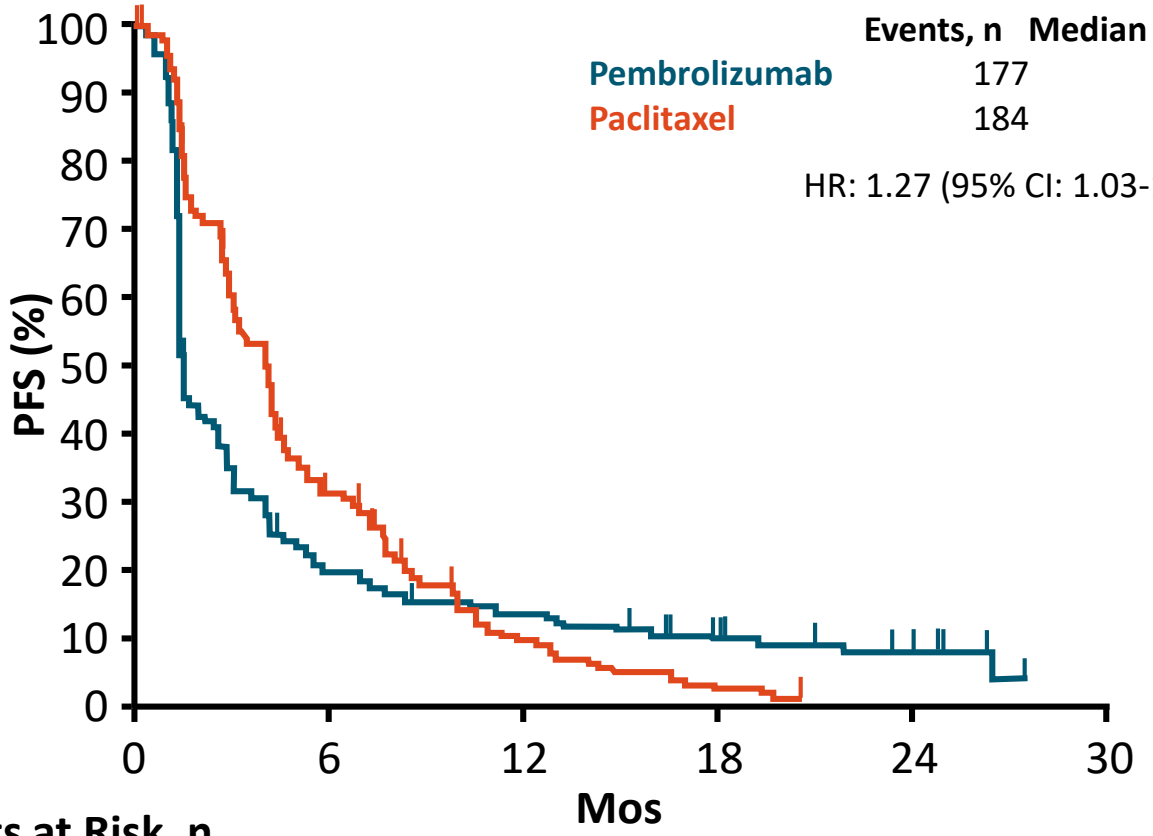
- No significant difference in OS for PD-L1 CPS ≥ 1 population or most protocol-specified subgroups
- Pembrolizumab improved OS in subgroups with ECOG PS 0, primary tumor in GEJ and in post-hoc analysis subgroups, PD-L1 CPS ≥ 10 and MSI-H

Result	Subgroup			
	ECOG PS 0 (n = 180)	Primary Tumor in GEJ (n = 135)	PD-L1 CPS ≥ 10 (n = 108)	MSI-H Tumors (n = 27)
HR for OS (95% CI)	0.69 (0.49-0.97)	0.61 (0.41-0.90)	0.64 (0.41-1.02)	0.42 (0.13-1.31)

Fuchs CS, et al. ASCO 2018. Abstract 4062. Shitara K, et al. Lancet. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

KEYNOTE-061: PFS in PD-L1 CPS ≥ 1 Population



	Events, n	Median PFS, Mos (95% CI)
Pembrolizumab	177	1.5 (1.4-2.0)
Paclitaxel	184	4.1 (3.1-4.2)

HR: 1.27 (95% CI: 1.03-1.57)

Patients at Risk, n

Pembrolizumab	196	38	25	15	7	0
Paclitaxel	199	57	15	4	0	0

Fuchs CS, et al. ASCO 2018. Abstract 4062. Shitara K, et al. Lancet. 2018;[Epub ahead of print].

Slide credit: clinicaloptions.com

KEYNOTE-061: Conclusions

- In the final analysis of this phase III study, second-line pembrolizumab did not significantly improve OS vs paclitaxel for advanced/metastatic gastric/GEJ cancer with PD-L1 CPS ≥ 1
  - HR for OS in PD-L1 CPS ≥ 1 population: 0.82 (95% CI: 0.66-1.03)
  - Pembrolizumab improved OS in subgroups with ECOG PS 0, primary tumor in GEJ, PD-L1 CPS ≥ 10, and MSI-H tumors
- Pembrolizumab was not associated with improved PFS or ORR
  - Responses to pembrolizumab more durable than to paclitaxel (median DoR: 18.0 vs 5.2 mos)
- Investigators concluded that results support efforts toward identifying subgroups likely to benefit from single-agent pembrolizumab and ongoing investigations into pembrolizumab-based combination treatments

Fuchs CS, et al. ASCO 2018. Abstract 4062. Shitara K, et al. Lancet. 2018;[Epub ahead of print].

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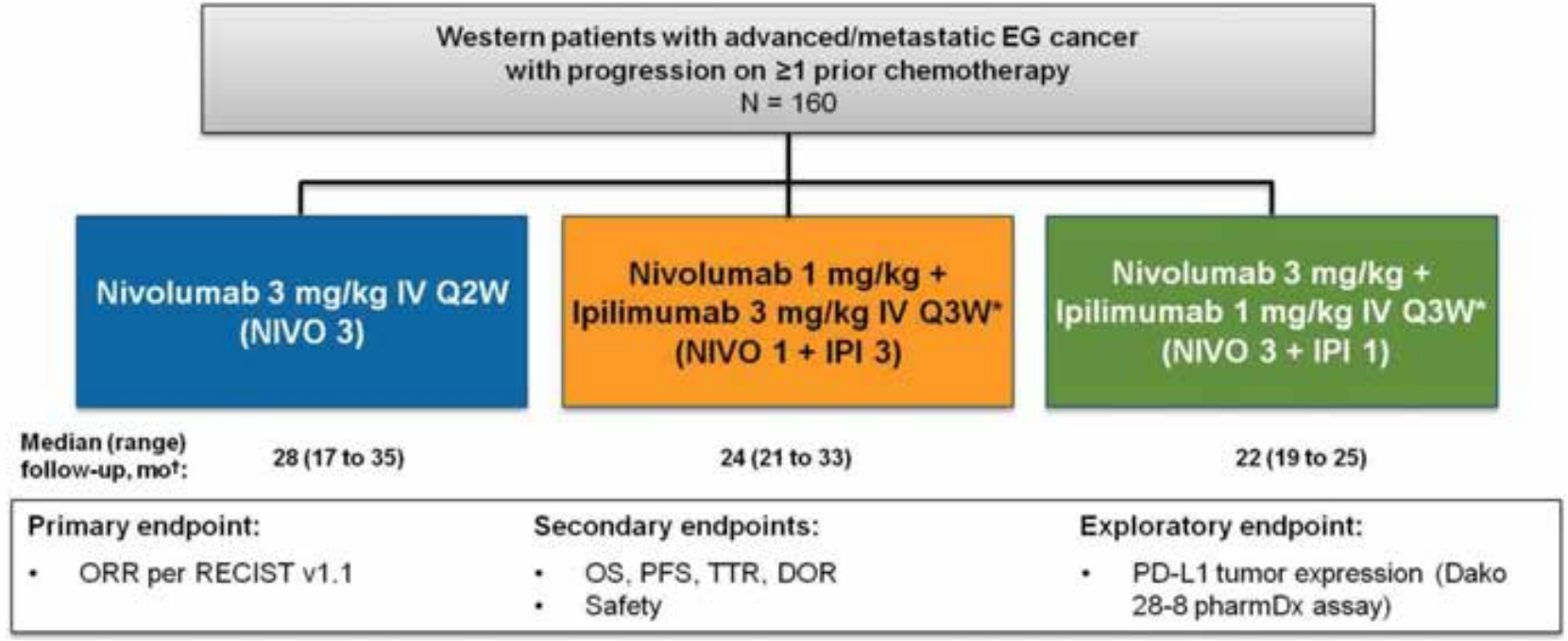
Checkmate 032 EG Cohort



DOR, duration of response; EG, esophagogastric (including gastric/esophageal/gastroesophageal junction cancer); TTR, time to response.
* Nivolumab + ipilimumab administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.
† Time from first dose to data cut-off; follow-up was shorter for patients who died prior to data cut-off.

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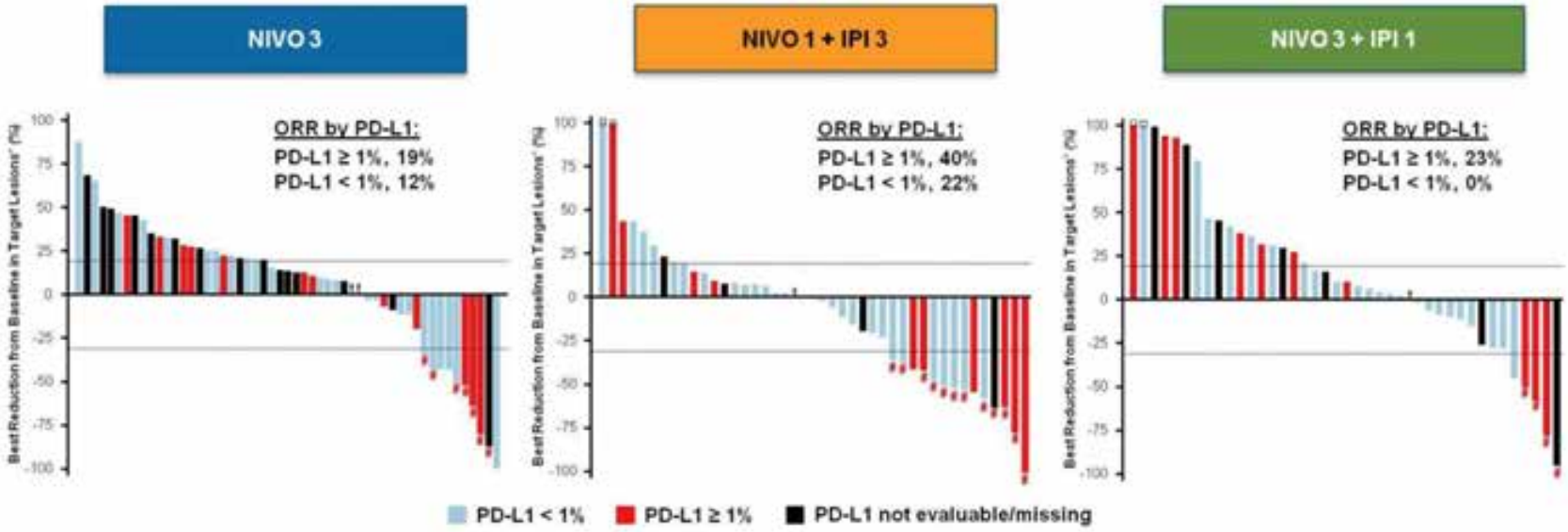
Best Reduction in Target Lesions



- Responses were observed regardless of PD-L1 expression

* Investigator review.
# Patients with confirmed response (complete or partial response).
† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 <1% (NIVO 1 + IPI 3).
□ change truncated to 100%

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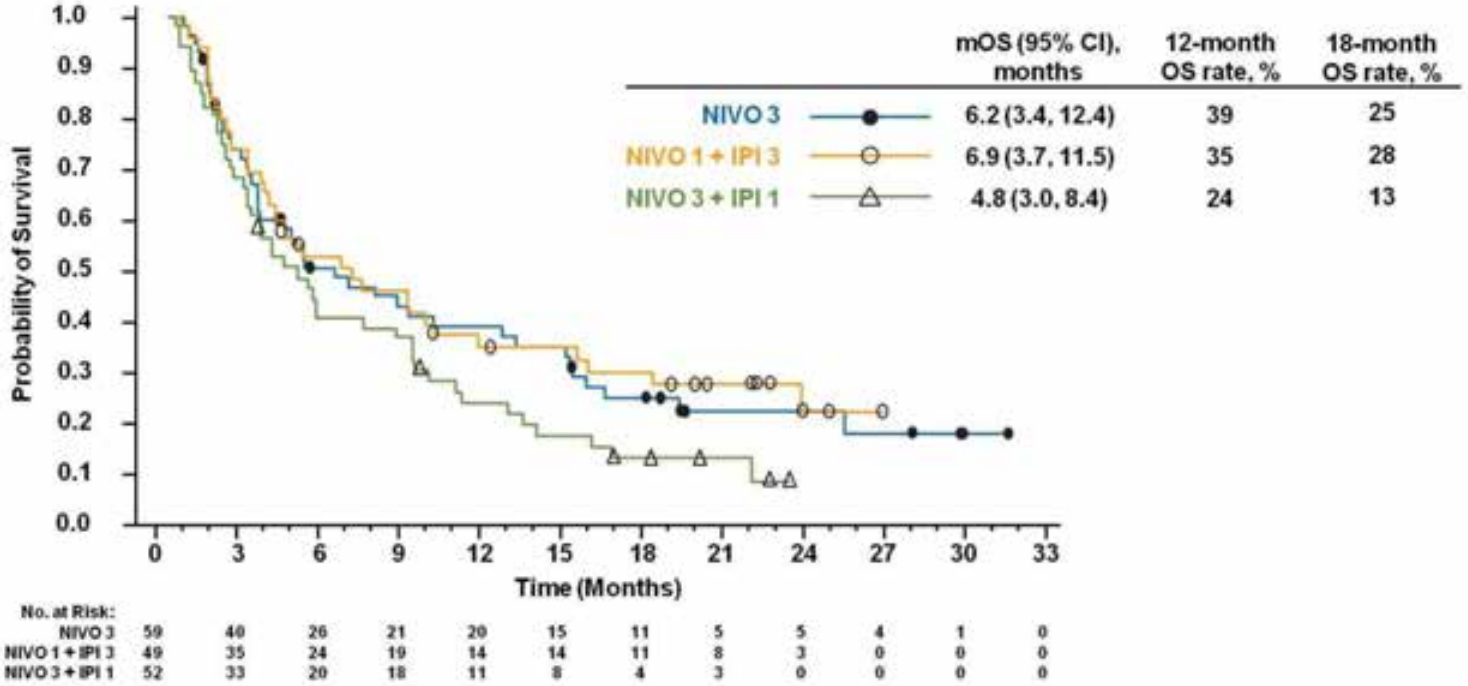
Overall Survival



	mOS (95% CI), months	12-month OS rate, %	18-month OS rate, %
NIVO 3	6.2 (3.4, 12.4)	39	25
NIVO 1 + IPI 3	6.9 (3.7, 11.5)	35	28
NIVO 3 + IPI 1	4.8 (3.0, 8.4)	24	13

mOS, median OS.

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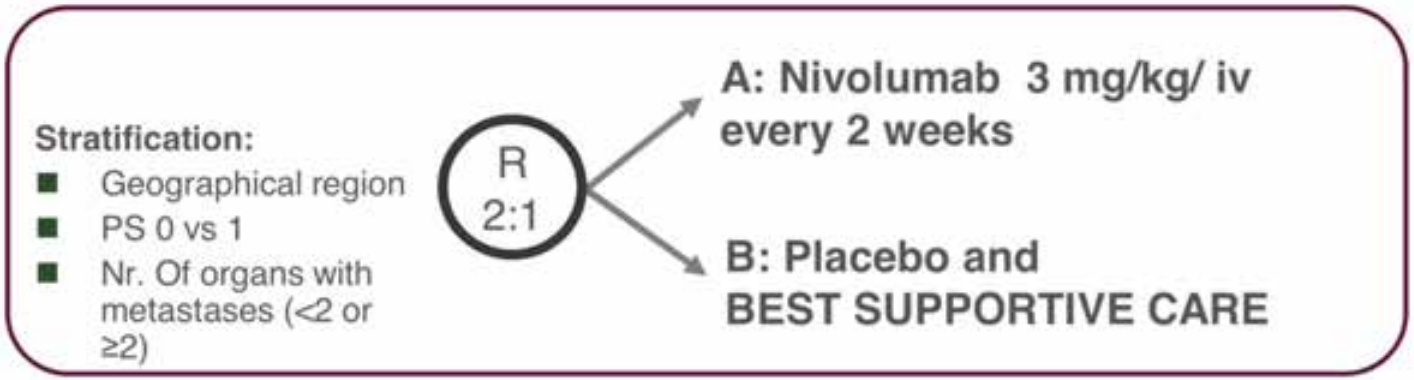
European Society for Medical Oncology

A Phase III Study of Nivolumab *vs* BSC in second line advanced gastroesophageal adenocarcinoma: The ATTRACTION-2 Trial



- **Objective I:** OS
- **Objectives II:**
  - PFS
  - Response rate, Duration of response, Disease Control rate
  - Time to progression
  - Safety

Japan , South Korea and Taiwan

Shitara, K. et al. Lancet 2018; 392:123–133.

