Update in Esophagogastric Cancer

Syma Iqbal, MD

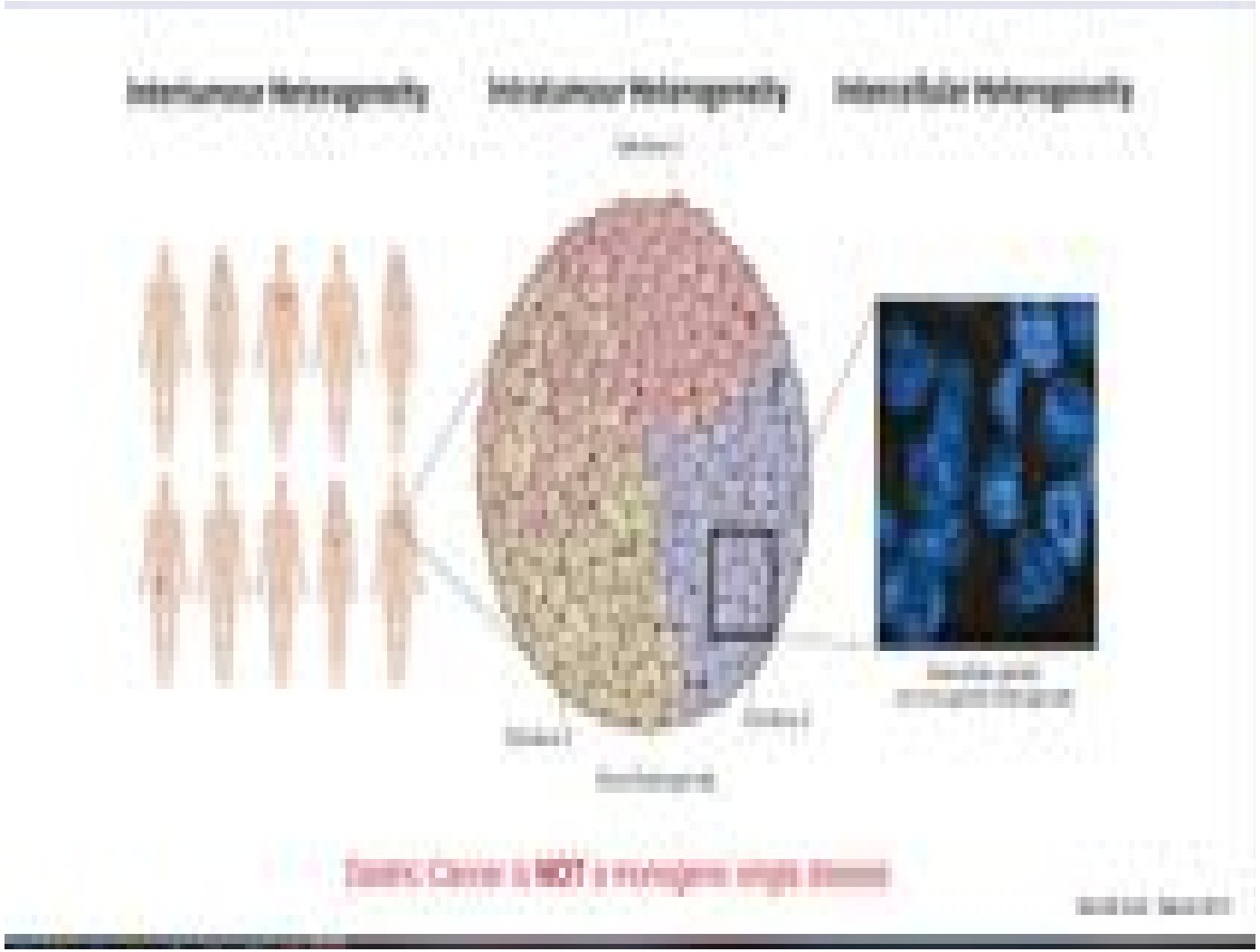
USC Norris Comprehensive Cancer Center

Keck Medicine of USC

USC Norris Comprehensive Cancer Center

Keck Medicine of USC

(Moving) Targets in EG Cancer



- Why have targeted therapy trials failed
- Inadequate study design
  - Lack of a biomarker
  - Difficulties in measuring the biomarker

- Intrinsic characteristics of GC/GEJC:
  - Inter-patient variability: different histology, molecular subtypes
  - Intra-patient variability: heterogeneity of expression at disease sites

Immunotherapy

Immunotherapy in EGC

- ATTRACTION-2: Phase III RCT third line
  - Nivo improves OS compared to placebo
- KEYNOTE 059: Phase II third line Pembrolizumab

- KEYNOTE 061: Phase III RCT second line PD-L1+
  - Pembro does not improve OS vs. paclitaxel
- JAVELIN 300: Phase III RCT second line
  - Avelumab does not improve OS vs. chemo

- KEYNOTE 062: Phase III RCT first line
  - Pembro non inferior to chemo (early death); Pembro _ chemo does not improve OS vs. chemo
- JAVELIN-100: Phase III RCT first line
  - Avelumab does not improve OS vs. chemo

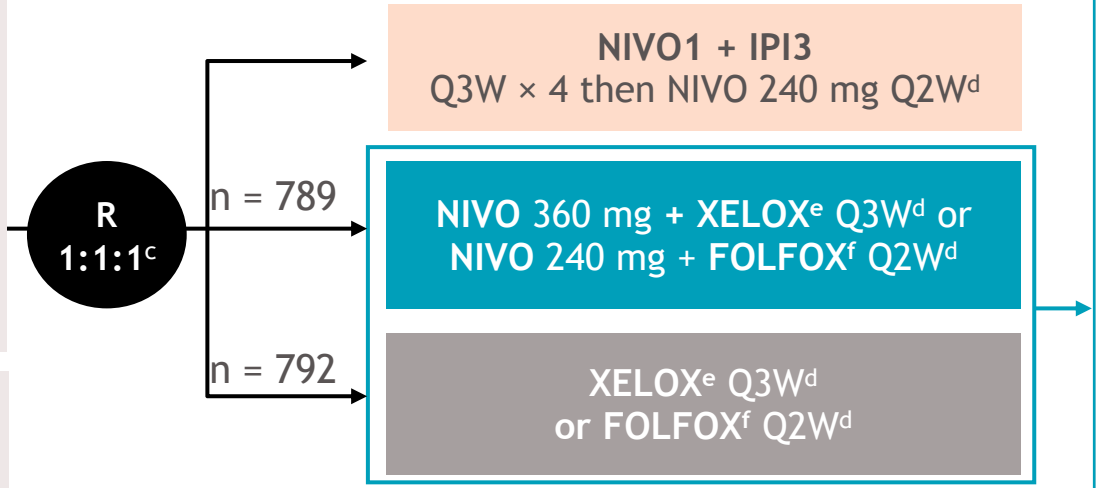
Kang et al, Lancet 2017 Dec 2;390(10111):2461; Fuchs C et al., JAMA Oncol 2018;4:e180013; Shitara K et al. Lancet 2018; 392:123-133; Bang et al., Ann Oncol 2018 Oct 1;29(10):2052-60; Shitara et al, JAMA Oncol. 2020;6(10):1571-1580; Moehler et al., JCO 2021 Mar 20;39(9):966-977

CheckMate 649 Study Design

- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0–1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)



Dual primary endpoints:
- **OS** and **PFS**[g] (PD-L1 CPS ≥ 5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1 or all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- **ORR**[g]

- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[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/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1–14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1–2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

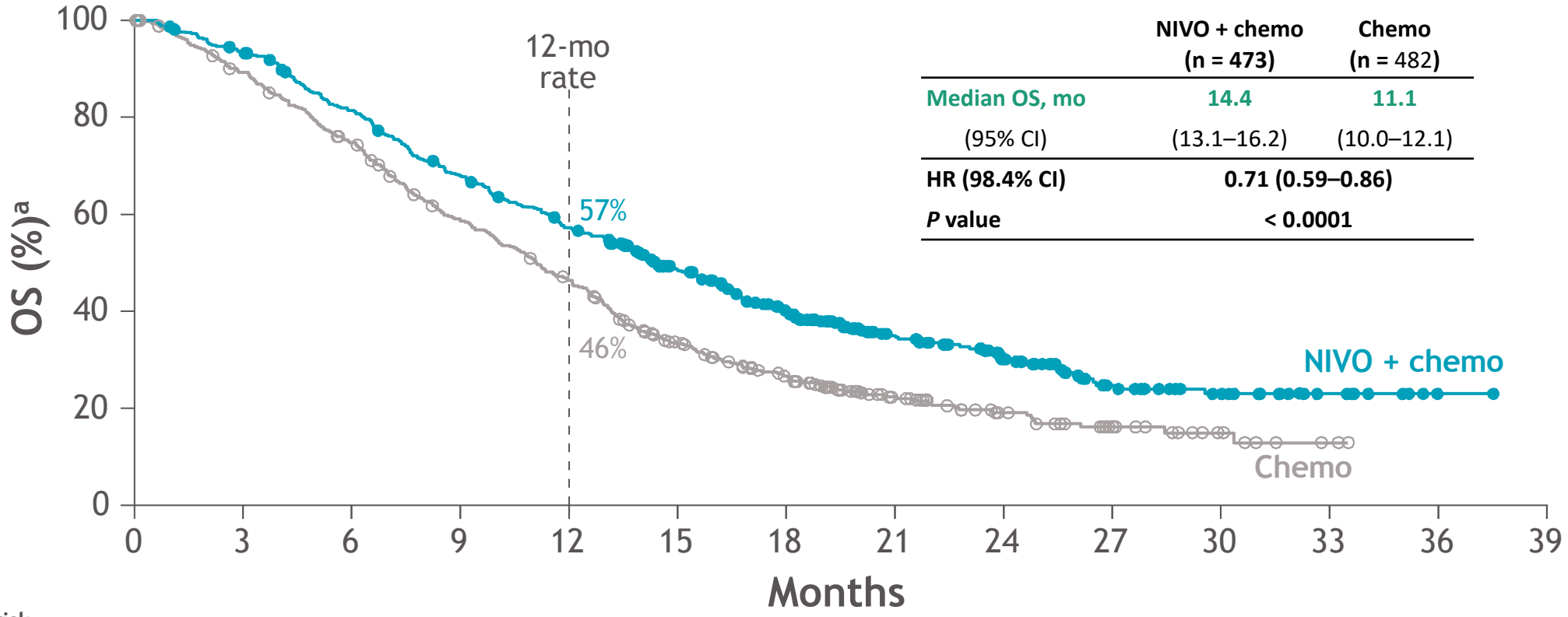
ECOG = Eastern Cooperative Oncology Group.

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40. Moehler M, et al. Presented at: ESMO; September 19-21, 2020; Virtual. Abstract LBA6.

- CheckMate 649

Overall Survival

Primary endpoint (PD-L1 CPS ≥ 5)



	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**	

No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

[a]Minimum follow-up 12.1 months.

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

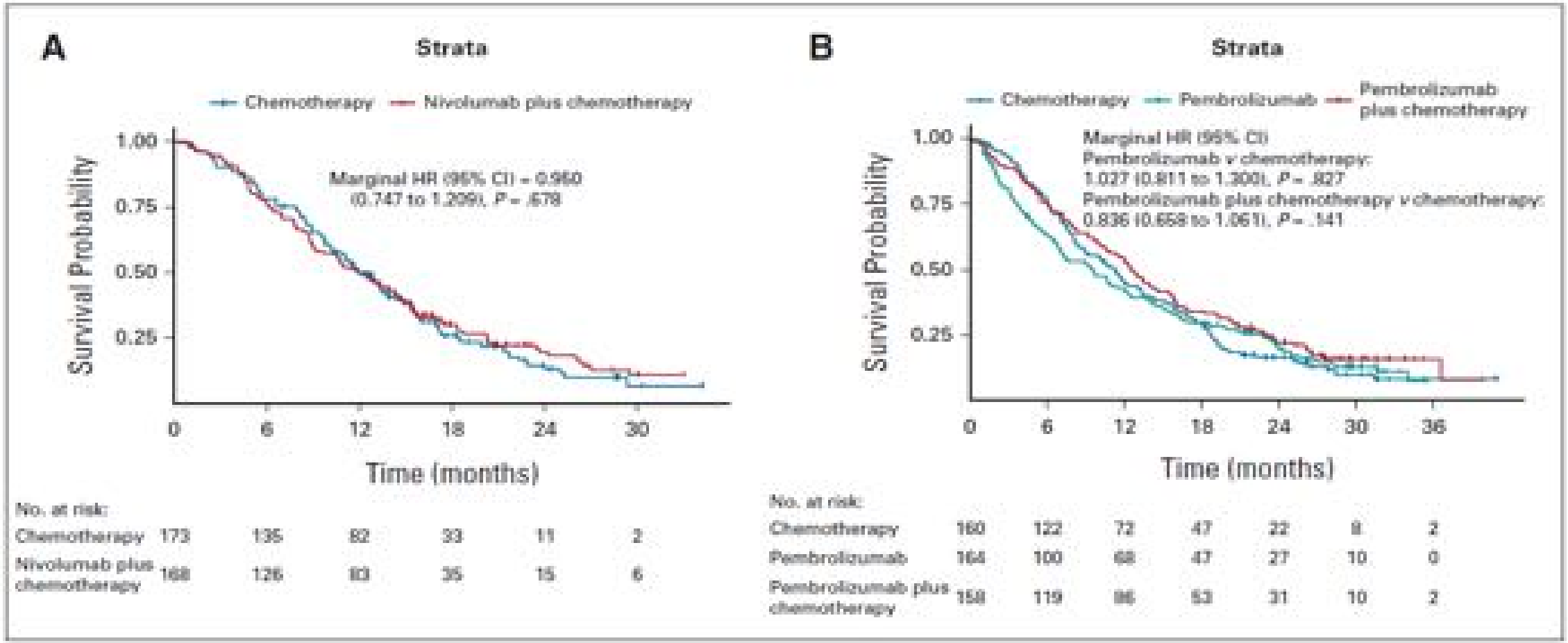
Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

Moehler M, et al. Presented at: ESMO; September 19-21, 2020; Virtual. Abstract LBA6.

Low Programmed Death-Ligand 1-Expressing Subgroup Outcomes of First –Line Immune Checkpoint Inhibitors in Gastric or Esophageal Adenocarcinoma

CheckMate-649 PD-L1 CPS 1-4

KEYNOTE-062 PD-L1 CPS 1-9



Zhao et al, Journal of Clinical Oncology 2021(40):392-402

KEYNOTE-590 Study Design (**NCT03189719**)

Key Eligibility Criteria

- Locally advanced unresectable or metastatic EAC or ESCC or advanced/metastatic EGJ Siewert type 1 adenocarcinoma
- Treatment naive
- ECOG PS 0 or 1
- Measurable disease (RECIST v1.1)

R (1:1)

Pembrolizumab 200 mg IV Q3W for ≤35 cycles
+
Chemotherapy
5-FU 800 mg/m^2 IV for days 1-5 Q3W for ≤35 cycles
+ Cisplatin 80 mg/m^2 IV Q3W for ≤6 cycles

Placebo[a]
+
Chemotherapy
5-FU 800 mg/m^2 IV for days 1-5 Q3W for ≤35 cycles
+ Cisplatin 80 mg/m^2 IV Q3W for ≤6 cycles

Stratification Factors

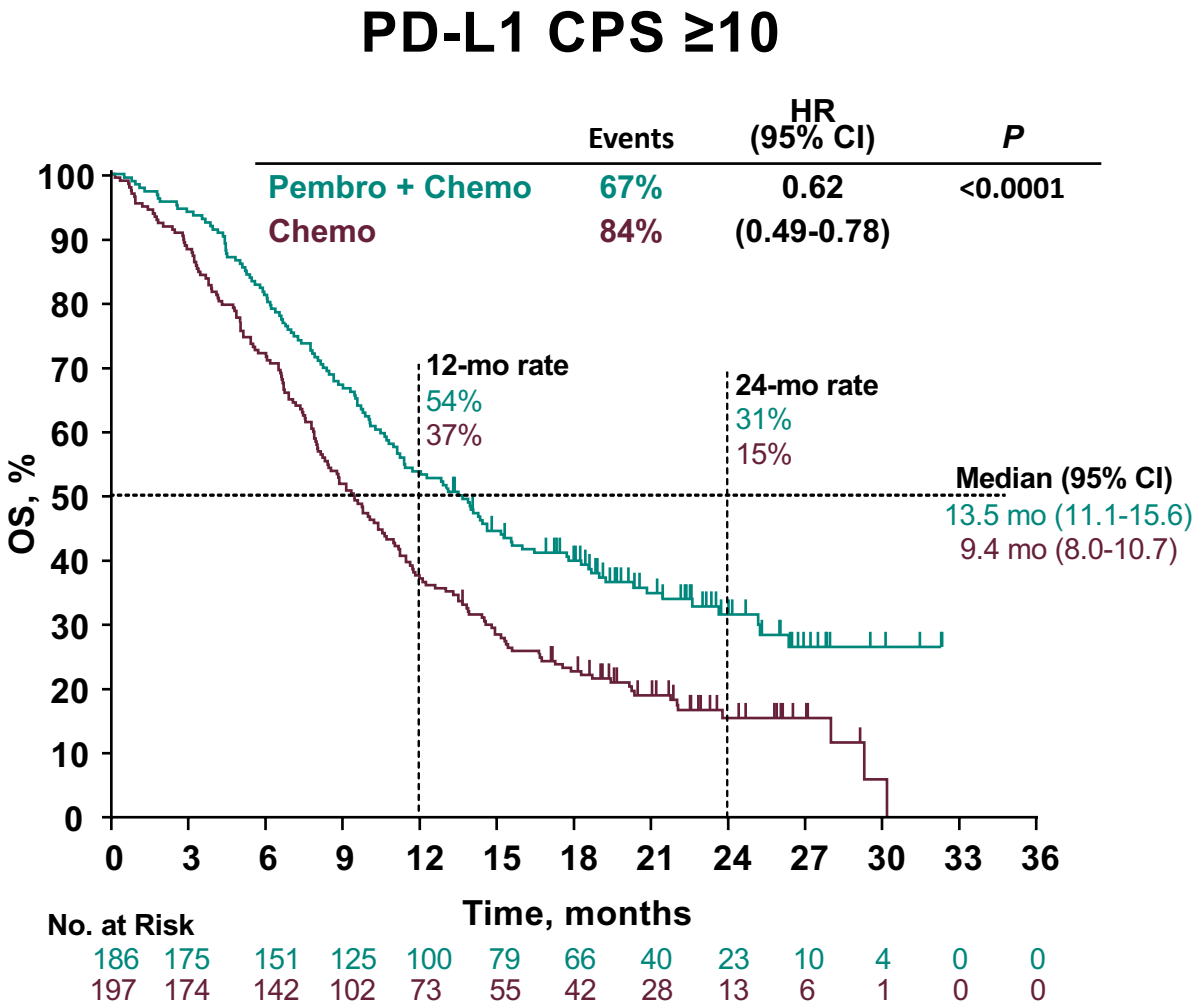
- Asia vs Non-Asia region
- ESCC vs EAC
- ECOG PS 0 vs 1