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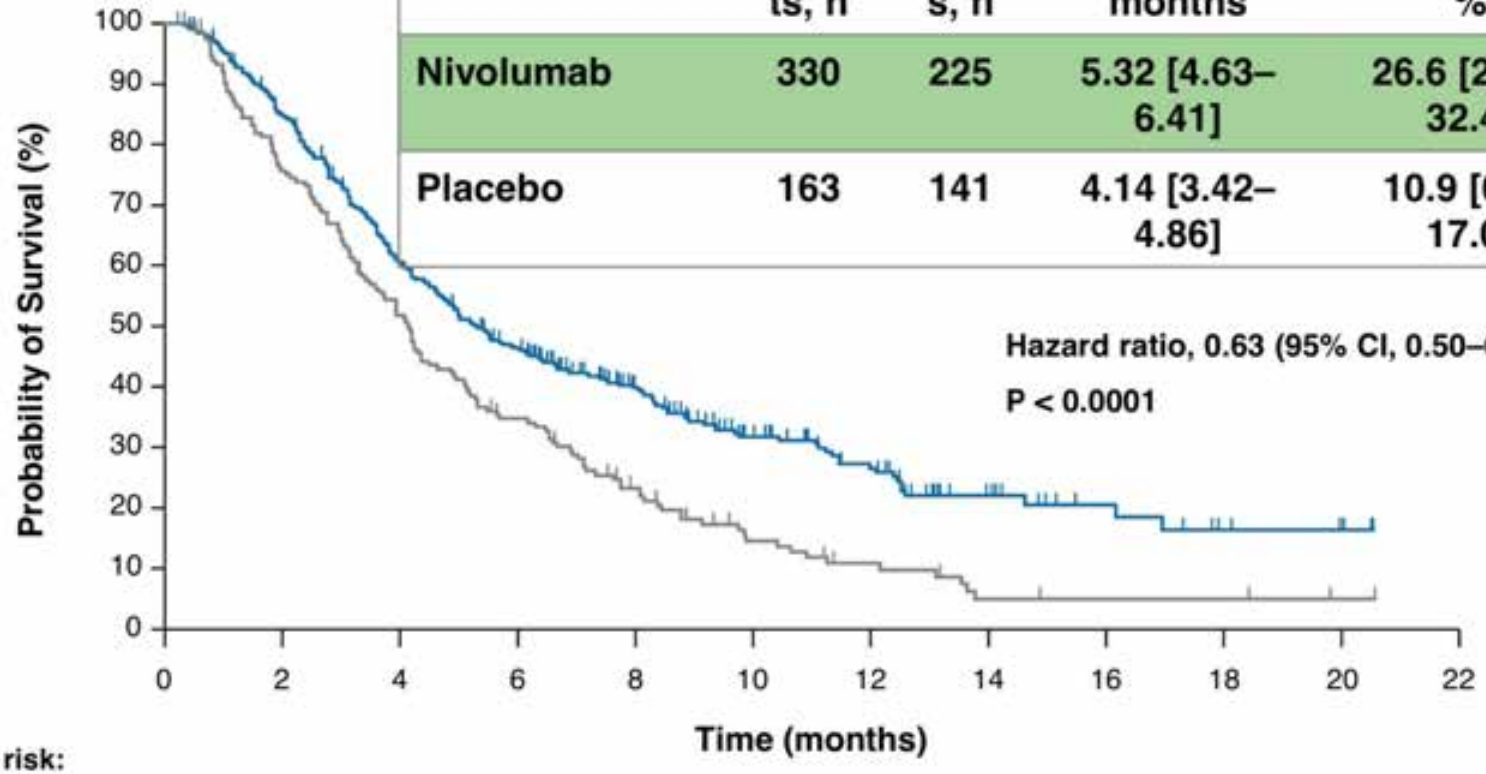
BEST PRACTICE
European Society for Medical Oncology

Overall Survival Nivolumab *vs* BSC in ATTRACTION-2 Trial

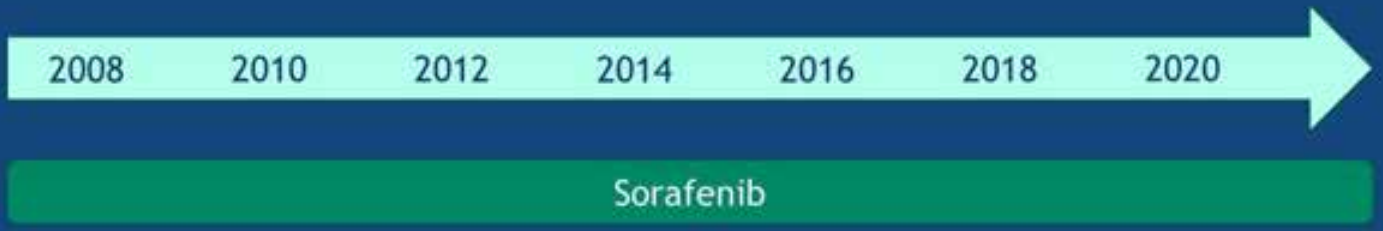
	Patients, n	Events, n	Median OS [95% CI], months	12-Month OS Rate [95% CI], %
Nivolumab	330	225	5.32 [4.63–6.41]	26.6 [21.1–32.4]
Placebo	163	141	4.14 [3.42–4.86]	10.9 [6.2–17.0]



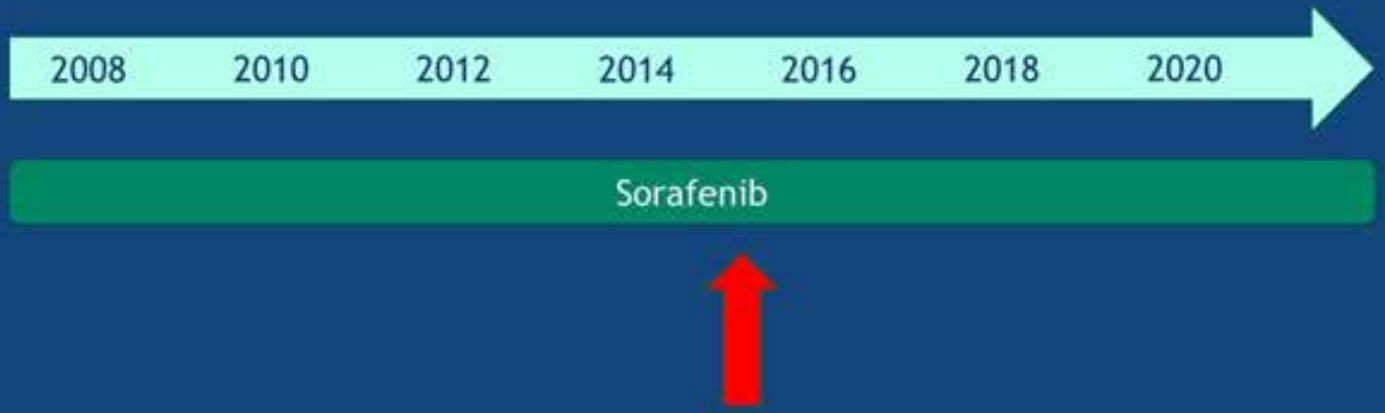
Kang YK, et al Lancet Oncol 2017; 390:2461-2471

HEPATOCELLULAR CARCINOMA

First Line



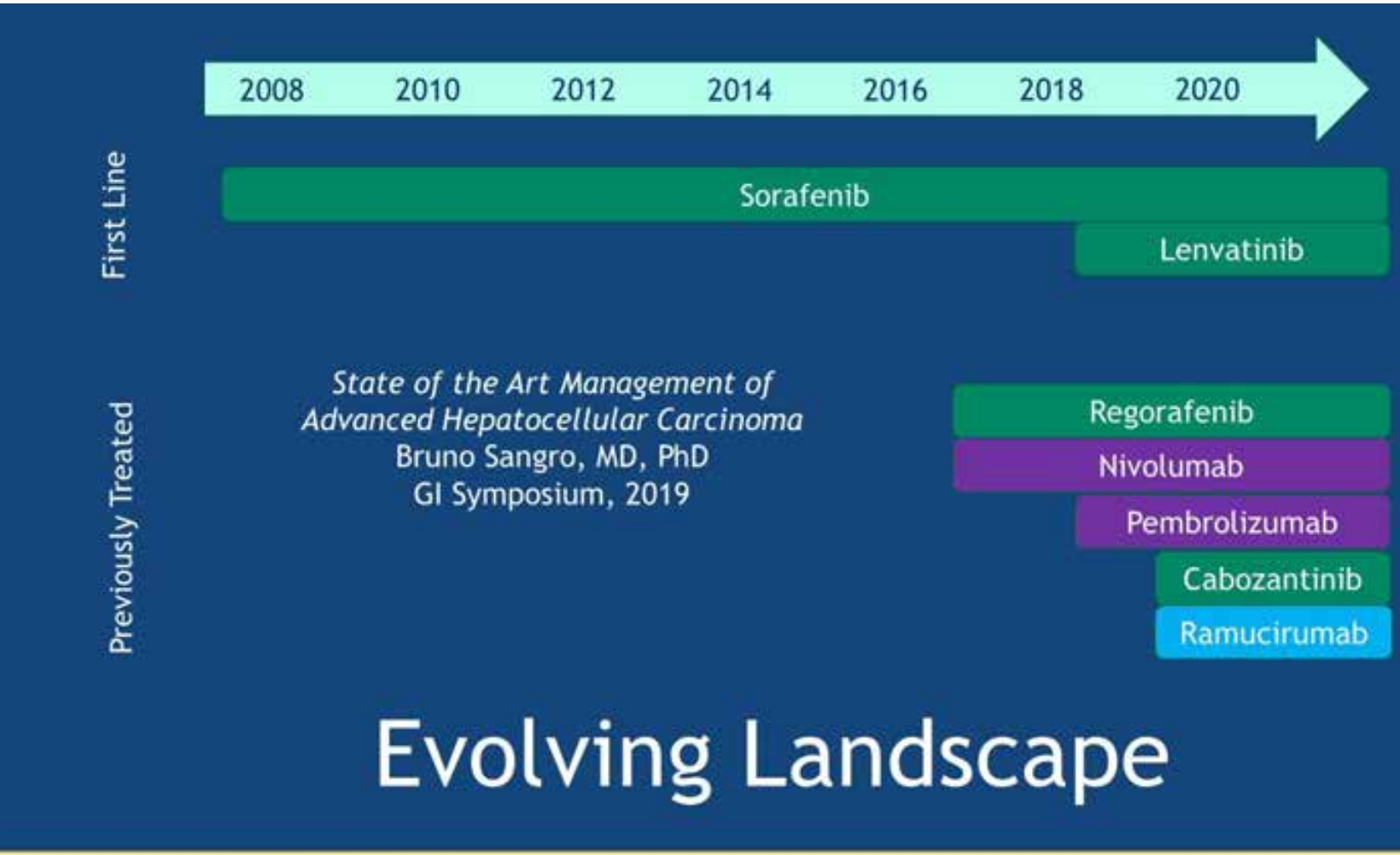
First Line



- LOTS of negative VEGF trials (e.g. sunitinib, brivanib, linifanib, bevacizumab, dovitinib, nintedanib)
- Minimal understanding of molecular underpinnings
- "Refining VEGF targeting does not improve survival"

  --Laura Goff, GI Symposium

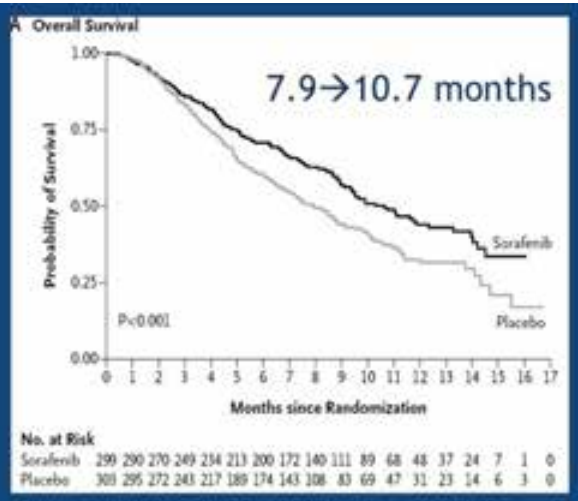
Presented By Laura Goff at 2019 ASCO Annual Meeting

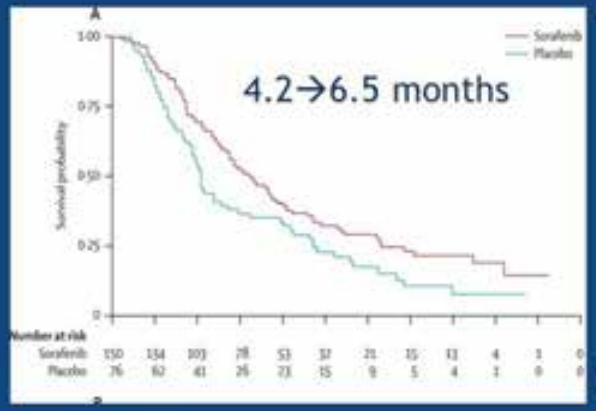


Presented By Laura Goff at 2019 ASCO Annual Meeting

SHARP and Asia-Pacific

	SHARP		Asia-Pacific	
End point	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
OS	0.69 (0.55-0.87)	<0.001	0.68 (0.50-0.93)	0.014
TTSP	1.08 (0.88-1.31)	0.768	0.90 (0.67-1.22)	0.498
TTP	0.58 (0.45-0.74)	<0.001	0.57 (0.42-0.79)	<0.001
PFS	0.65 (0.52-0.79)	<0.001	0.62 (0.46-0.82)	<0.001





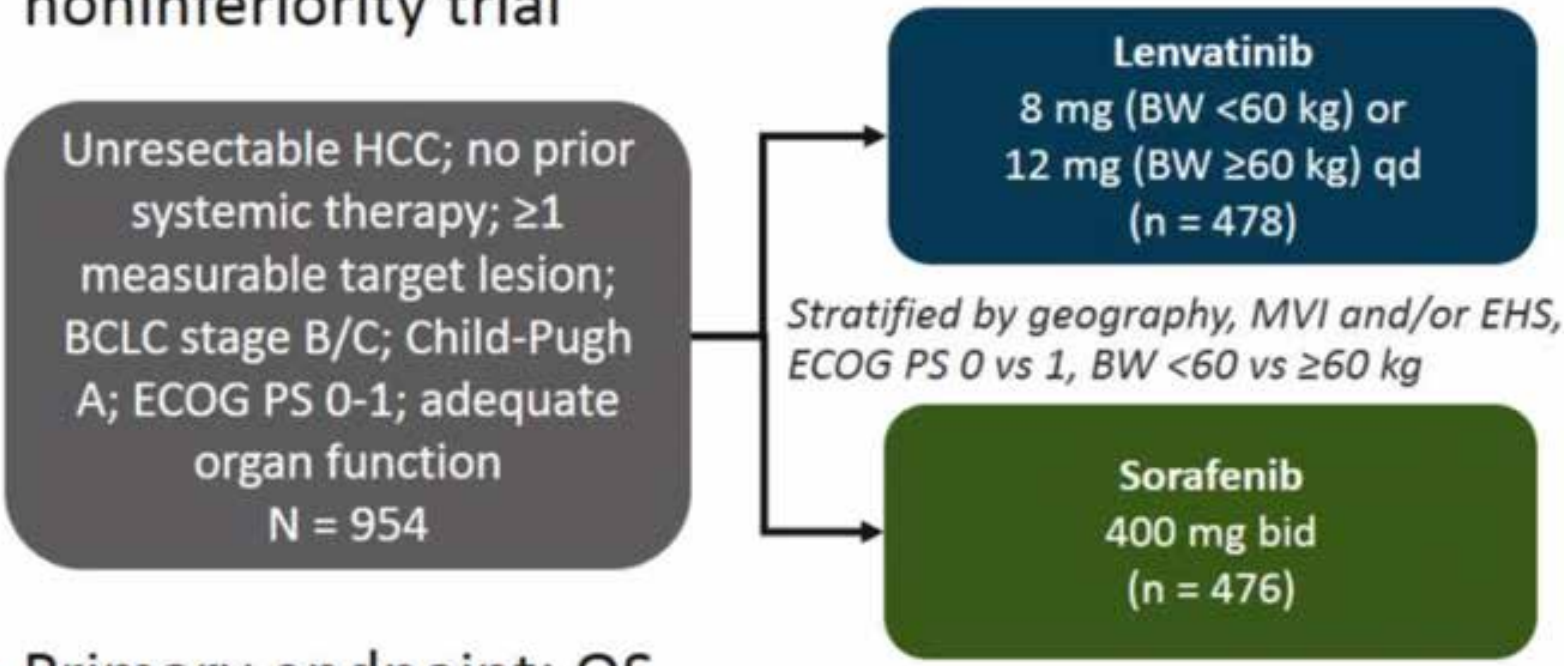
Llovet et al, NEJM 2008; Cheng et al, Lancet Oncol 2009

Presented By Laura Goff at 2019 ASCO Annual Meeting

REFLECT: First-Line Lenvatinib vs Sorafenib in HCC

Study Design

- Multicenter, randomized, open-label, phase 3 noninferiority trial



- Primary endpoint: OS
- Secondary endpoints: PFS, TTP, ORR, QoL, lenvatinib PK

Noninferiority margin = 1.08; met if upper limit of 2-sided 95% CI <1.08.

Cheng A-L, Finn RS, Qin S, et al. Phase III trial of lenvatinib vs sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma. Presented at ASCO 2017. Abstract 4001. Reprinted with permission.

REFLECT: First-Line Lenvatinib vs Sorafenib in HCC
Efficacy Outcomes

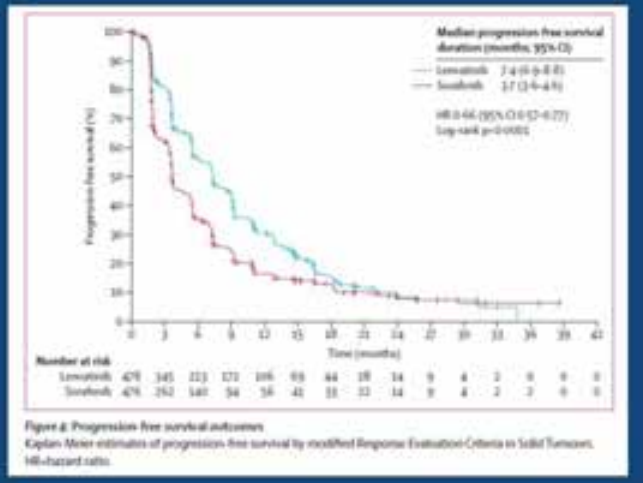
Efficacy outcome*	Lenvatinib (n = 478)	Sorafenib (n = 476)	HR (95% CI)	*P* value
Median OS, mo	13.6	12.3	0.92 (0.79-1.06)	NR
Median PFS, mo	7.4	3.7	0.66 (0.57-0.77)	< .00001
Median TTP, mo	8.9	3.7	0.63 (0.53-0.73)	< .00001
ORR, %	24.1	9.2	OR: 3.13 (2.15-4.56)	< .00001

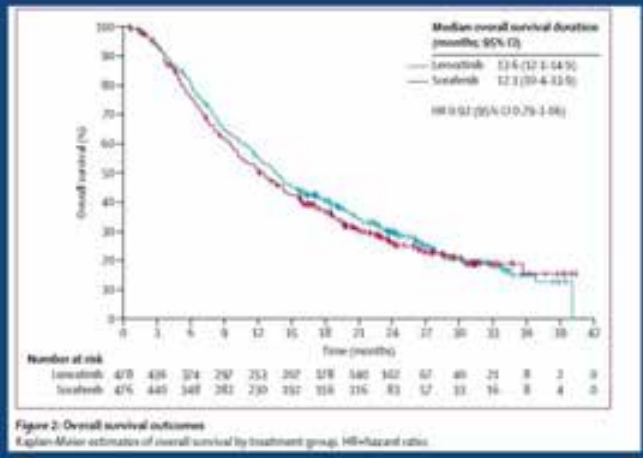
*Tumor assessments by investigator according to mRECIST

Cheng A-L, Finn RS, Qin S, et al. Phase III trial of lenvatinib vs sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma. Presented at ASCO 2017. Abstract 4001. Reprinted with permission.

Lenvatinib non-inferior to sorafenib for OS

	Sorafenib	Lenvatinib
mOS	12.3 months	13.6 months
ORR (mRECIST)	9.2%	24.1%
mTTP	3.7 months	8.9 months
Adverse events	More hand-foot syndrome and diarrhea	More hypertension, decreased appetite, fatigue and hypothyroidism

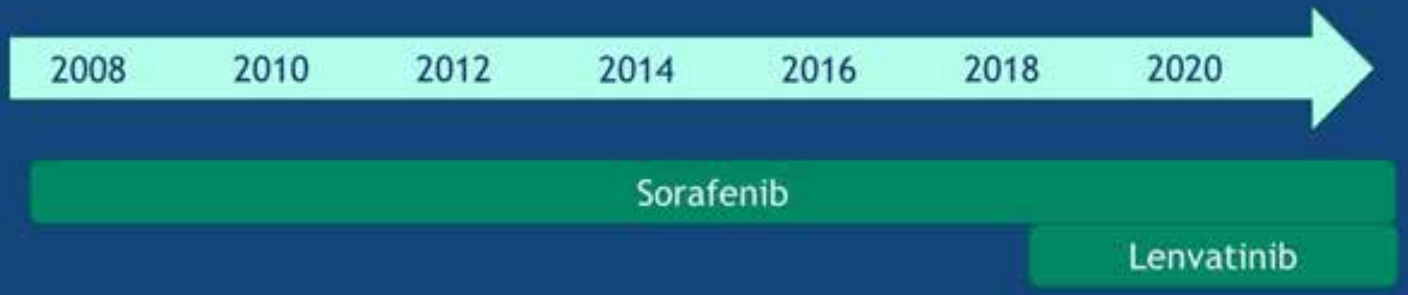




www.thelancet.com Vol 391 March 24, 2018

Presented By Laura Goff at 2019 ASCO Annual Meeting

First Line



Both are standard first line options

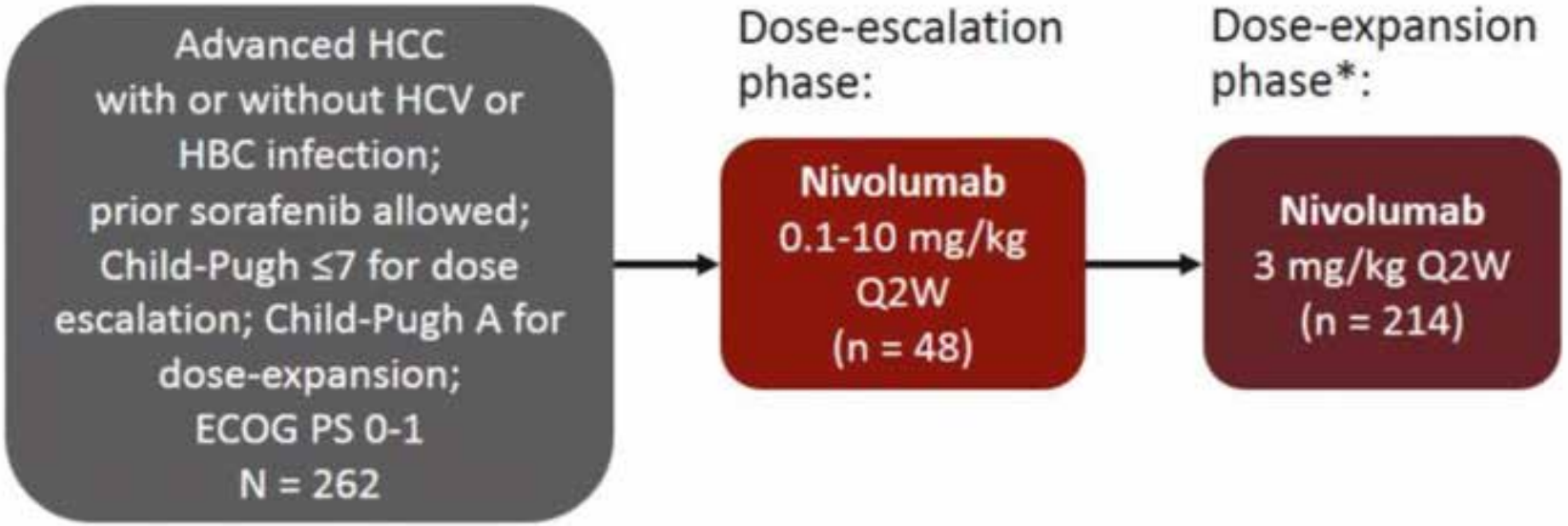
VEGF-inhibitor Contraindications

- Variceal bleeding
- Cardiovascular disease
- Recurrent thromboembolism
- Severe hepatic dysfunction

Can we consider a checkpoint inhibitor?

CheckMate 040: Nivolumab in HCC Study Design

- Phase 1/2 open-label, noncomparative dose-escalation and expansion trial

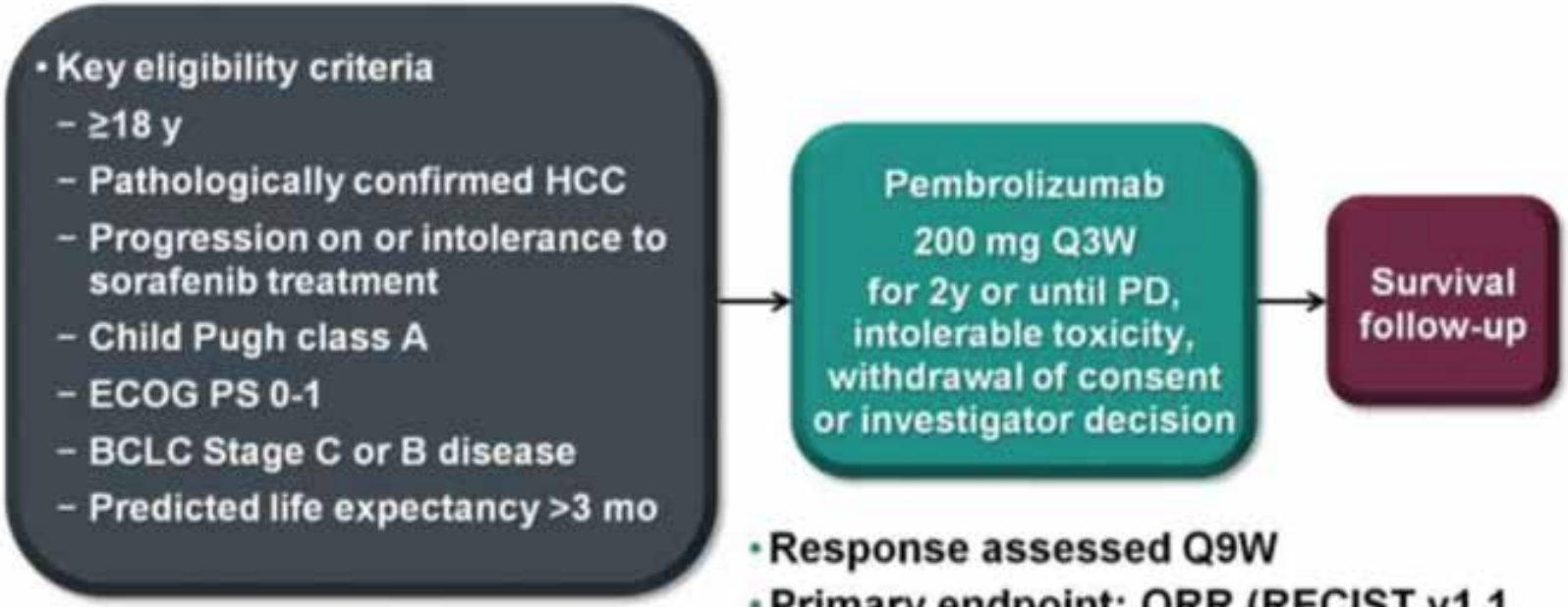


- Primary endpoint: safety, tolerability for the escalation phase and ORR

*4 cohorts: sorafenib-untreated or intolerant without viral hepatitis; sorafenib progressor without viral hepatitis; HCV-infected; HBV-infected.

El-Khoueiry AB, et al. *Lancet*. 2017;389:2492-2502.

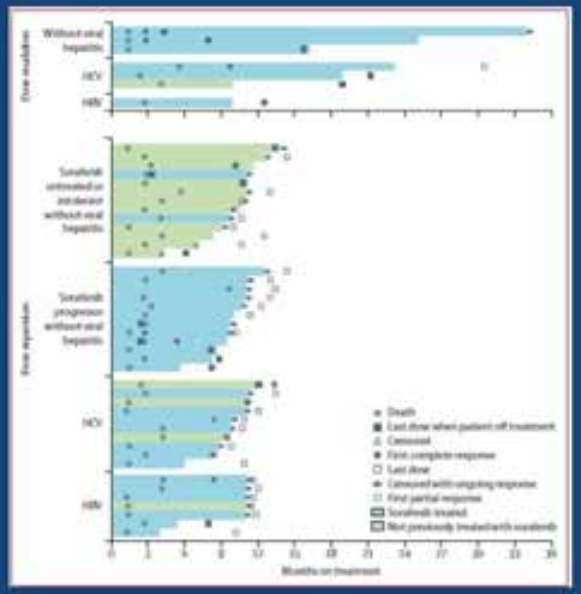
KEYNOTE-224 – Study Design



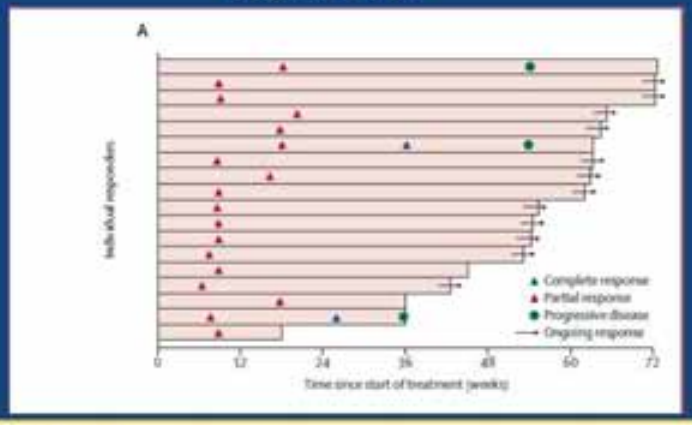
Zhu AX et al. ASCO GI 2018; abstr 209

	Nivolumab	Pembrolizumab
ORR	15-20%	17%
mDOR	9.9 months	NR
mOS	NR	12.9 months
mTTP	4.1 months	4.9 months

CheckMate 040



Keynote 224

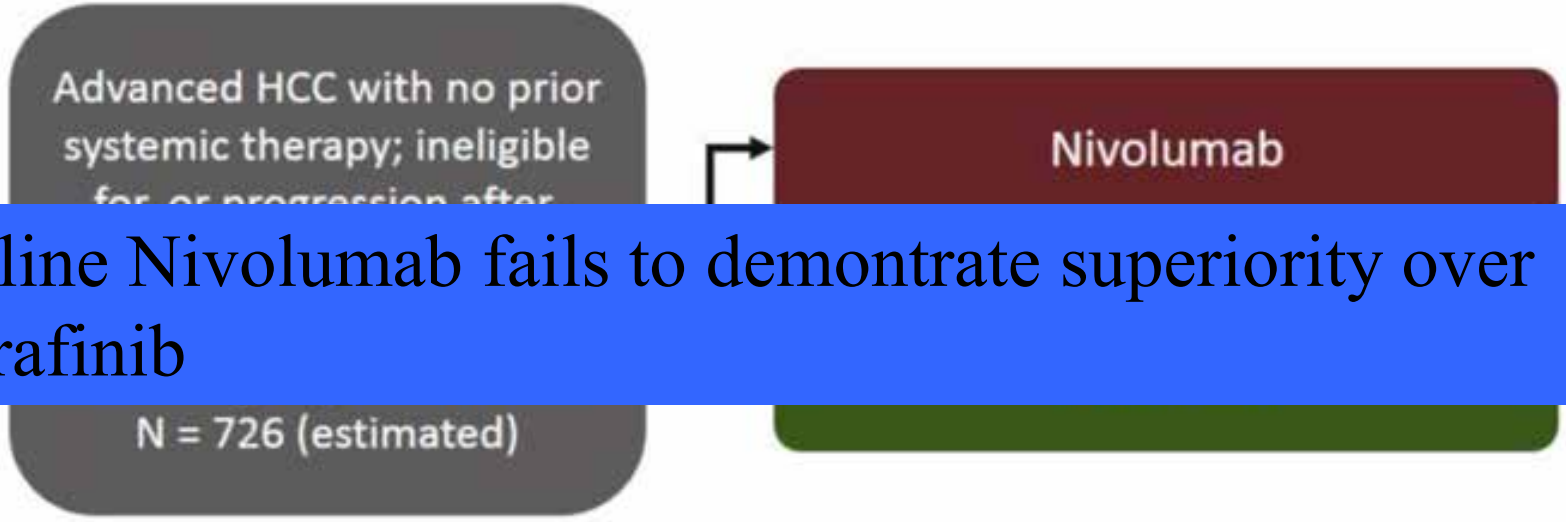


El-Khoueiry et al, Lancet 2017;
Zhu et al, Lancet Oncol 2018

FDA has approved Nivolumab and Pembrplizumab as 2 line treatment HCC

CheckMate 459: Nivolumab vs Sorafenib as First-Line Treatment in Advanced HCC

- Randomized, multicenter, open-label, phase 3 trial



1st line Nivolumab fails to demontrate superiority over Sorafinib

- Primary endpoint: OS
- Secondary endpoints: ORR, PFS, PD-L1 expression

ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02576509.