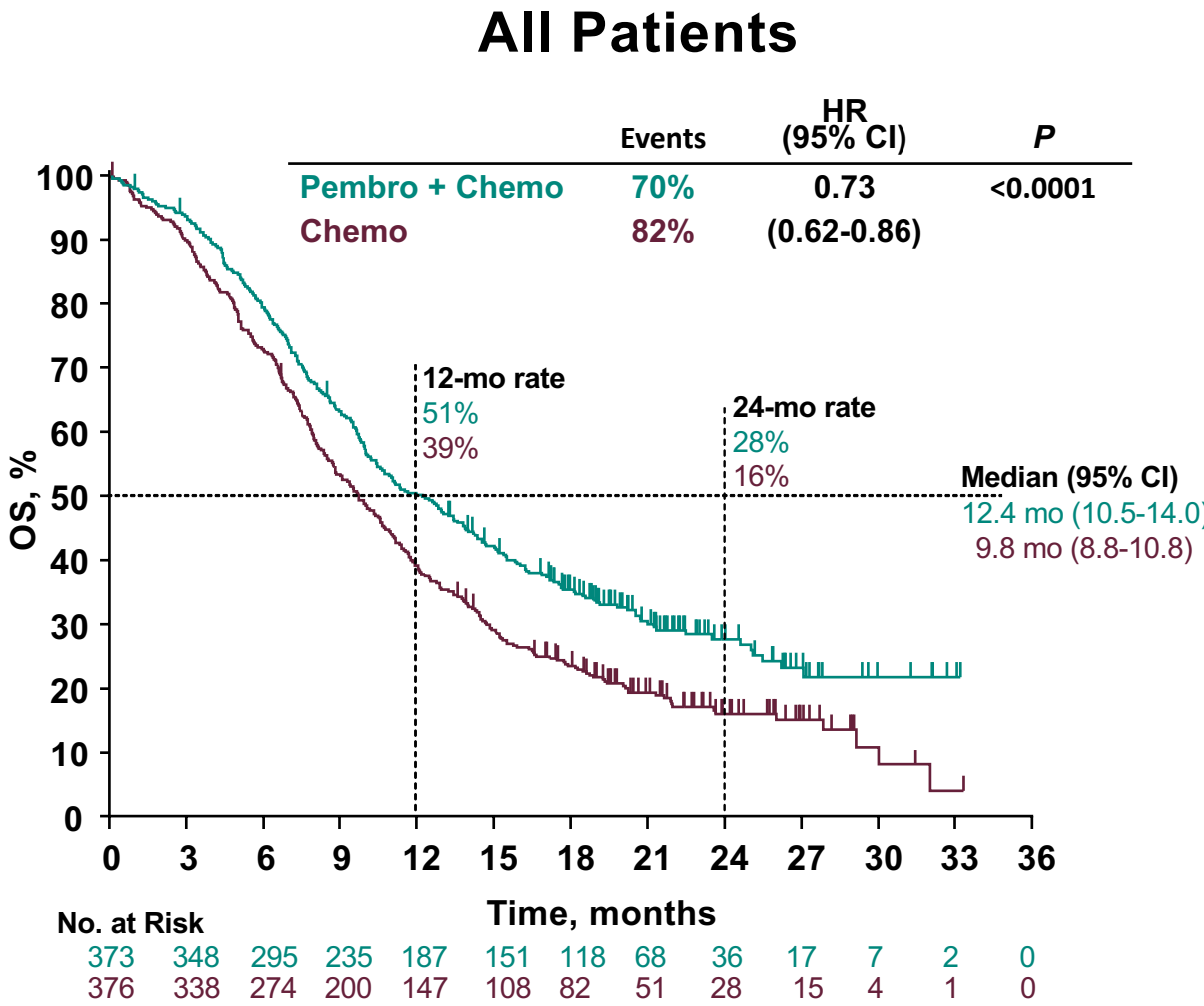
- **Dual-Primary endpoints: OS and PFS (RECIST v1.1, investigator)**
- **Secondary endpoint: ORR (RECIST v1.1, investigator)**
- **Tumor response assessed at week 9 then Q9W (RECIST v1.1, investigator)**

[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.

NCT03189719 [clinicaltrials.gov]. Updated January 25, 2022. Accessed July 21, 2022. https://clinicaltrials.gov/ct2/show/NCT03189719.

Overall Survival



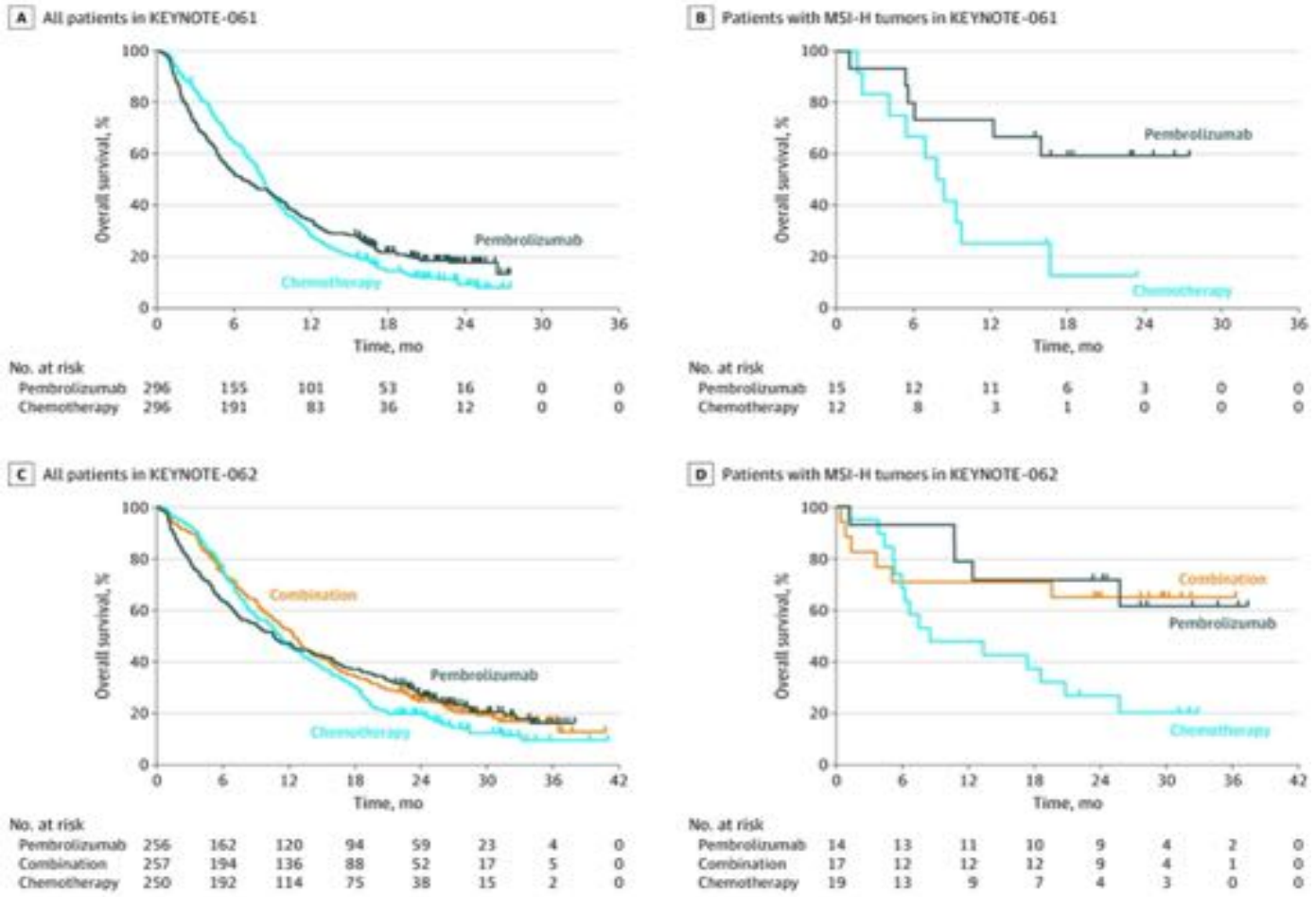


- Data cut-off: July 2, 2020.

CPS = combined positive score.

Sun J-M, et al. *Lancet*. 2021;398(10302):759-771. Kato K, et al. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.

Assessment of Pembrolizumab Therapy for the Treatment of Microsatellite Instability-High Gastric or Gastroesophageal Junction Cancer among Patients in the KEYNOTE-059, KEYNOTE-061, and KEYNOTE-062 Clinical Trials

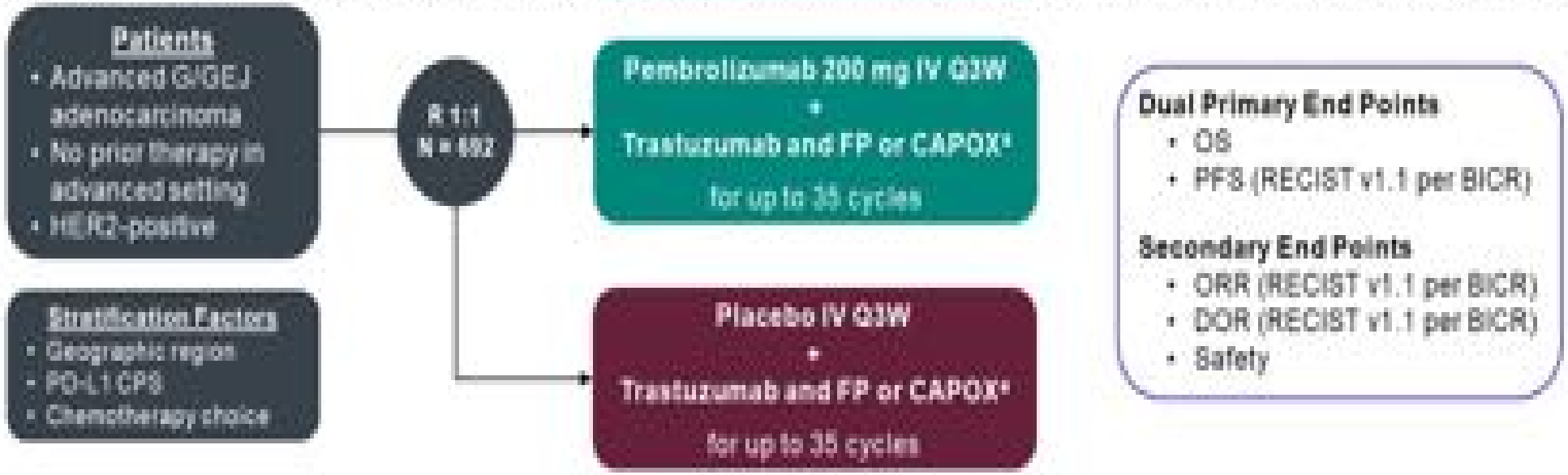


- Pembrolizumab or pembrolizumab plus chemotherapy provided durable antitumor activity vs chemotherapy alone among patients with MSI-H gastric or gastroesophageal junction cancer regardless of the line of therapy in which it was received
- MSI-H gastric cancer responds worse to chemotherapy alone