KEYNOTE-240: Study Design

- Randomized, double-blind phase III trial

Stratified by region (Asia without Japan vs non-Asia with Japan), macrovascular invasion (yes vs no), AFP level (≥ vs < 200 ng/mL)

Patients with HCC that progressed on/intolerant to sorafenib; Child-Pugh class A; BCLC stage B/C; ECOG PS ≤ 1; no invasion of main portal vein
(N = 413)

Randomized 2:1

Pembrolizumab 200 mg Q3W + **BSC** for up to 35 cycles
(n = 278)

Placebo (saline) + **BSC** for up to 35 cycles
(n = 135)

- Coprimary endpoints: PFS,* OS
  - Efficacy boundaries: PFS at first interim cutoff, *P* = .0020 (primary analysis for PFS); OS at final analysis cutoff, *P* = .0174
- Secondary endpoints: ORR,* DoR, DCR, TTP, safety

*PFS, secondary response outcomes centrally reviewed per RECIST v1.1. Response evaluated Q6W.

Finn. ASCO 2019. Abstr 4004. NCT02702401.

Slide credit: clinicaloptions.com

KEYNOTE-240: OS (Coprimary Endpoint)

- Median OS prolonged with pembrolizumab vs placebo in overall population: 13.9 vs 10.6 mos (HR: 0.781; 95% CI: 0.611-0.998; *P* = .0238)
  - Failed to reach prespecified level of statistical significance (*P* = .0174)
  - Subgroup analyses showed more favorable OS outcomes with pembrolizumab in patients regardless of age, ECOG PS (0/1), macrovascular invasion, hepatitis viral status, AFP level, extrahepatic spread, and BCLC stage (B/C)

Data cutoff: January 2, 2019.

Finn. ASCO 2019. Abstr 4004.

Slide credit: clinicaloptions.com

KEYNOTE-240: PFS (Coprimary Endpoint)

Outcomes	Primary Analysis		Final Analysis	
	Pembrolizumab (n = 278)	Placebo (n = 135)	Pembrolizumab (n = 278)	Placebo (n = 135)
Events, n	203	105	214	118
mPFS, mos	3.0	2.8	3.0	2.8
HR (95% CI)	0.775 (0.609-0.987)		0.718 (0.570-0.904)	
P value	.0186		.0022	

- PFS did not meet prespecified level of statistical significance (*P* = .002) with pembrolizumab vs placebo in overall population
  - Subgroup analyses showed more favorable PFS with pembrolizumab in patients regardless of age, ECOG PS (0/1), macrovascular invasion, hepatitis viral status, AFP level, reason for sorafenib discontinuation, extrahepatic spread, and BCLC stage (B/C)

Data cutoffs: primary analysis, March 26, 2018; final analysis, January 2, 2019.

Finn. ASCO 2019. Abstr 4004.

Slide credit: clinicaloptions.c

KEYNOTE-240: Response at Final Analysis

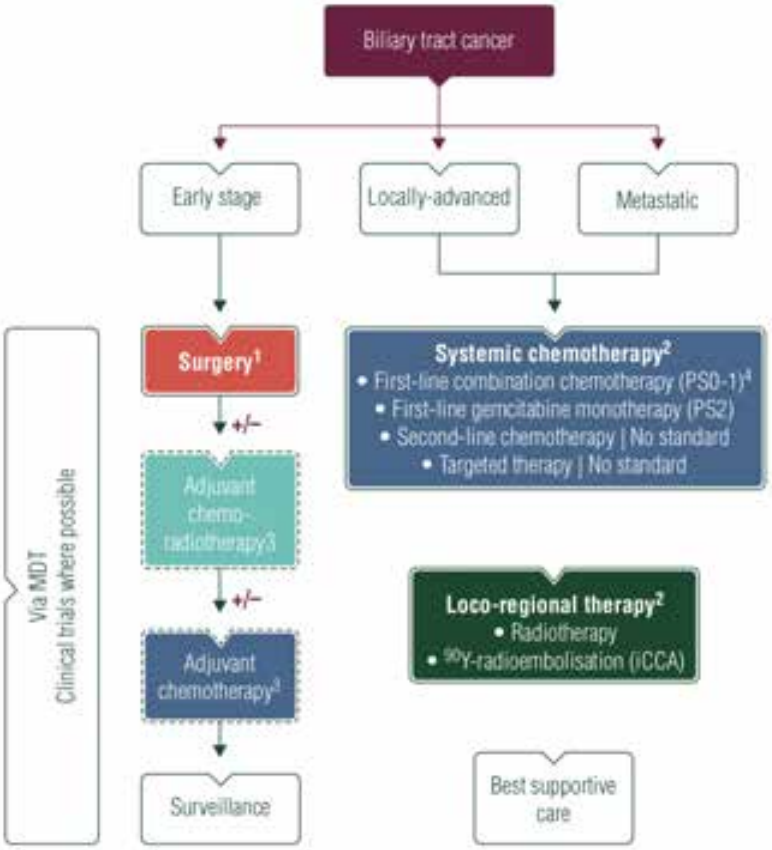
- ORR was significantly higher with pembrolizumab vs placebo
  - 18.3% vs 4.4% (*P* = .00007

Outcome, n (%)	Pembrolizumab (n = 278)	Placebo (n = 135)
Best overall response		
▪ CR	6 (2.2)	0
▪ PR	45 (16.2)	6 (4.4)
▪ SD	122 (43.9)	66 (48.9)
▪ SD ≥ 23 wks	37 (18.3)	20 (14.8)
PD	90 (32.4)	57 (42.2)
DCR (CR + PR + SD)	173 (62.2)	72 (53.3)

Data cutoff: January 2, 2019.

Finn. ASCO 2019. Abstr 4004.

Slide credit: clinicaloptions.com



[1] Special considerations:
- Need for pre-operative biliary drainage
- Avoid percutaneous biopsy in resectable disease
- Assess Future Liver Remnant
- Assess need for Portal Vein Embolisation
- Neoadjuvant approach (selected cases)
- Completion surgery for incidental gallbladder cancer of T-stage T1b and above

[2] Option of salvage surgery should be considered in responding patients with initially inoperable disease
[3] Level of recommendation IV,C
[4] Cisplatin and gemcitabine [category IA], other gemcitabine-based combination [category IIB]

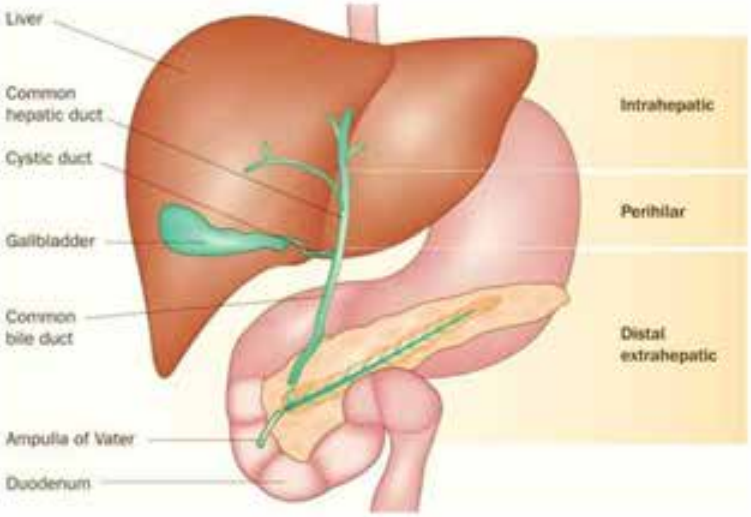
Annals of Oncology 27 (Supplement 5): v28–v37, 2016

CHOLANGIOCARCINOMA

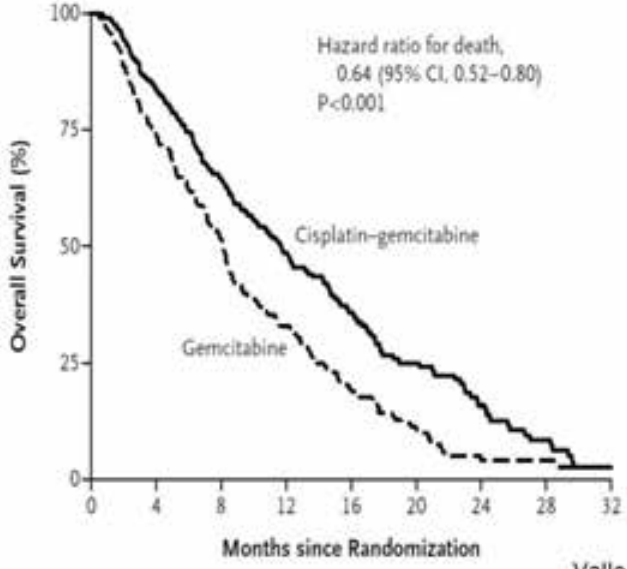
The NEW ENGLAND JOURNAL of MEDICINE

Cisplatin plus Gemcitabine versus Gemcitabine for Biliary Tract Cancer

Juan Valle, M.D., Harpreet Wasan, M.D., Daniel H. Palmer, M.D., Ph.D., David Cunningham, M.D., Alan Anthoney, M.D., Anthony Maraveyas, M.D., Ph.D., Srinivasan Madhusudan, M.D., Ph.D., Tim Iveson, M.D., Sharon Hughes, B.Sc., Stephen P. Pereira, M.D., Ph.D., Michael Roughton, M.Sc., and John Bridgewater, M.D., Ph.D., for the ABC-02 Trial Investigators*



Blechacz et al Nat Rev Gastroenterol Hepatol 2011: 8(9)



Valle, J, et al. NEJM 2010

Presented By Lipika Goyal at 2019 ASCO Annual Meeting

ABC-02 - Study schema

Eligible patients (n=400*)

+ QoL

Randomized 1:1

(stratified by centre, primary site, PS, prior therapy and locally advanced vs. metastatic)

Arm A	Arm B
Gem *1000 mg/m²* D1,8,15 q 28d	Cisplatin *25 mg/m²* + Gem *1000 mg/m²* D1,8 q 21d
24 weeks (6 cycles)	24 weeks (8 cycles)

Upon disease progression, management will be on clinician's discretion (mostly best supportive care)

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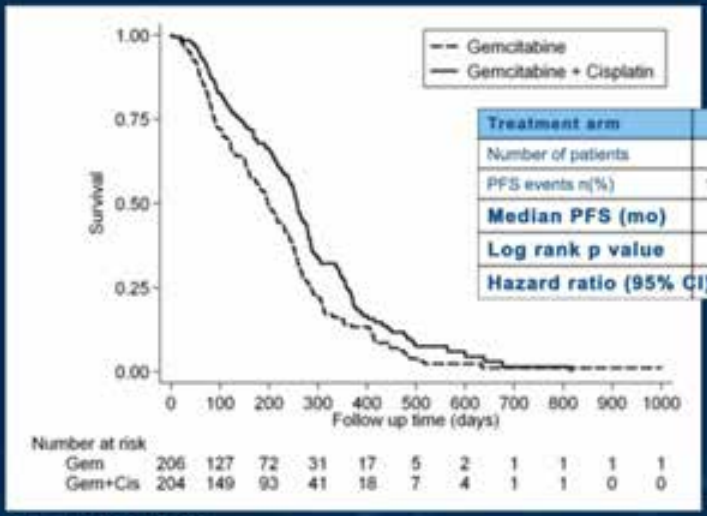
** Including 86 patients in ABC-01*

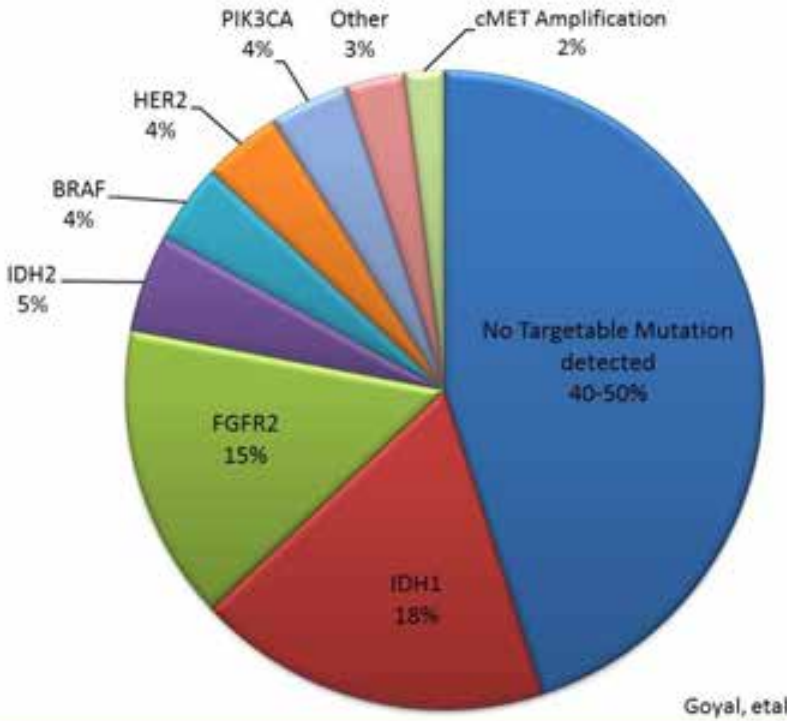
ABC-02 Results: Progression-free survival (ITT)



Treatment arm	Gem	Gem + Cis
Number of patients	n=206	n=204
PFS events n(%)	155 (75.2)	135 (66.2)
Median PFS (mo)	**6.5**	**8.4**
Log rank p value	**0.003**	
Hazard ratio (95% CI)	**0.72 (0.57, 0.90)**	

ASCO | Annual '09 Meeting

Frequent Targetable Mutations in Intrahepatic Cholangiocarcinoma



Goyal, etal, GI ESMO, 2017

Riener, et al. Genes Chromosomes Cancer 2008
Desphande, et al. BMC Cancer, 2011
Borger, et al. The Oncologist, 2012
Wang, et al. Oncogene 2012
Voss, et al. Human Pathology, 2013
Sia, et al. Gastroenterology, 2013
Jiao, et al. Nature Genetics, 2013
Chan-on, et al. Nature Genetics, 2013
Wu, et al. Cancer Discovery, 2013
Ross,et al. The Oncologist, 2014
Graham, et al. Human Pathology 2014
Arai, et al. Hepatology 2014
Sia, et al. Nature Communications, 2015
Javle, etal, Cancer, 2016
Jusakul, etal, Cancer Discov, 2017
Wardell, etal, J Hepatol 2018
Lowery, etal, Clin Cancer Res 2019

Ivosidenib (AG120) Phase I CCA Cohort Results

- First-in-class oral, selective IDH1 inhibitor
- Phase I *mIDH1* solid tumor study (NCT02073994):
  - N=73 CCA (89% intrahepatic)
  - 77% *IDH1* R132C
  - Median 2 prior therapies (range: 1-5)

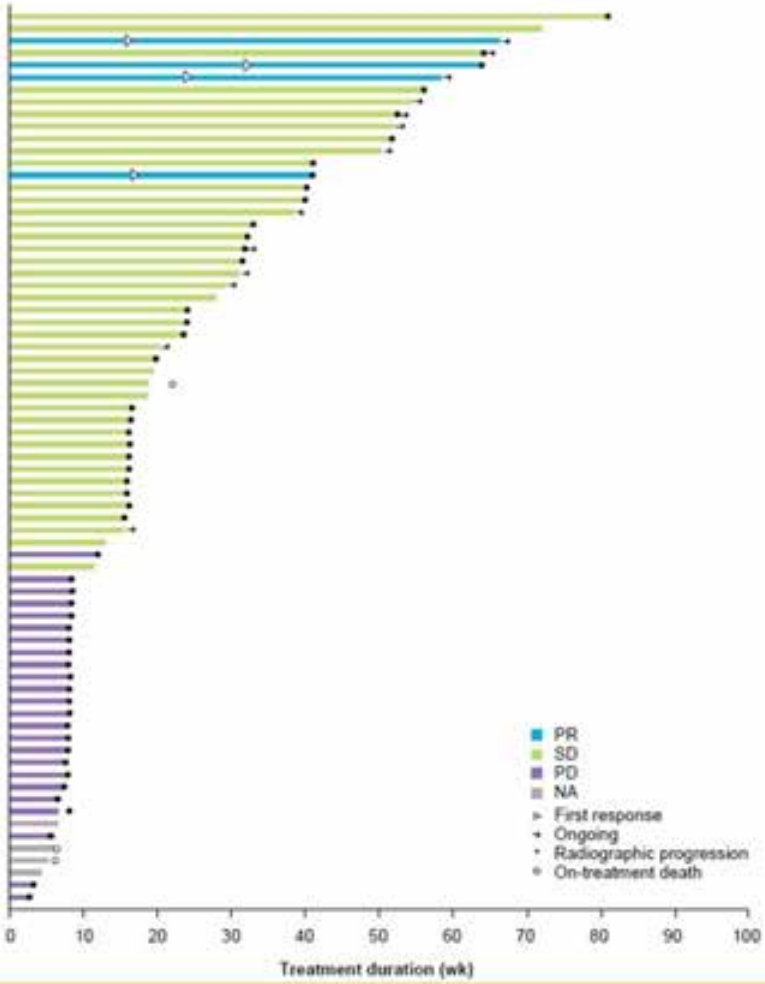
Best response:

Partial response: 5%

Stable disease: 56%

Median PFS: 3.8 mos. (95% CI: 3.6, 7.3)

Progression Free @ 6 months: 38.5%



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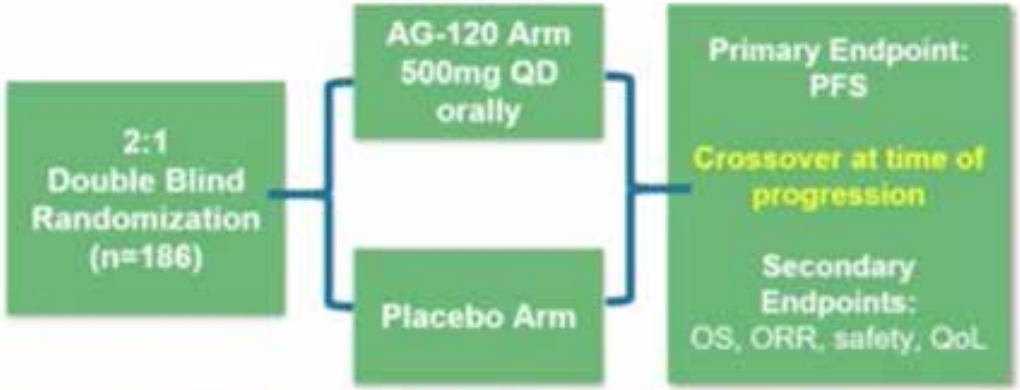
Phase 3 Randomized Placebo-controlled trial of AG120 in IDH mutant Cholangiocarcinoma

- Randomized, multicenter, global double-blinded placebo controlled study
- Eligibility: One or two prior lines of systemic therapy for advanced CCA
- Central confirmation of the IDH1 mutation in tumor tissue



Statistics: Assuming a median PFS of 3 months in the control arm, the study has 96% power to detect a **hazard ratio of 0.5** with a one-sided alpha of 0.025

Phase 3 Randomized Placebo-controlled trial of AG120 in IDH mutant Cholangiocarcinoma

- Randomized, multicenter, global double-blinded placebo controlled study
- Eligibility: One or two prior lines of systemic therapy for advanced CCA
- Central confirmation of the IDH1 mutation in tumor tissue

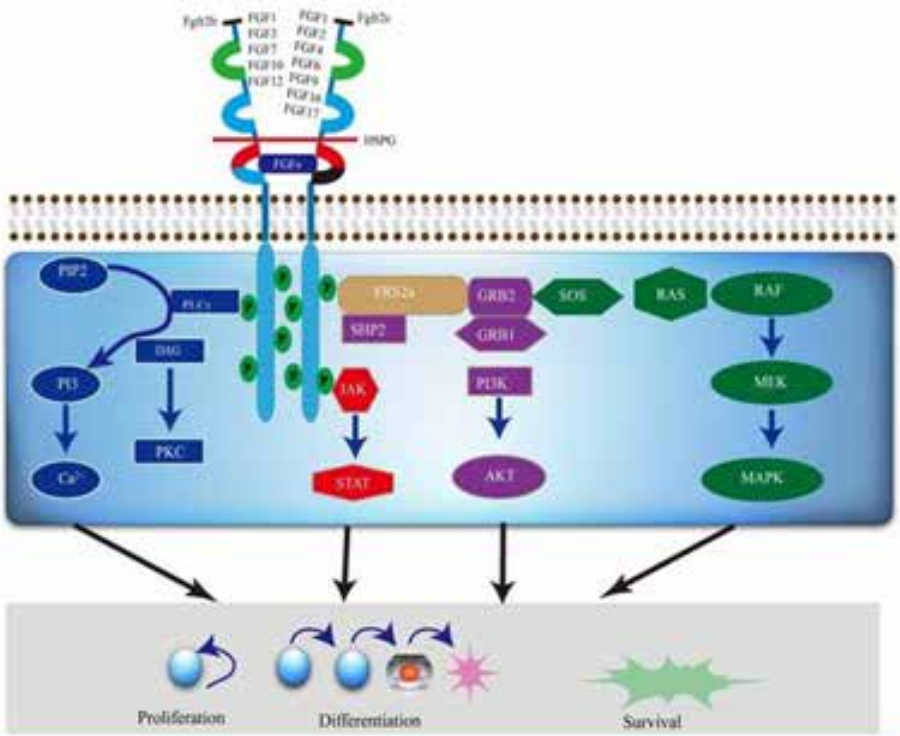
agios

Agios Announces the Randomized Phase 3 ClarIDHy Trial of TIBSOVO® (ivosidenib) Achieved its Primary Endpoint in Previously Treated IDH1 Mutant Cholangiocarcinoma Patients

OS, ORR, safety, QoL

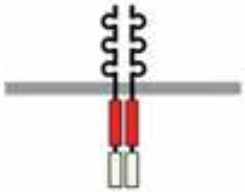
Statistics: Assuming a median PFS of 3 months in the control arm, the study has 96% power to detect a **hazard ratio of 0.5** with a one-sided alpha of 0.025

Fibroblast Growth Factor Receptor (FGFR)



Gene fusion (Type 2)

Bladder cancer
Cholangiocarcinoma
Glioblastoma
Lung cancer



FGFR1-TACC1
FGFR2-AFF3
FGFR2-BICC1
FGFR2 CASP7
FGFR2-CCAR2
FGFR2-CCDC6
FGFR2-CIT
FGFR2-OFD1
FGFR2-PPHLN1
FGFR3-BAIAP2L1
FGFR3-JAKMIP1
FGFR3-TACC3

- Fibroblast growth factor (FGF) signaling is mediated by a family of four receptor tyrosine kinases (FGFR1-4) and 18 associated ligands (FGF1-FGF10, FGF16-FGF23).
- The FGFR2 fusions in ICC are in-frame fusion proteins that generate constitutive activation of the FGFR pathway through ligand independent dimerization

INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 38: 3-15, 2016

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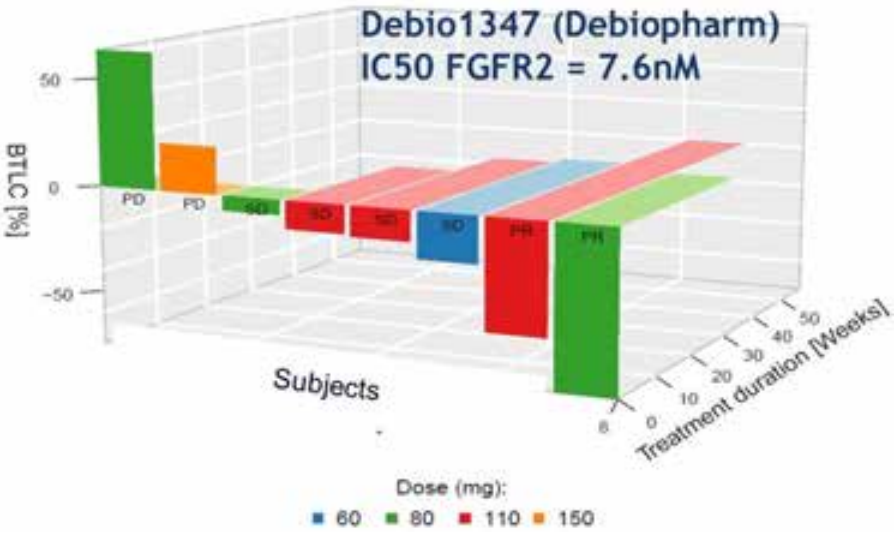
TAS120 (Taiho)
IC50 FGFR2 = 1.3nM
Best Overall Response (N=28)
PR (n=7)
SD (n=15)
PD (n=2)
NE (n=4)


INCB054828 (Incyte)
IC50 FGFR2 = 3-50nM
Best % Change From Baseline

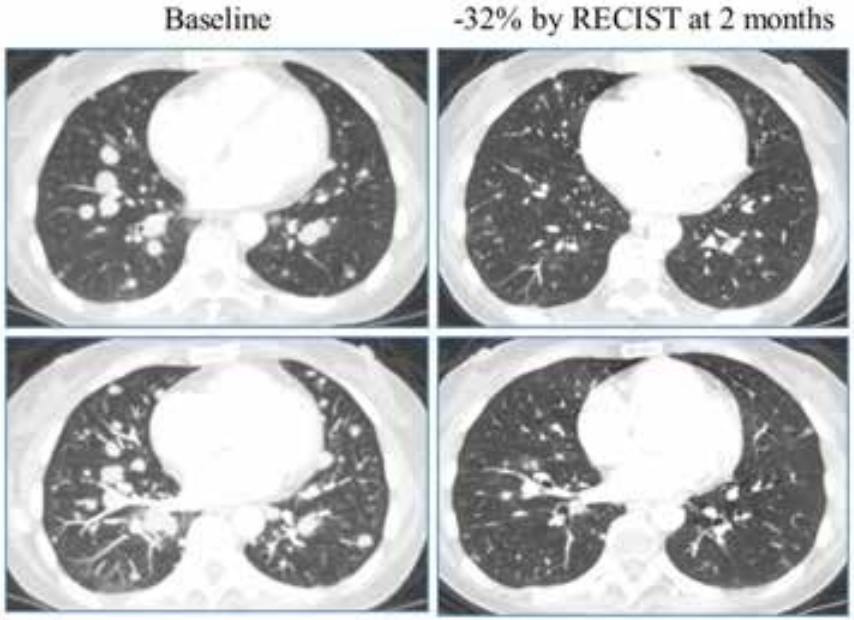

ARQ187 (Arqule)
IC50 FGFR2 = 1.8nM
Partial response
Stable disease
Progressive disease
Best Change of Target Lesion from Baseline (%)
*Patients with iCCA with FGFR2 genetic aberrations (amplification or mutation)
Patient ID


Debio1347 (Debiopharm)
IC50 FGFR2 = 7.6nM
BTLC [%]
Subjects
Treatment duration [Weeks]
Dose (mg):
60
80
110
150

53F with FGFR2-ATF1 fusion+ Intrahepatic Cholangio

- She progressed on Gemcitabine/Cisplatin, and then went onto TAS120 for 7 months

Best Response on FGFR inhibitor TAS120



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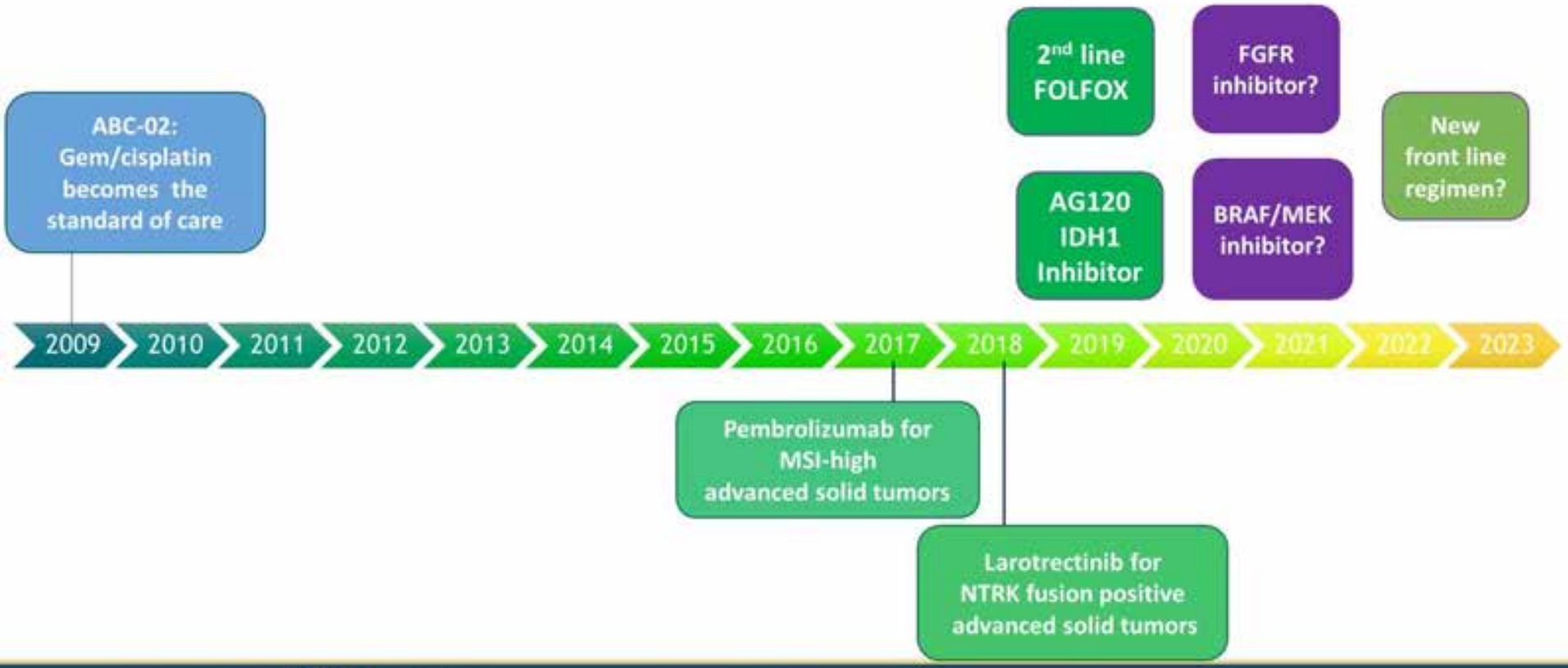
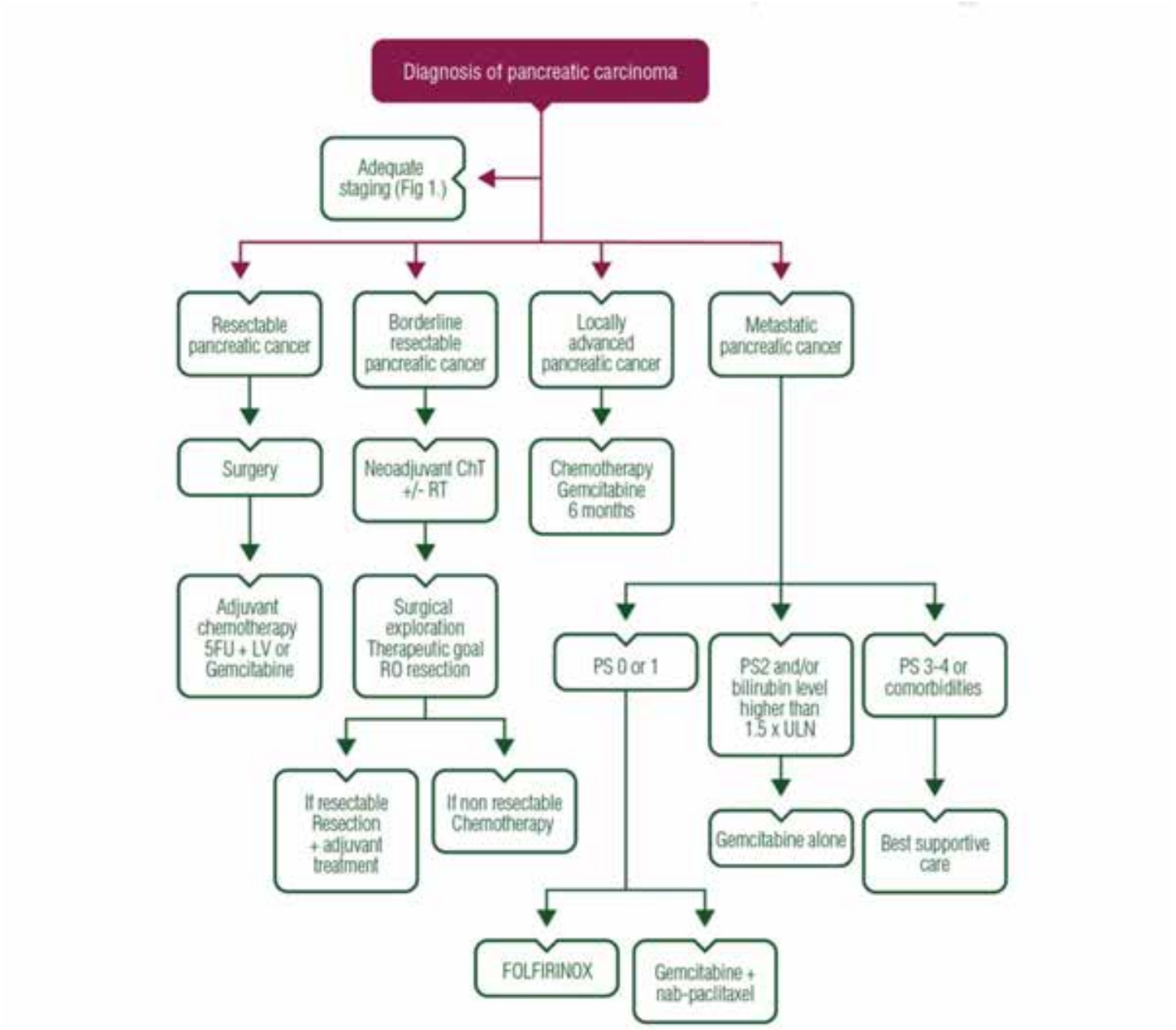
Standard Systemic Therapy for Advanced BTC