Chao J, et al. *JAMA Oncol*. 2021;7(6):895-902

KEYNOTE-811 Global Cohort

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)

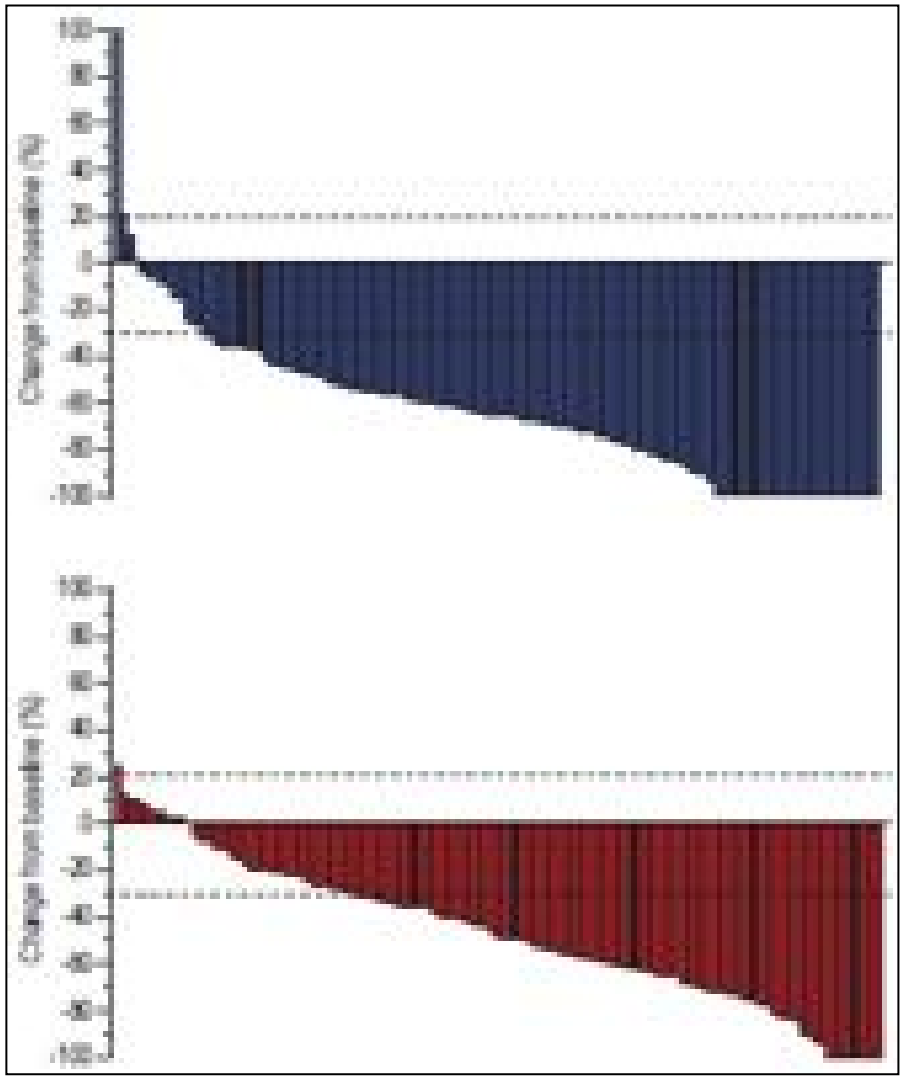


260 patients

Primary endpoint: To assess addition of pembro to trastuzumab improved response rate

Jangigian YY, et al. *J Clin Oncol*. 2021;39(15_suppl.):4013. Jangigian YY, et al. *Nature*. 2021;600(7890):727-730.

KEYNOTE 811: Interim Analysis Results



Jangigian YY, et al. *J Clin Oncol*. 2021;39(15_suppl.):4013.

IO in Esophagogastric Cancer Summary

- Nivolumab in combination with chemotherapy is standard of care for patients with advanced/metastatic disease esophagogastric cancer
- Pembrolizumab in combination with chemotherapy standard of care option for patients with esophageal cancer adenocarcinoma or SCC.
- Pembrolizumab in combination with chemotherapy standard of care for patients with HER2+ gastric, GEJ adenocarcinoma
- No new toxicities
- FDA approval regardless of PD-L1 status
- NCCN guidelines PD-L1 CPS score $\geq$5
- Patients with MSI high advanced disease benefit from immunotherapy or immunotherapy with chemotherapy
- Immunotherapy second-line and beyond
  - Negative second-line studies
  - ODAC withdrew approval of Pembro in third-line setting

NCCN = National Comprehensive Cancer Network; ODAC = Oncologic Drugs Advisory Committee.

Perioperative Therapy

CheckMate 577 Study Design

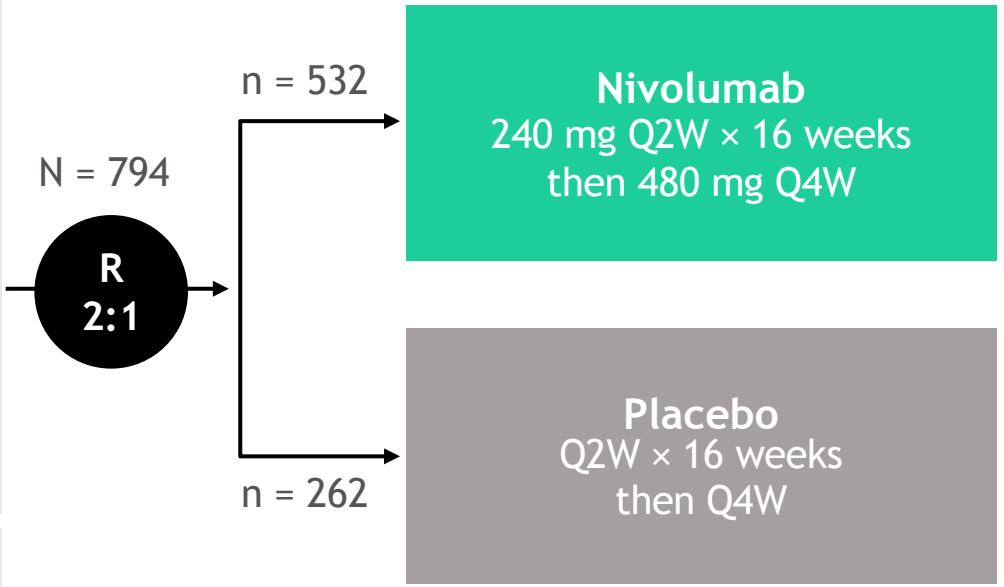
• CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- **Residual pathologic disease**
  - **≥ ypT1 or ≥ ypN1**
- ECOG PS 0–1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Total treatment duration of up to 1 year[d]

Primary endpoint:

- DFS[e]

Secondary endpoints:

- OS[f]
- OS rate at 1, 2, and 3 years

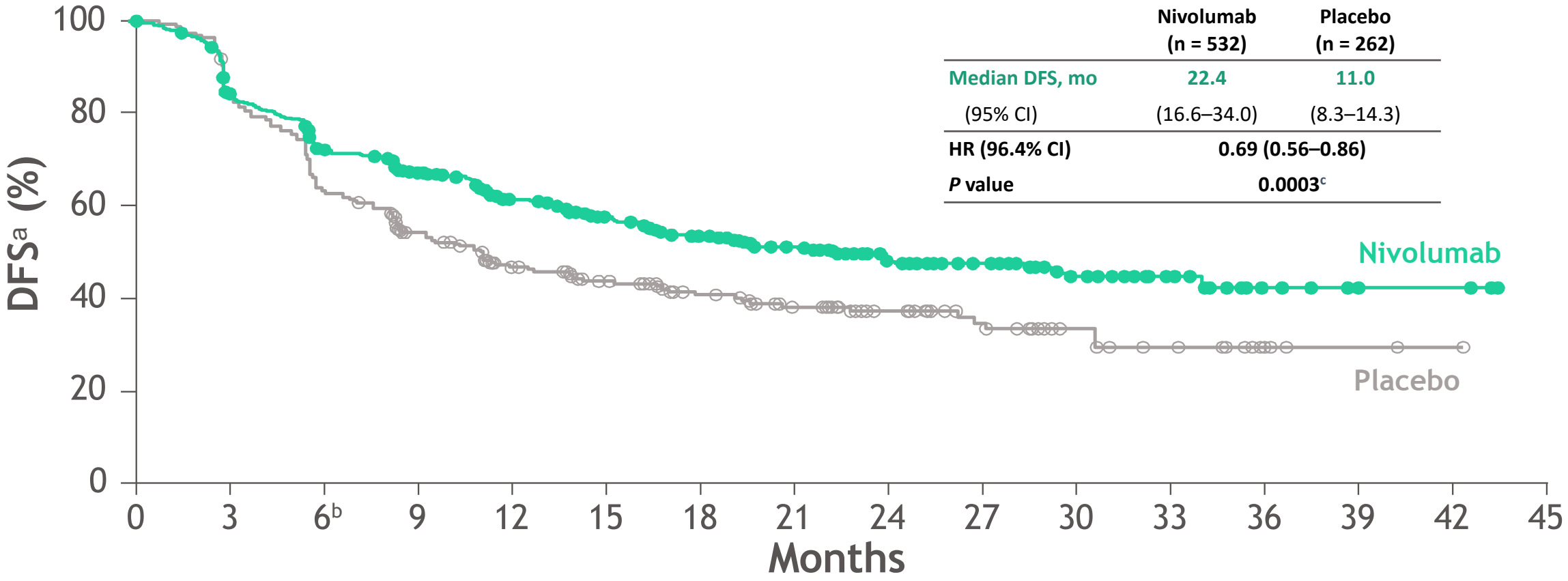
- Median follow-up was 24.4 months (range, 6.2–44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

[a]ClinicalTrials.gov number, NCT02743494; [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins; [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression; [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent; [e]Assessed by investigator, the study required at least 440 DFS events to achieve 91% power to detect an average HR of 0.72 at a 2-sided α of 0.05, accounting for a pre-specified interim analysis; [f]The study will continue as planned to allow for future analysis of OS; [g]Time from randomization date to clinical data cutoff (May 12, 2020).