Presented By Lipika Goyal at 2019 ASCO Annual Meeting

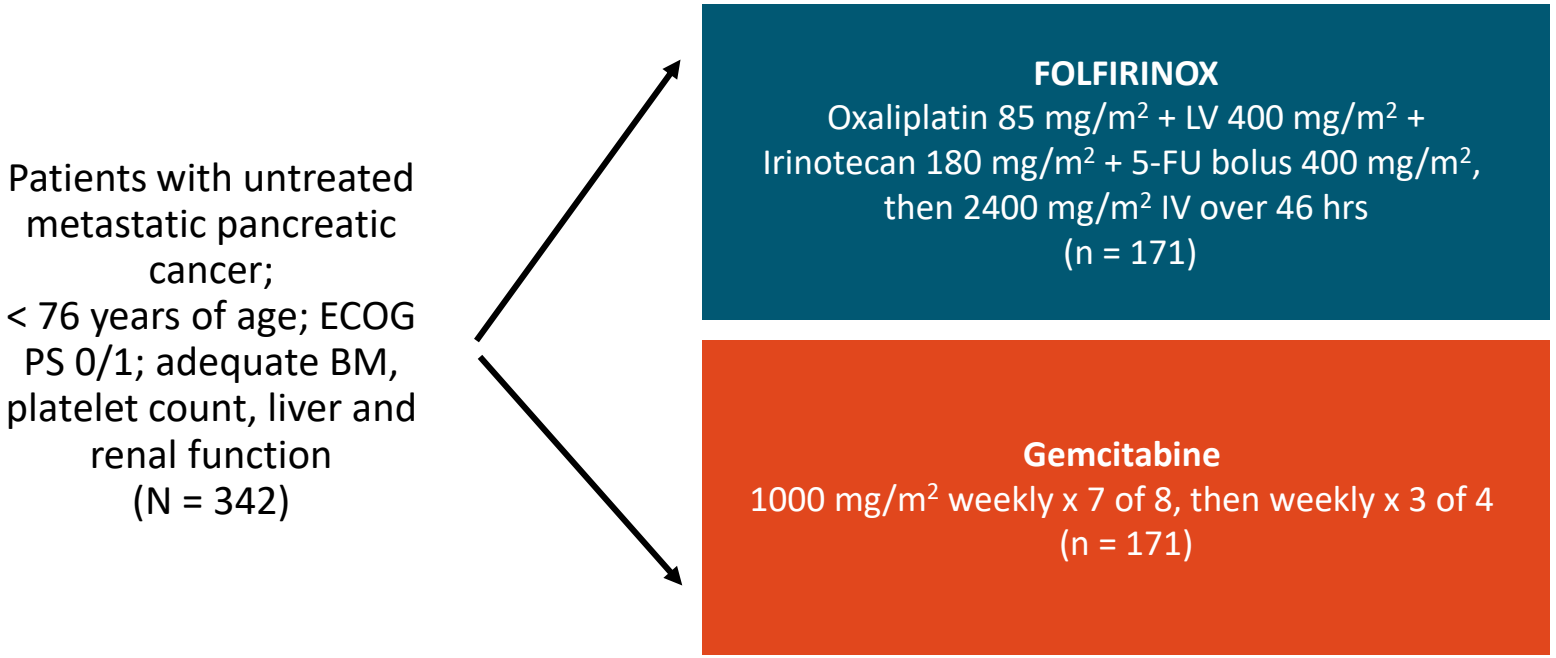
PANCREATIC CANCER



Annals of Oncology 26 (Supplement 5): v56–v68, 2015

FOLFIRINOX vs Gemcitabine for Patients With Metastatic Pancreatic Cancer

- Multicenter, randomized, phase II/III trial

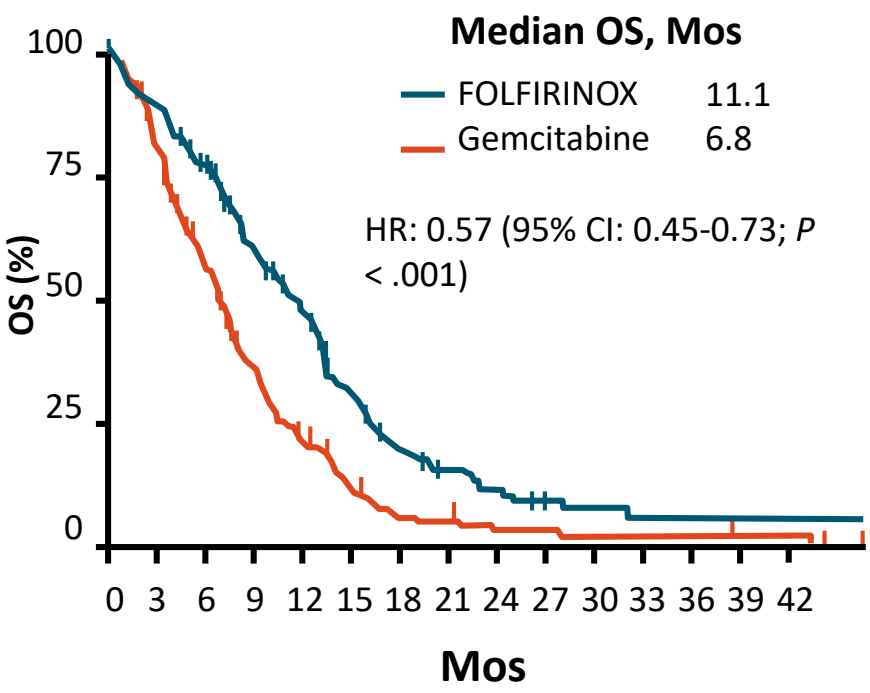


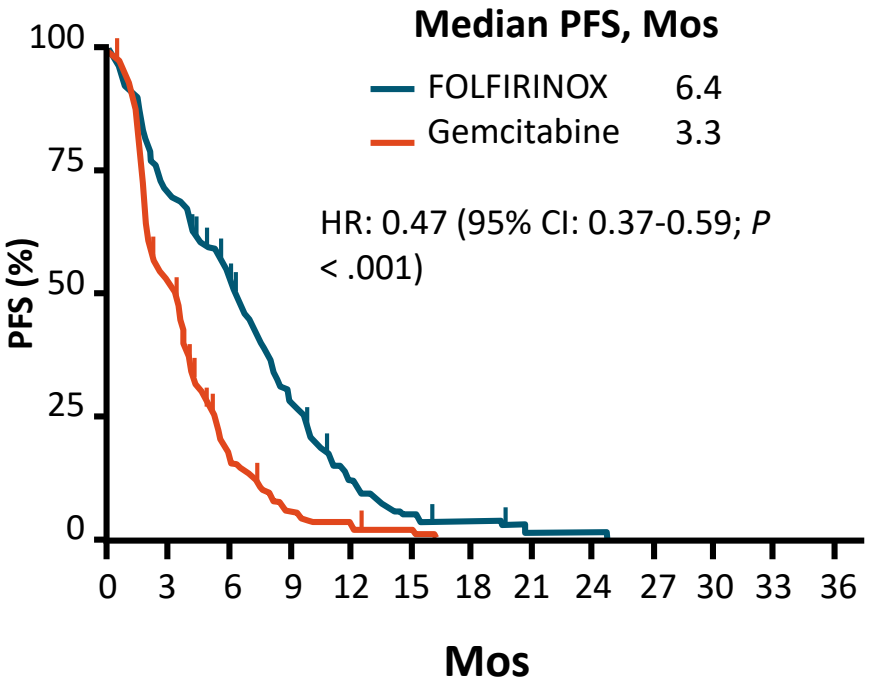
- Primary endpoints: ORR (phase II), OS (phase III)

Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

FOLFIRINOX vs Gemcitabine: OS and PFS



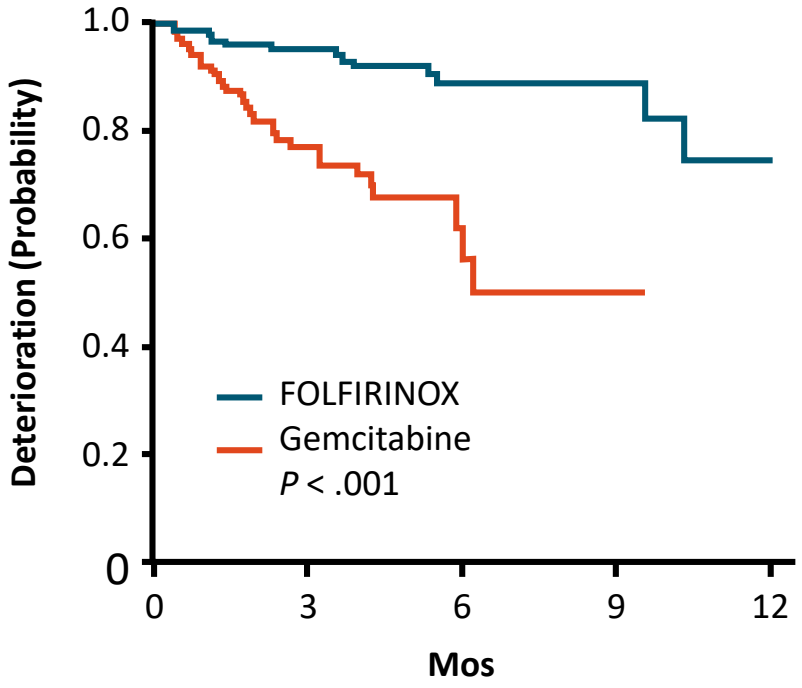


Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

FOLFIRINOX vs Gemcitabine: Quality of Life

Time Until Definitive Deterioration > 20 Points, EORTC-C30 Global Health Status/QoL Questionnaire



- Prolongation of QoL in patients treated with FOLFIRINOX compared with gemcitabine, despite greater toxicity
- Specifically, longer time to deterioration in:
  - Global health status
  - Physical, cognitive, and social functioning
  - Symptoms such as fatigue, nausea/vomiting, pain, and anorexia

Gourgou-Bourgade. JCO. 2013;31:23.

Slide credit: clinicaloptions.com

FOLFIRINOX vs Gemcitabine: Safety

Grade 3/4 AE, %	FOLFIRINOX (n = 171)	Gemcitabine (n = 171)	*P* Value
Hematologic			
▪ Neutropenia	45.7	21.0	< .001
▪ Febrile neutropenia	5.4	1.2	.03
▪ Thrombocytopenia	9.1	3.6	.04
Nonhematologic			
▪ Fatigue	23.6	17.8	NS
▪ Vomiting	14.5	8.3	NS
▪ Diarrhea	12.7	1.8	< .001
▪ Sensory neuropathy	9.0	0.0	< .001
▪ Elevated ALT	7.3	20.8	< .001

Conroy. NEJM. 2011;364:1817.

Slide credit: clinicaloptions.com

Select Phase III Trials of Gemcitabine-Based Combinations in Advanced Pancreatic Cancer

Study Regimen (vs Gemcitabine)	N	Median OS, Mos	
		Gemcitabine alone	Gemcitabine Combination
Gemcitabine + cisplatin[1]	190	6.0	7.5
Gemcitabine + oxaliplatin[2]	313	7.1	9.0
Gemcitabine + 5-FU[3]	322	5.4	6.7
Gemcitabine + capecitabine[4]	533	6.2	7.1
Gemcitabine + pemetrexed[5]	565	6.3	6.2
Gemcitabine + irinotecan[6]	360	6.6	6.3

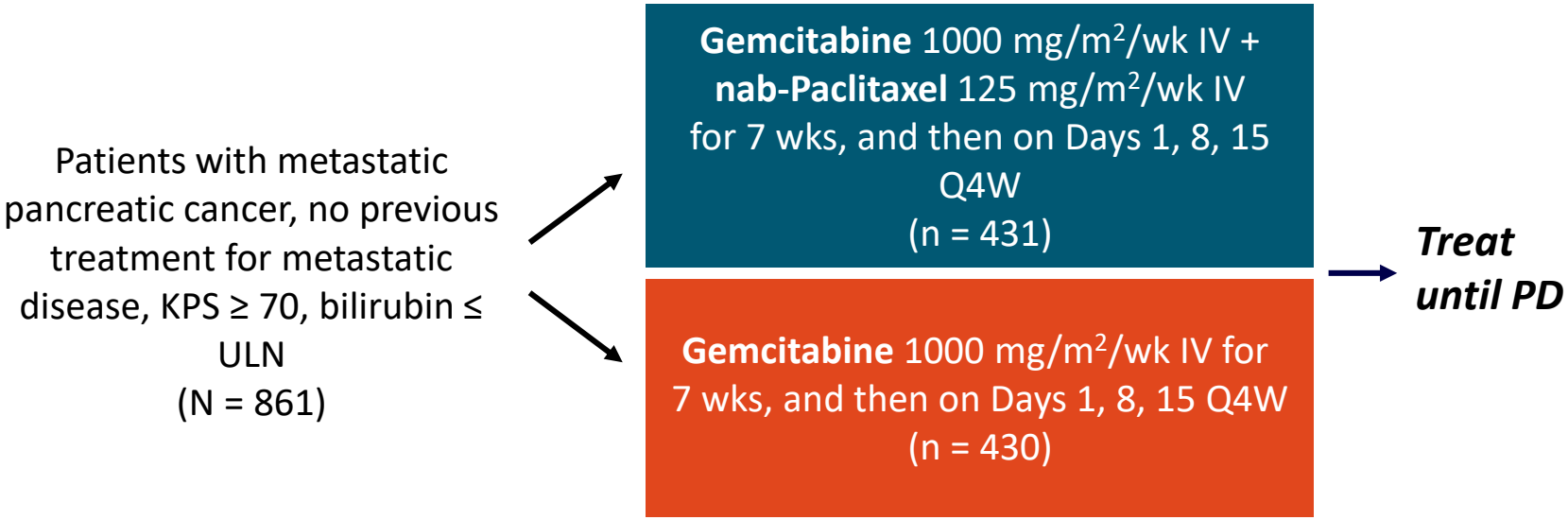
Study Regimen (vs Gemcitabine)	N	Median OS, Mos	
		Gemcitabine alone	Gemcitabine Combination
Gemcitabine + tipifarnib[7]	688	6.1	6.4
Gemcitabine + erlotinib[8]*	**569**	**5.9**	**6.2**
Gemcitabine + bevacizumab[9]	602	5.9	5.8
Gemcitabine + cetuximab[10]	743	5.9	6.3
Gemcitabine + axitinib[11]	630	8.3	8.5
Gemcitabine + nab-paclitaxel[12]*	**861**	**6.6**	**8.7**
Gemcitabine + evofosfamide[13]	693	7.6	8.7

1. Heinemann. JCO. 2006;24:3946. 2. Louvet. JCO. 2005;23:3509. 3. Berlin. JCO. 2002;20:3270. 4. Cunningham. JCO. 2009;27:5513. 5. Oettle. Ann Oncol. 2005;16:1639. 6. Rocha Lima. JCO. 2004;22:3776. 7. Van Cutsem. JCO. 2004;22:1430. 8. Moore. JCO. 2007;25:1960. 9. Kindler. JCO. 2010;28:3617. 10. Philip. JCO. 2010;28:3605. 11. Kindler. Lancet Oncol. 2011;12:256. 12. Von Hoff. NEJM. 2013;369:1691. 13. Van Cutsem. ASCO 2016. Abstr 4007.

*Median survival and/or OS significantly prolonged with combination treatment.

MPACT: Gemcitabine ± nab-Paclitaxel for Patients With Metastatic Pancreatic Cancer

- Multicenter, open-label, randomized, phase III trial

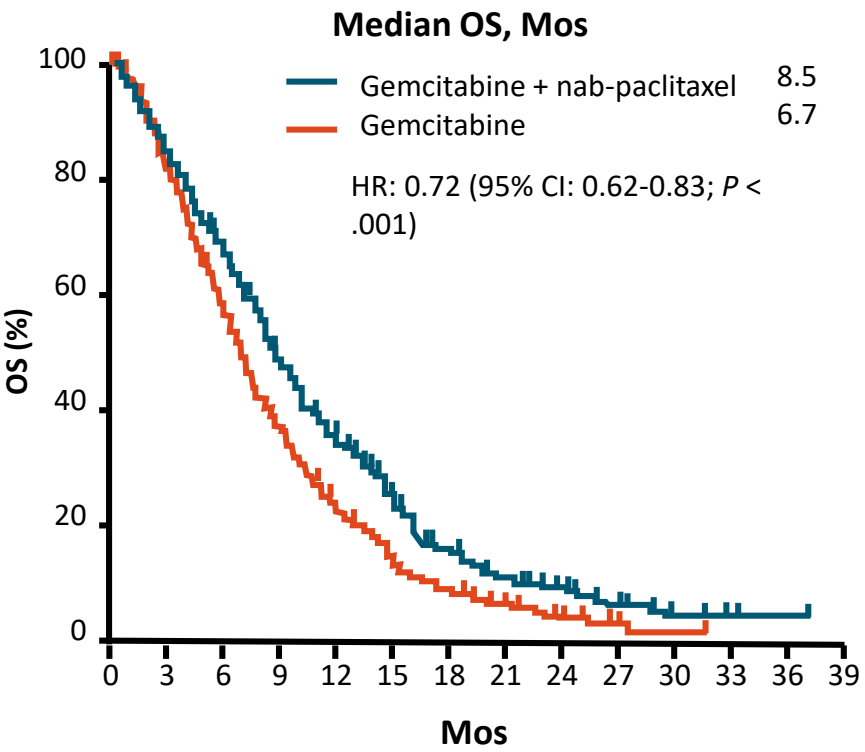


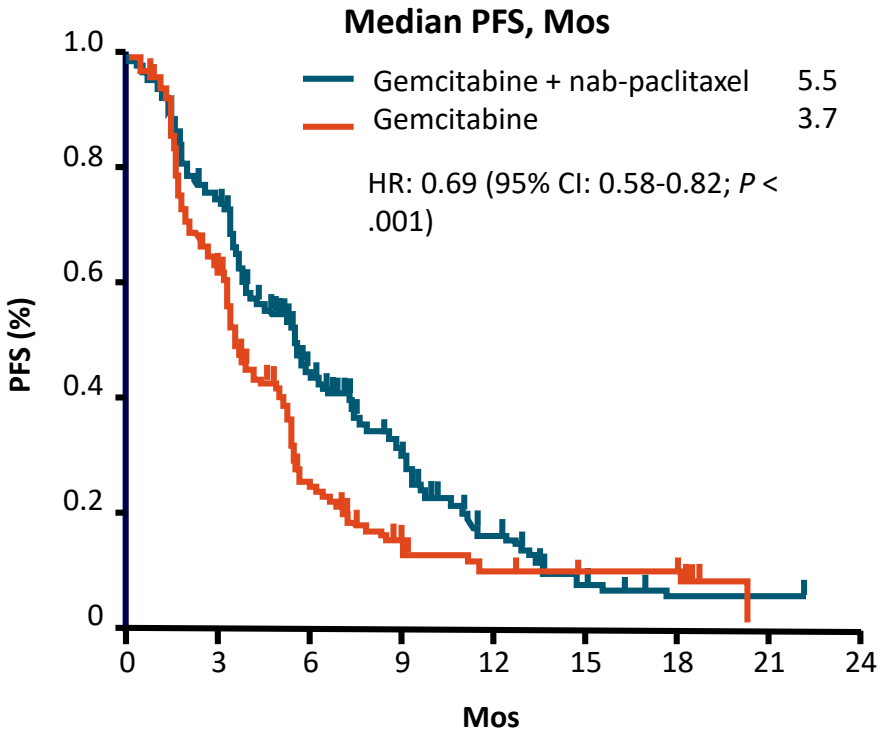
- Primary endpoint: OS
- Secondary endpoints: PFS, ORR, safety

Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

MPACT: OS and PFS





Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

MPACT: Safety

Event, %	Gemcitabine + nab-Paclitaxel (n = 421)	Gemcitabine (n = 402)
AE leading to death	4	4
Hematologic AEs grade ≥ 3		
▪ Neutropenia	38	27
▪ Leukopenia	31	16
▪ Thrombocytopenia	13	9
▪ Anemia	13	12
Receipt of growth factors	26	15
Febrile neutropenia	3	1
Nonhematologic AEs grade ≥ 3 in ≥ 5% of patients		
▪ Fatigue	17	7
▪ Peripheral neuropathy	17	1
▪ Diarrhea	6	1

Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

Frontline Regimens for Patients With Metastatic Pancreatic Cancer

Trial Characteristics and Outcomes	FOLFIRINOX vs Gem (N = 342)[1]	nab-Pac + Gem vs Gem (N = 861)[2]
Median age, yrs (range)	61 (25-76)	62 (27-86)
Male, %	62	57
Region (NA/WE/EE/A), %	0/100 (France)/0/0	62/9/15/14
ECOG PS/KPS (0/100, 1/80-90, 2/60-70), %	37/62/1	16/76/8
Tumor location (H/B/T), %	39/31/26	43/31/25
Median involved metastatic sites, n	2	2.5
ORR, %	32 vs 9	23 vs 7
Disease control rate, %	70 vs 51	48 vs 33
Median PFS, mos	6.4 vs 3.3	5.5 vs 3.7
Median OS, mos	11.1 vs 6.8	8.5 vs 6.7

1. Conroy. NEJM. 2011;364:1817. 2. Von Hoff. NEJM. 2013;369:1691.

Slide credit: clinicaloptions.com

Abstract 4000

APACT: Phase III, Multicenter, International, Open-Label, Randomized Trial of Adjuvant *nab*®-Paclitaxel Plus Gemcitabine vs Gemcitabine for Surgically Resected Pancreatic Adenocarcinoma

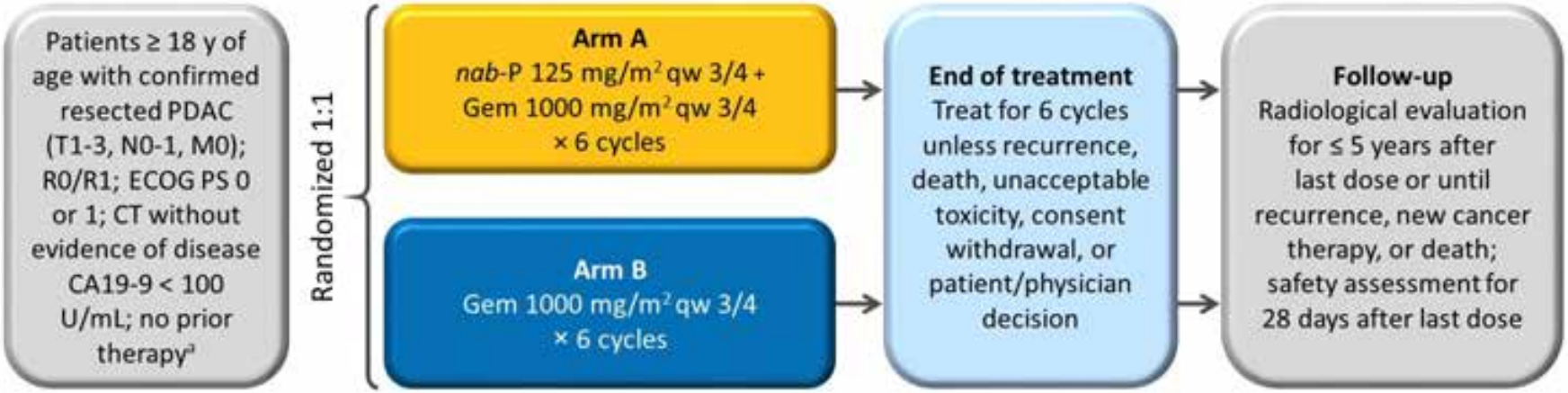
Margaret A. Tempero,[1] Michele Reni,[2] Hanno Riess,[3] Uwe Pelzer,[3] Eileen M. O'Reilly,[4] Jordan Winter,[5] Do-Youn Oh,[6] Chung-Pin Li,[7] Giampaolo Tortora,[8,9] Heung-Moon Chang,[10] Charles D. Lopez,[11] Josep Tabernero,[12] Eric Van Cutsem,[13] Philip Philip,[14] David Goldstein,[15] Jordan D. Berlin,[16] Stefano Ferrara,[17] Mingyu Li,[17] Brian Lu,[17] Andrew Biankin[18]

[1]University of California, San Francisco, Helen Diller Comprehensive Cancer Center, San Francisco, CA; [2]IRCCS Ospedale San Raffaele, Milan, Italy; [3]Charité-Universitätsmedizin Berlin, Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Berlin, Germany; [4]Memorial Sloan Kettering Cancer Center, New York City, NY; [5]Thomas Jefferson University Hospital, Philadelphia, PA; [6]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea; [7]Taipei Veterans General Hospital, Taipei, Taiwan; [8]Azienda Ospedaliera Universitaria, Verona, Italy; [9]Fondazione Policlinico Universitario Gemelli, IRCCS, Rome, Italy; [10]Asan Medical Center, Seoul, South Korea; [11]Oregon Health and Science University, Portland, OR; [12]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; [13]University Hospitals Gasthuisberg/Leuven and KU Leuven, Leuven, Belgium; [14]Karmanos Cancer Institute, Detroit, MI; [15]Nelune Cancer Centre, Prince of Wales Hospital, University of New South Wales, Randwick, NSW, Australia; [16]Vanderbilt-Ingram Cancer Center, Nashville, TN; [17]Celgene Corporation, Summit, NJ; [18]University of Glasgow, Glasgow, Scotland

STUDY DESIGN

apact

APACT: phase III, multicenter, international, open-label, randomized trial



- Patients were randomized as early as possible after adequate recovery from surgery but no later than 12 weeks after surgery
- Stratification factors: resection status (R0 vs R1); lymph node status (LN+ vs LN−); geographic region (North America, Europe and Australia vs Asia Pacific)

CA19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; LN, lymph node; PDAC, pancreatic ductal adenocarcinoma; qw 3/4, the first 3 of 4 weeks; R0/R1, macroscopic complete resection with tumor-free/microscopically positive margin.

[a] Neoadjuvant, radiation, or systemic therapy.

Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant nab-Paclitaxel Plus Gemcitabine vs Gemcitabine

STATISTICAL DESIGN

- **Primary endpoint:** Independently assessed DFS
  - APACT is the first adjuvant trial in pancreatic ductal adenocarcinoma to use independently assessed DFS as the primary endpoint
  - Central review was conducted by radiologists not involved in the trial without clinical or laboratory data
- **Secondary endpoints:** OS; safety
- **Exploratory endpoints:** Tumor & blood biomarker analysis; quality of life
- **Prespecified sensitivity analyses included:** Investigator-assessed DFS

Sample Size and Power Considerations

Endpoint	*nab*-P + Gem		Gem
Primary (independently assessed DFS)			
Median, months	18.5		13.5
HR for disease recurrence or death		0.73	
Events required for 90% power at 2-sided α of 0.05, n		438	
Secondary (OS)			
Events to be analyzed as supportive analysis, n		≈ 630	
Type 1 error control for OS		None	

EORTC, European Organisation for Research and Treatment of Cancer.

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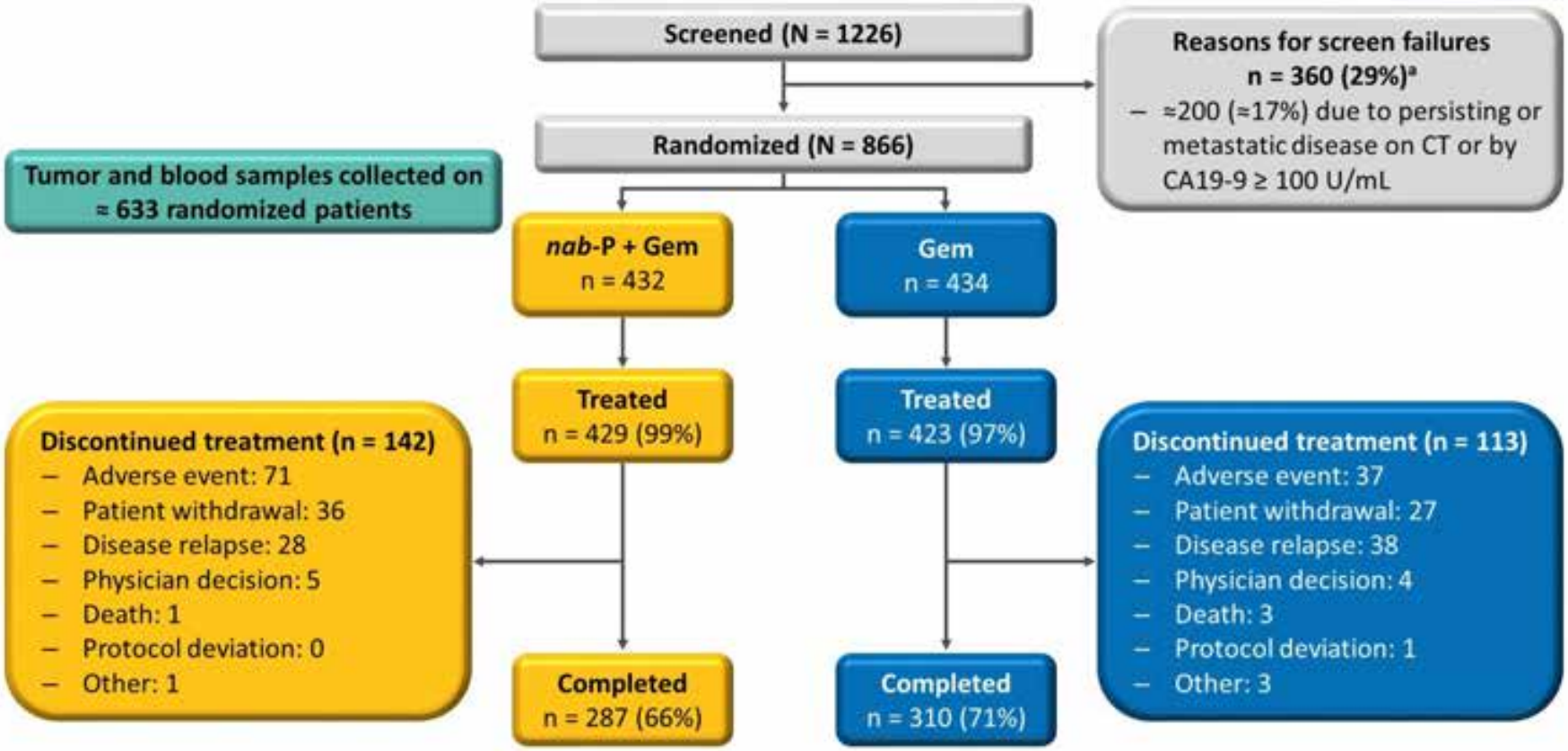
PATIENT DISPOSITION



a Patients could have > 1 reasons for screen failures.