Kelly R, et al. Presented at: ESMO; September 19-21; 2020; Virtual. Abstract LBA9. Kelly R, et al. *N Engl J Med* 2021; 384:1191-1203.

- CheckMate 577

Disease-free Survival



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6–34.0)	(8.3–14.3)
HR (96.4% CI)	0.69 (0.56–0.86)	
P value	0.0003[c]	

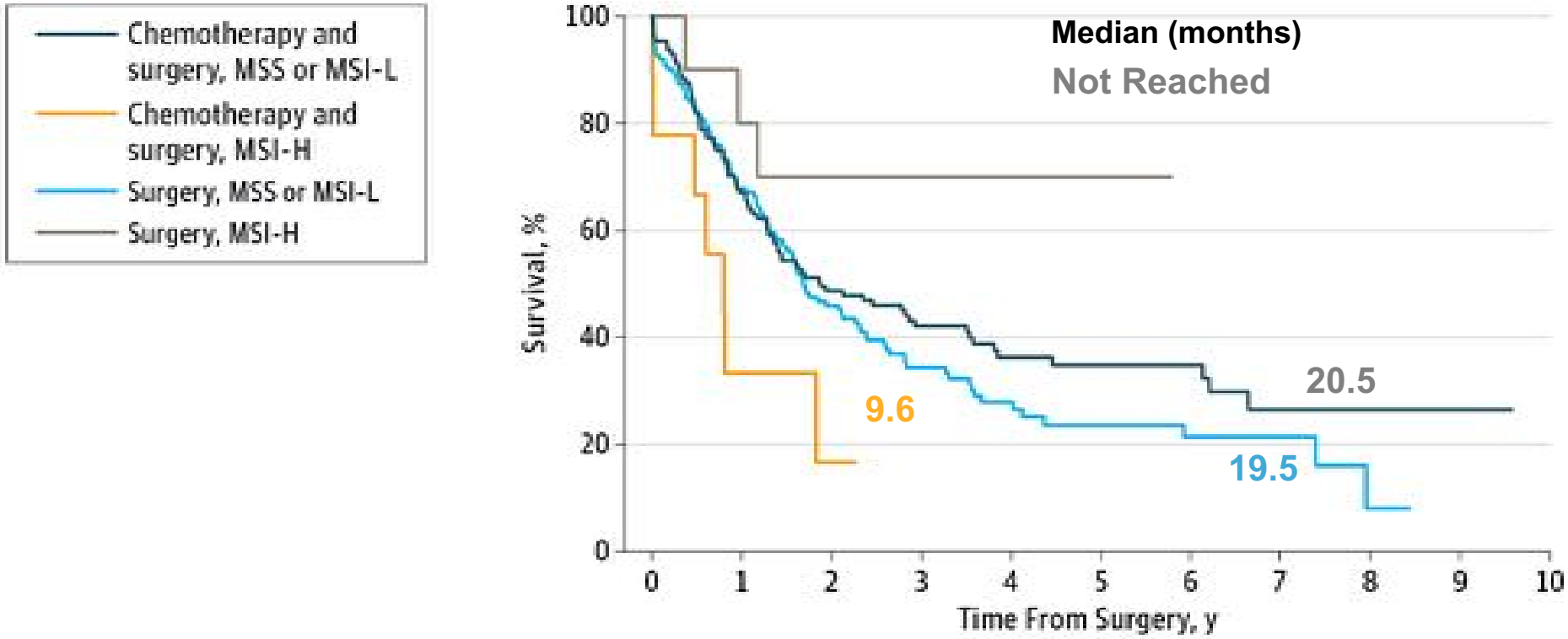
No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

Kelly R, et al. Presented at: ESMO; September 19-21; 2020; Virtual. Abstract LBA9. Kelly R, et al. *N Engl J Med* 2021. 384:1191-1203.

MSI-H EG Tumors Are Chemotherapy Resistant: *OS In Adjuvant MAGIC Study*



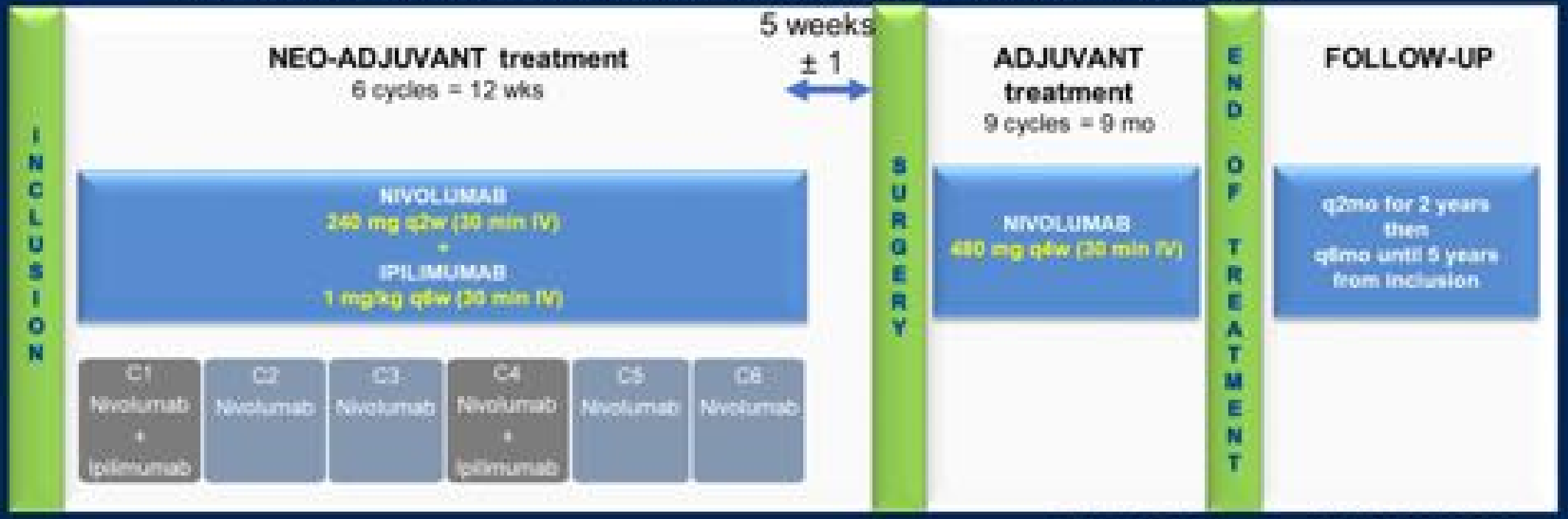
No. at risk

Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1
Chemotherapy and surgery, MSI-positive patients	9	3	1							
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	
Surgery, MSI-positive patients	10	8	6	3	1	1				

Smyth EC, et al. JAMA Oncol. 2017;3(9):1197-1203.
Courtesy of Yelena Y Janjigian, MD.

NEONIPIGA: Study design/metods

- Phase II study evaluating efficacy of neo-adjuvant nivolumab and ipilimumab followed by adjuvant nivolumab in pts with resectable OGA MSI/dMMR, T2-T4 NxM0
- The primary objective was pathological complete response rate (pCRR).



ClinicalTrials.gov: NCT04006262

Andre T, et al. 2022. *J Clin Oncol*. 2022;40(4_suppl):244.

Results (1): Surgery and TNM and Tumor Regression Grading (TRG)

Type of surgery (N=29)	N	%
R0	29	100
Total oesogastrectomy	1	3,5
Total gastrectomy	7	24
4/5 gastrectomy	9	31
Lewis-Santy procedure	11	38
Pancreaticoduodenectomy	1	3,5

ypT stage (N=32)	
ypT0*	19
ypT1a	1
ypT1b	2
ypT2	2
ypT3	5
unknown**	3
ypN stage (N=32)	
ypN0	23
ypN1	6
unknown*	3

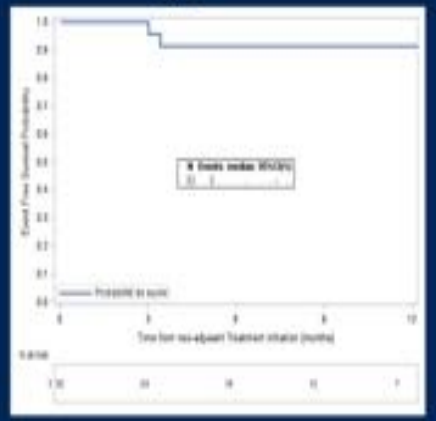
TRG Mandard (N=29)	N	%
TRG 1: complete regression/fibrosis with no tumor cells	17	58.6
TRG 2: fibrosis with scattered tumor cells	4	13.8
TRG 3: fibrosis and tumor cells with a dominance of fibrosis	2	6.9
TRG 4: fibrosis & tumor cells with dominance of tumor cells	4	13.8
TRG 5: tumor without evidence of regression	2	6.9
TRG Becker (N=29)		
TRG 1a: complete tumor regression without residual tumor	17	58.6
TRG 1b: < 10% residual tumor per tumor bed	4	13.8
TGR 2: 10% to 50% residual tumor	2	6.9
TRG 3: > 50% residual tumor cells	6	21.7

- * 2 patients ypT0 and ypN1 (residual tumoral cells < 10% in only one node)
- ** 3 patients without surgery, 1 in metastatic PD and 2 in complete response in endoscopy with no tumoral cell on biopsy

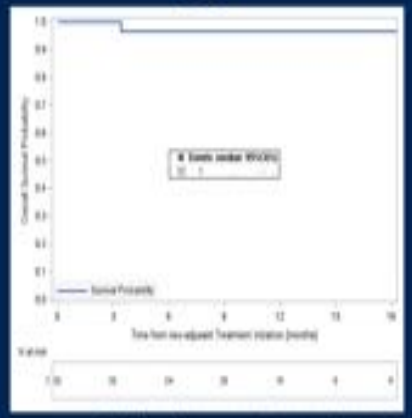
Results (2)

- With a median follow-up of 12 months (95%CI: 7.8-14.2), 2 patients had events (death or relapse)
  - one death at day 3 post surgery*
  - one progressive disease with metastatic disease PD after 6 cycles (surgery not performed)
  - 31 patients alive and 30 without relapse

EFS



OS



* History of severe cardio vascular co-morbidity and sudden death

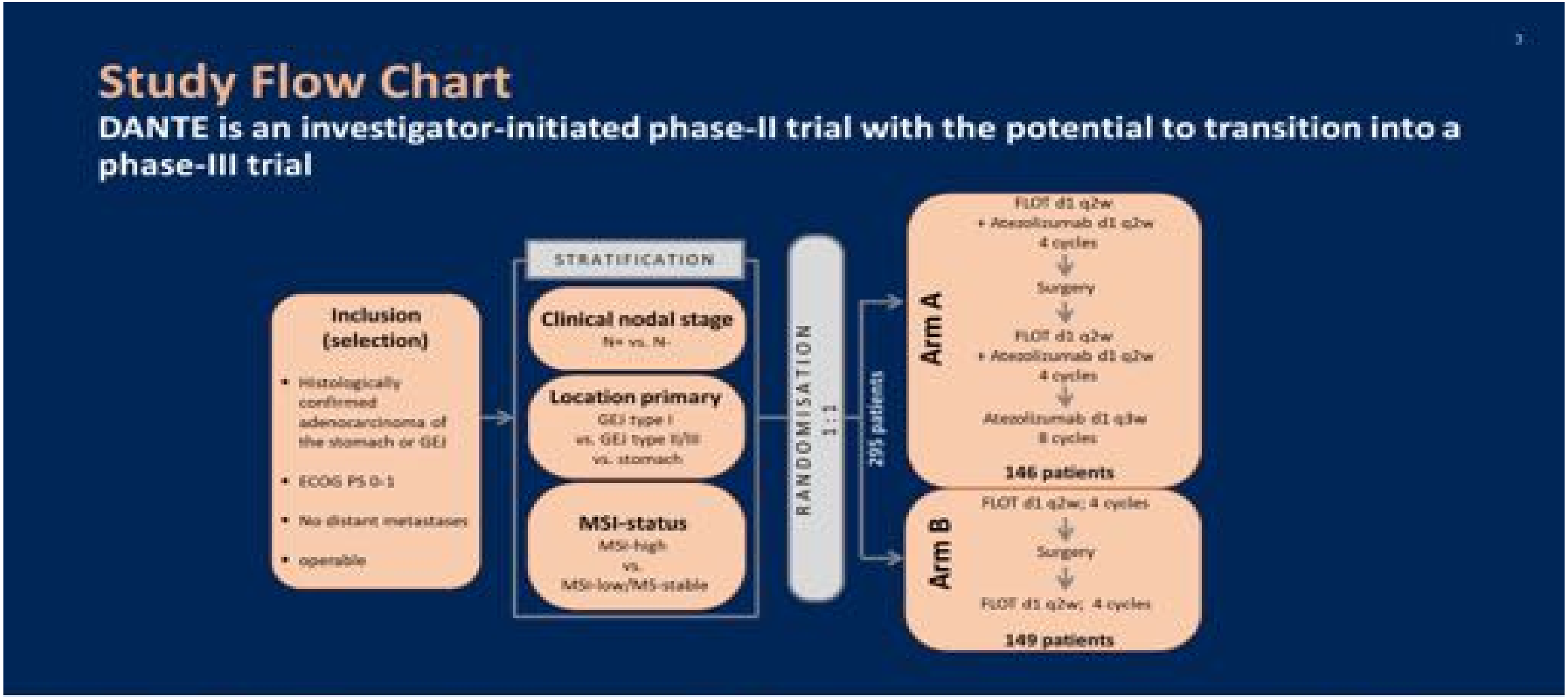
ASCO Gastrointestinal Cancers Symposium #GI22 Thierry André, MD Abstract 244 ASCO

ASCO Gastrointestinal Cancers Symposium #GI22 Thierry André, MD Abstract 244 ASCO

Results (1): Surgery and TNM and Tumor Regression Grading (TRG)

Andre T, et al. 2022. *J Clin Oncol*. 2022;40(4_suppl):244.

Surgical and Pathological Outcome in Patients Receiving Perioperative Atezolizumab in Combination with Flot vs Flot Alone for Resectable Ega: Interim Results from DANTE, a Randomized, Multicenter, Phase IIb Trial of The Flot-aio German Gastric Cancer Group and Swiss Sakk



Al-Batran S-E, et al. *J Clin Oncol*. 2022;40(16_suppl):4003.

Pathological response (local vs. central assessment)

Pathological Regression FLOT + Atezolizumab (arm A) vs. FLOT (arm B)	Local assessment				Central assessment[1]			
	TRG1a[2]		TRG1a/b[3]		TRG1a[2]		TRG1a/b[3]	
	A	B	A	B	A	B	A	B
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)	37 (25%)	36 (24%)	72 (49%)	66 (44%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)	21 (26%)	20 (23%)	43 (52%)	41 (47%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)	13 (33%)	9 (22%)	21 (53%)	19 (46%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)	11 (41%)	5 (19%)	19 (70%)	13 (50%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

[1]central assessment by one pathologist based on a representative tumor sample
[2]pathological complete regression acc. to Becker
[3]pathological subtotal regression acc. to Becker

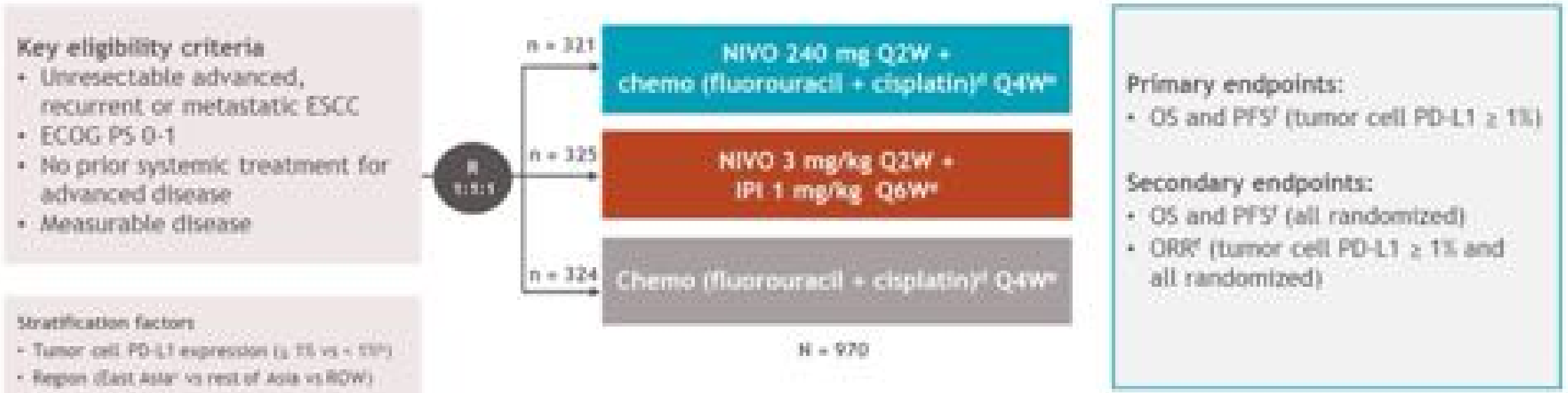
Al-Batran S-E, et al. *J Clin Oncol*. 2022;40(16_suppl):4003.
Presented at: ASCO 2022.

IO in Perioperative Treatment Summary

- Adjuvant nivolumab is now standard following trimodality therapy for esophageal/GEJ adenocarcinoma and SCC for residual disease
- MSI-high patients may not benefit from perioperative chemotherapy, consider IO alone
- Ongoing studies assessing the addition of perioperative immunotherapy in patients with resectable esophagogastric cancer
  - KEYNOTE 585, MATTERHORN, KEYNOTE 975, EA2174, SKYSCRAPER-07