Presented by Margaret Tempero, MD, at ASCO 2019; abstract 4000: Adjuvant nab-Paclitaxel Plus Gemcitabine vs Gemcitabine

SELECTED BASELINE CHARACTERISTICS (ITT POPULATION)

Characteristic	*nab*-P + Gem (n = 432)	Gem (n = 434)	Total (N = 866)
Age, median (range), years	64.0 (34 - 83)	64.0 (38 - 86)	64.0 (34 - 86)
Sex, male, n (%)	228 (53)	253 (58)	481 (56)
ECOG PS, n (%)			
0	252 (58)	268 (62)	520 (60)
1	180 (42)	166 (38)	346 (40)
Resection status, n (%)			
R0 (tumor-free margin)	327 (76)	334 (77)	661 (76)
R1 (microscopically positive margin)	105 (24)	100 (23)	205 (24)
Nodal status, n (%)			
Lymph node negative	121 (28)	122 (28)	243 (28)
Lymph node positive	311 (72)	312 (72)	623 (72)
Baseline CA19-9			
n	423	429	852
Median, U/mL	14.31	12.90	13.65
Tumor grade, n (%)			
Well differentiated	49 (11)	55 (13)	104 (12)
Moderately differentiated	264 (61)	241 (56)	505 (58)
Poorly differentiated	101 (23)	115 (26)	216 (25)
Undifferentiated	1 (< 1)	2 (< 1)	3 (< 1)
Other/unknown	17 (4)	21 (5)	38 (4)

Gem, gemcitabine; ITT, intention-to-treat; *nab*-P, *nab*-paclitaxel.

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Presented By Margaret Tempero at 2019 ASCO Annual Meeting

TREATMENT EXPOSURE AND DOSE MODIFICATIONS (TREATED POPULATION)

Parameters	*nab*-P + Gem		Gem
Treatment exposure	**(n = 429)**		**(n = 423)**
Treatment duration, median (range), weeks	24.0 (0.7 - 33.0)		24.0 (1.3 - 31.9)
Treatment cycles, median (range), n	6.0 (1 - 6)		6.0 (1 - 6)
	***nab*-P**	**Gem**	
Relative dose intensity, median, %	75.1	80.0	91.2
Cumulative dose, median, mg/m^2	1500	13,200	15,000
Dose modifications			
Patients with ≥ 1 dose reduction, n (%)	273 (64)	266 (62)	213 (50)

- Overall, 69% of patients completed 6 treatment cycles (*nab*-P + Gem, 66%; Gem, 71%)
- 59% of patients on *nab-P* + Gem received dosing of *nab-P* in cycle 6

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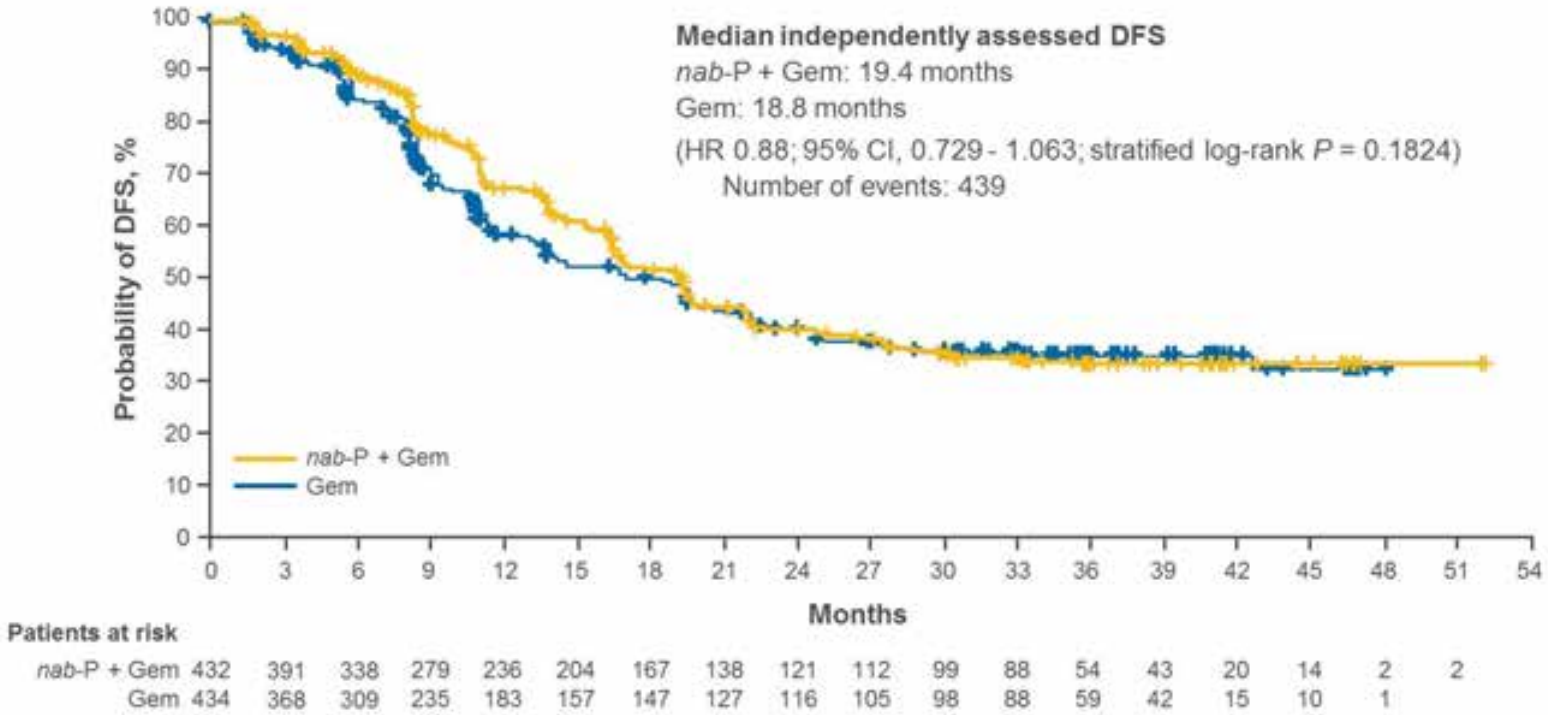
PRIMARY ENDPOINT: INDEPENDENTLY ASSESSED DFS (ITT POPULATION)



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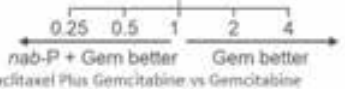
PRESPECIFIED SUBGROUP ANALYSIS: INDEPENDENTLY ASSESSED DFS (ITT POPULATION)

apact

Subgroup	*nab*-P + Gem	Gem	HR for disease recurrence or death (95% CI)
	No. of events/no. of patients		
All patients	226/432	213/434	0.88 (0.729-1.063)
Age			
< 65 yrs	111/221	113/225	0.80 (0.614-1.041)
≥ 65 yrs	115/211	100/209	0.97 (0.739-1.270)
Sex			
Female	110/204	93/181	0.88 (0.664-1.158)
Male	116/228	120/253	0.88 (0.680-1.136)
Region			
North America	75/144	78/156	0.75 (0.546-1.041)
Europe	111/203	101/205	0.98 (0.746-1.283)
Australia	19/30	10/20	1.05 (0.477-2.305)
Asia Pacific	21/55	24/53	0.73 (0.405-1.331)
Baseline ECOG performance status			
0	130/252	138/268	0.89 (0.699-1.131)
1	96/180	75/166	0.87 (0.635-1.185)
Microscopic distance from tumor to the closest margin			
< 1 mm	79/114	61/112	0.95 (0.674-1.327)
≥ 1 mm	134/287	136/292	0.85 (0.665-1.074)
Pancreas position			
Head	193/354	179/347	0.87 (0.708-1.067)
Other	33/78	34/87	0.88 (0.541-1.425)
Tumor grade			
Well differentiated	24/49	21/55	1.19 (0.645-2.180)
Moderately differentiated	136/264	126/241	0.72 (0.559-0.915)
Poorly differentiated and undifferentiated	61/102	56/117	1.15 (0.798-1.670)
Resection status			
R0	156/327	156/334	0.90 (0.724-1.130)
R1	70/105	57/100	0.75 (0.527-1.069)
Nodal status			
LN−	46/121	39/122	1.28 (0.837-1.970)
LN+	180/311	174/312	0.80 (0.649-0.986)
Level of CA19-9 at baseline			
WNL	170/351	173/345	0.80 (0.644-0.986)
ULN - < 100 U/mL	48/70	39/81	1.14 (0.735-1.760)
≥ 100 U/mL	2/2	1/3	–



ULN, upper limit of normal; WNL, within normal limits.

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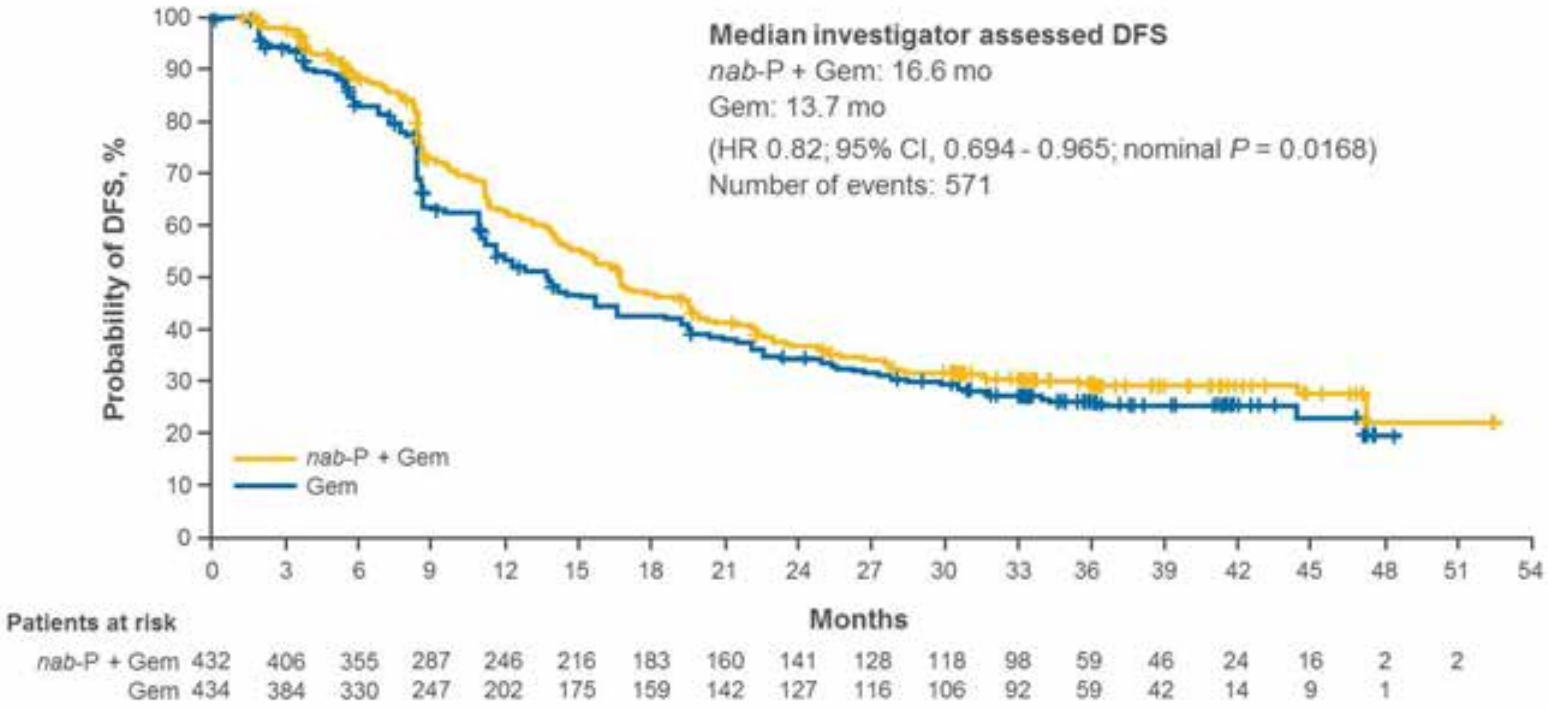
PRESPECIFIED SENSITIVITY ANALYSIS: INVESTIGATOR ASSESSED DFS (ITT POPULATION)



- The concordance rate between disease recurrence by independent radiological review and by investigator review was 77%

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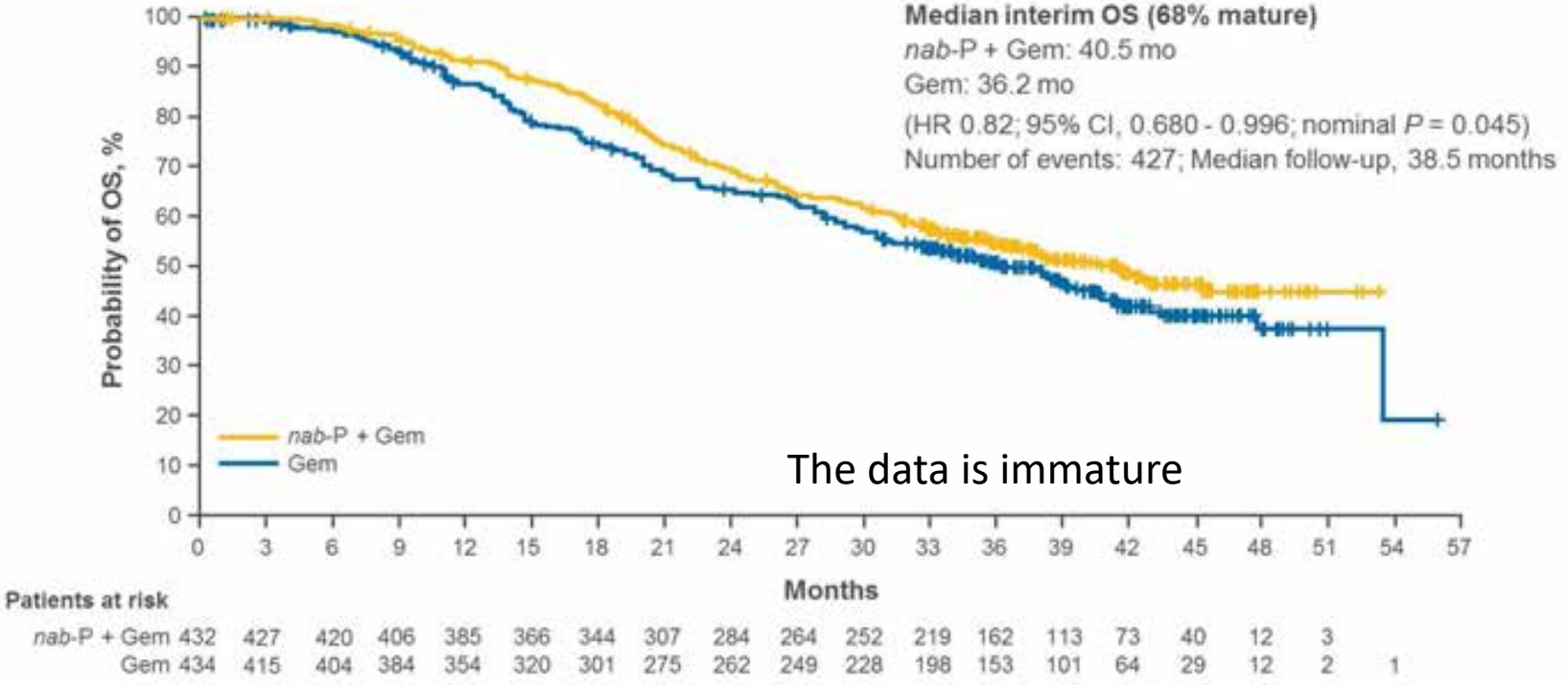
SECONDARY ENDPOINT: INTERIM OS (ITT POPULATION)



The data is immature

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CONCLUSIONS

- The primary endpoint of independently assessed DFS was not met
  - APACT is the first trial of adjuvant therapy in PC to use independently assessed DFS
  - 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[1]
- 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 in resected PC
  - Continued investigation of the regimen (eg, in patients with positive lymph nodes or R1 resection as well as those who are not candidates for FOLFIRINOX) is warranted

1. Von Hoff DD, et al. *N Engl J Med*. 2013; 369:1691-1703.

THANK YOU