Squamous Cell Carcinoma

CheckMate 648: Study Design



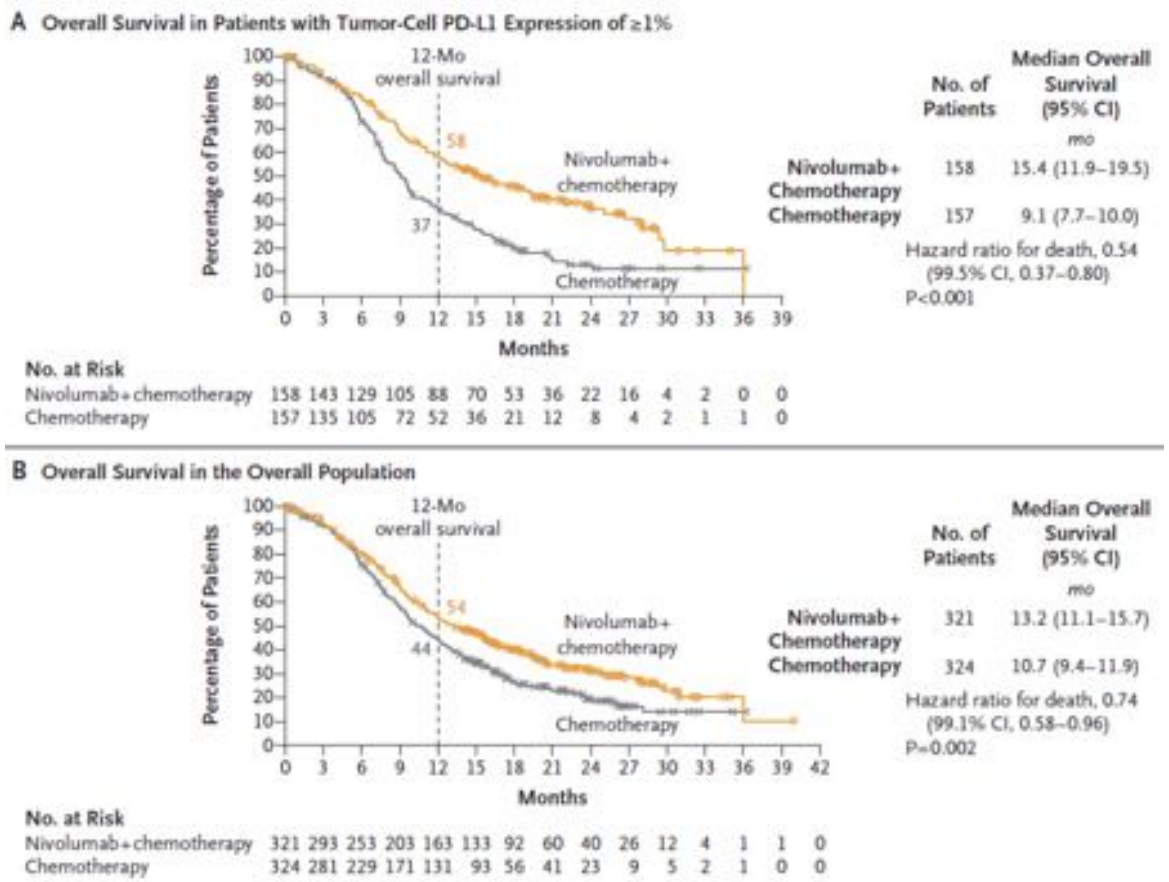
- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[f]

[a]ClinicalTrials.gov, NCT03143153; [a]≥ 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [b]East Asia includes patients from Japan, Korea, and Taiwan; [c]Fluorouracil 800 mg/m² IV daily (days 1-5) and cisplatin 80 mg/m² IV (day 1); [c]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [e]Per blinded independent central review (BICR); [f]Time from last patient randomized to clinical data cutoff.

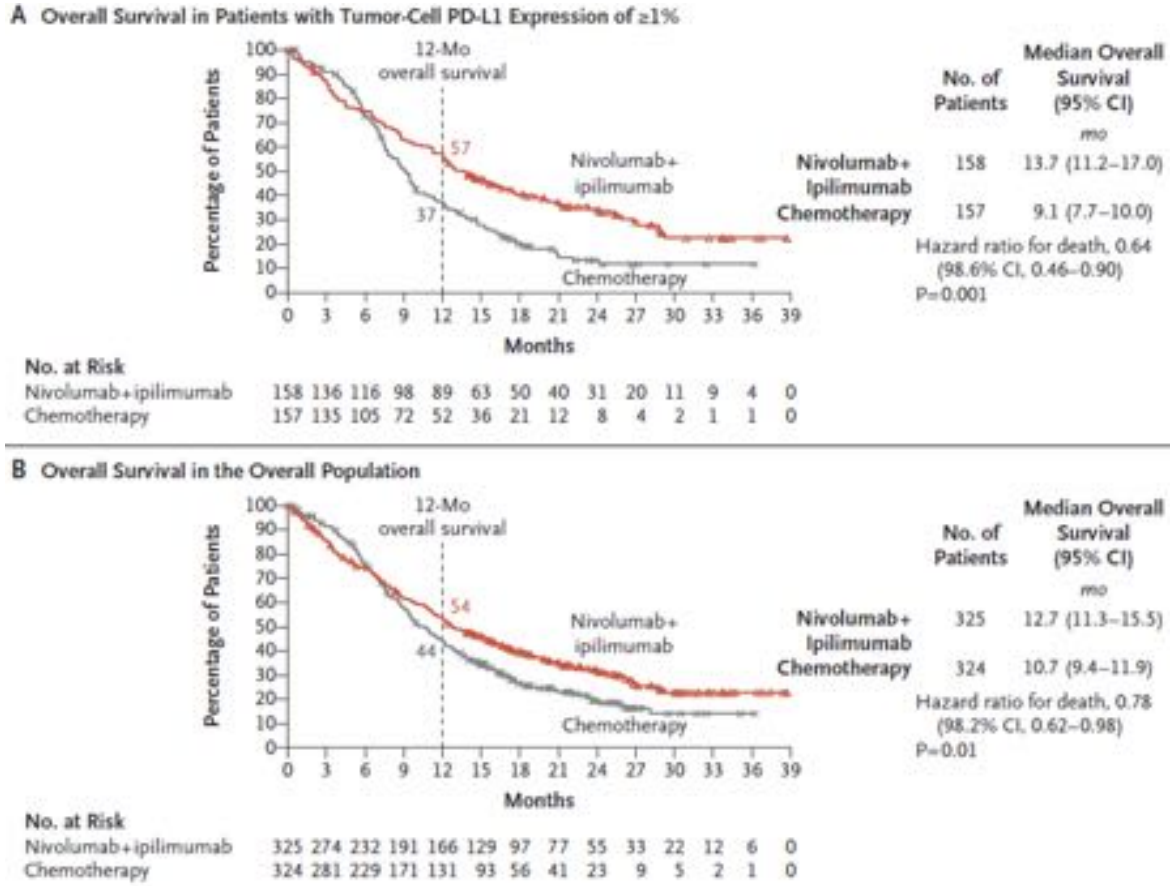
Doki Y, et al. *N Engl J Med.* 2022;386(5):449-462.

CheckMate 648: Efficacy Results

Chemo + Nivo vs Chemo



Ipi + Nivo vs Chemo



Doki Y, et al. *N Engl J Med.* 2022;386(5):449-462.

ESCC IO Trials

Study	Tumor Location and Histology	Geography	Biomarker Selection and Antibody Used	Study Design	OS, months (mo)	ORR
First Line Trials						
ORIENT-15	ESCC N=659	China	PD-L1 CPS ≥ 10 All	Sintilimab plus chemotherapy[4] vs. chemotherapy*	17.2 vs. 13.6 mo in PD-L1 CPS ≥10%, HR 0.638, p 0.0018 16.7 vs. 12.5 mo in all, HR 0.628, p < 0.0001	66.1 vs. 45.5 in all
ESCORT-1	ESCC N=596	China	None	Camrelizumab vs placebo + chemotherapy[4]	15.3 vs. 12.0 mo, HR 0.70, p 0.001	72.1% vs 62.1%
JUPITER-06	ESCC N=514	China	None	Toripalimab plus chemotherapy vs. placebo plus chemotherapy	17.0 vs. 11.0 mo, HR 0.58, p 0.00036	Not available
Second Line and Later Trials						
KEYNOTE-181	Esophageal/GEJ adenocarcinoma or squamous cancer (64%) N=628	39% Asia 61% Rest of world	PD-L1 CPS ≥10 N=222	Pembrolizumab vs. paclitaxel, docetaxel, or irinotecan	9.3 vs 6.7 mo in PD-L1 CPS≥10%, HR 0.69, p 0.0074 8.2 vs. 7.1 mo in all ESCC, HR 0.78, p 0.0095 7.1 vs. 7.1 mo in all, HR 0.89, p 0.0560	21.5% vs. 6.1% in PD-L1 CPS≥10%
RATIONALE 302	ESCC N=512	79% Asia, 21% Europe and North America	None	Tislelizumab vs. paclitaxel, docetaxel, or irinotecan	8.6 vs. 6.3 mo, HR 0.70, p 0.001	20.3% vs. 9.8%
ATTRACTION-3	ESCC N=419	Japan, Korea, Taiwan	None	Nivolumab vs. paclitaxel or docetaxel	10.9 vs. 8.4 mo, HR 0.68, p 0.0007	19% vs. 22%

Xu R-H, et al. **Ann Oncol. 2021;32(suppl_5):S1040-S1075.** XU R-H, et al. J Clin Oncol. **2021;39(15_suppl):4000.**
Chau I, et al. *J Clin Oncol*. 2021;39(15_suppl):LBA4001. Kokima T, et al *J Clin Oncol*. 2020;38(35):4138-4148.
Shen L, et al. *J Clin Oncol*. 2021;39(15_suppl):4012. Kato K, et al. *Lancet Oncol.* 2019;20(11):1506-1517.

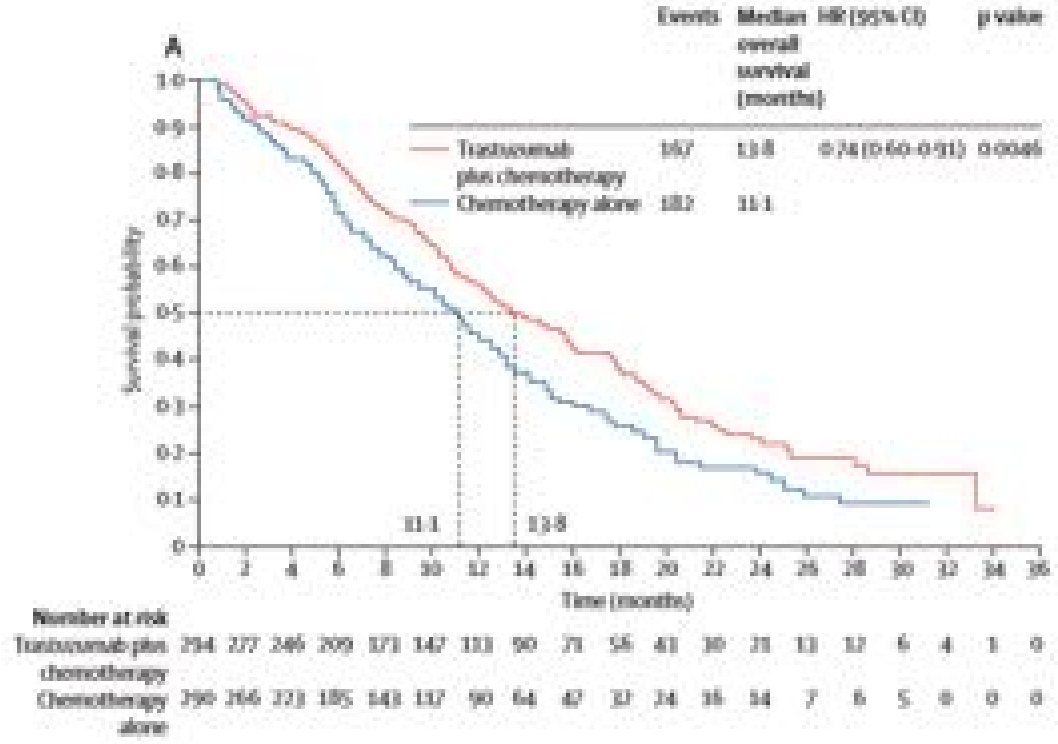
Courtesy of Zev Wainberg

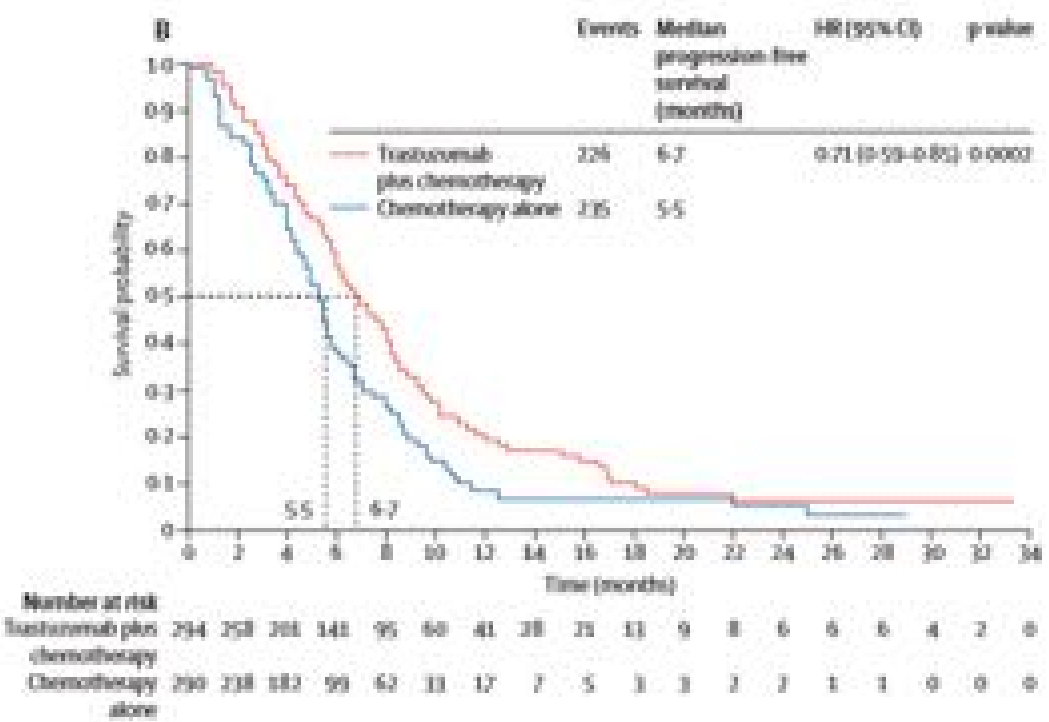
IO for patients with Esophageal SCC

- Nivolumab in combination with chemotherapy demonstrates superior OS, PFS vs. chemotherapy alone in patients with advanced/metastatic esophageal squamous cell cancer (SCC) in front line
- Nivolumab with ipilumumab demonstrates superior OS, PFS vs. chemo alone in patients with advanced ESCC in the front line, with caveat – 6 mos
- Pembrolizumab with chemotherapy demonstrates superior PFS, OS vs. chemotherapy in first line treatment of patients with advanced ESCC
- Second-line therapy with Pembrolizumab, Nivolumab, Tislelizumab
- Adjuvant therapy post trimodality treatment with residual disease benefit of nivolumab on DFS.

Targeting HER2

ToGA Phase III Study





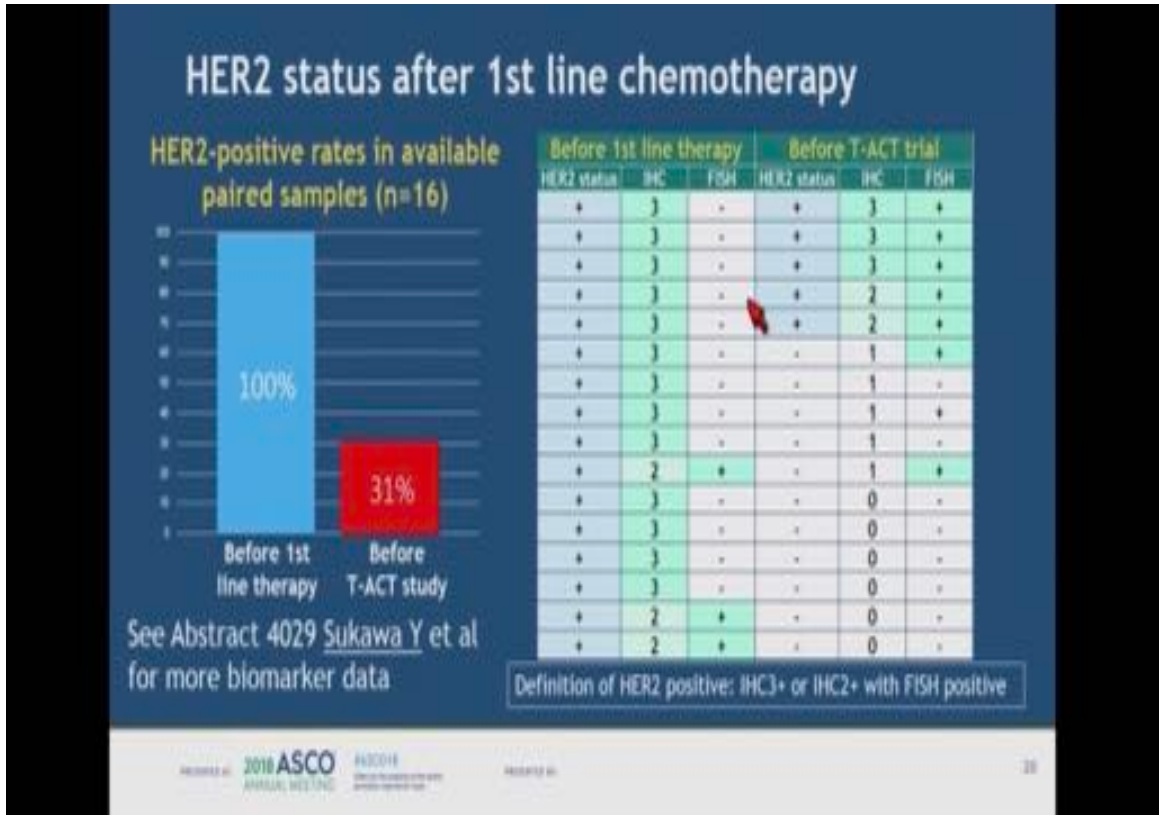
Bang Y-J, et al. *Lancet*. 2010;376(9742):687-97.

Landmark Clinical Trials of HER2-positive Gastric Cancer

Trials	Patients	Line	Region	Phase	Study arms	Results
ToGA	HER2-positive, locally advanced, recurrent or metastatic gastric and GEJ adenocarcinoma	1st	Global	3	Trastuzumab plus chemotherapy (fluorouracil or capecitabine and cisplatin) vs chemotherapy alone	Improvement of median OS with trastuzumab plus chemotherapy (13.8 vs 11 months, *P* = 0.0046)
HELOISE	HER2-positive metastatic gastric cancer and GEJ cancer	1st	Global	3	Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg VS 10 mg/kg every 3 weeks) plus cisplatin (80 mg/m^2 on day 1) and capecitabine (800 mg/BIDdays 1-14)	No difference in median OS 12.5 vs 10.6 months (stratified HR, 1.24; 95% CI 0.86–1.78; *P* = 0.2401)
TyTAN	HER2 FISH-positive IHC 3+ advanced gastric cancer	2nd	Asia	3	Lapatinib plus weekly paclitaxel vs paclitaxel alone	No difference in median OS (11.0 vs 8.9 months, *P* = 0.1044) nor median PFS (5.4 vs 4.4 months)
LOGIC	HER2-positive advanced or metastatic esophageal, gastric or GEJ adenocarcinoma	1st	Asia	3	Lapatinib with capecitabine plus oxaliplatin vs capecitabine plus oxaliplatin	No difference in median OS (12.2 vs 10.5 months, HR, 0.91; 95% CI 0.73–1.12, *P* = 0.3492) and median PFS (6.0 vs 5.4 months, *P* = 0.0381).
JACOB	HER2-positive metastatic gastric cancer or GEJ cancer	1st	Global	3	Pertuzumab, trastuzumab, and chemotherapy vs trastuzumab and chemotherapy	No difference in median OS (17.5 vs 14.2 months, *P* = 0.057)
GATSBY	HER2-positive gastric cancer	2nd	Global	2/3	IV TD-M1(2.4 mg/kg weekly) vs taxane (docetaxel 75 mg/m^2 every 3 weeks or paclitaxel 80 mg/m^2 weekly)	No difference in median OS (7.9 vs 8.6 months, *P* = 0.86).
T-ACT	HER2-positive advanced gastric or GEJ adenocarcinoma	2nd	Japan	2	Paclitaxel 80 mg/m^2 on days 1, 8, and 15 every 4 weeks vs paclitaxel plus trastuzumab	No difference in median PFS (3.19 vs 3.68 months, *P* = 0.334) and median OS (9.95 vs 10.20 months, *P* = 0.199).
DESTINY	HER2-positive, advanced	2nd+	Global	2	Trastuzumab-Deruxtecan vs. physician's choice of chemotherapy	Improvement in OS 12.5 vs. 8.4 mos, P=0.0097 and PFS 5.6 vs. 3.5 mos

Zhao D, et al. *J Hemat Oncol*. 2019;12(1):50.

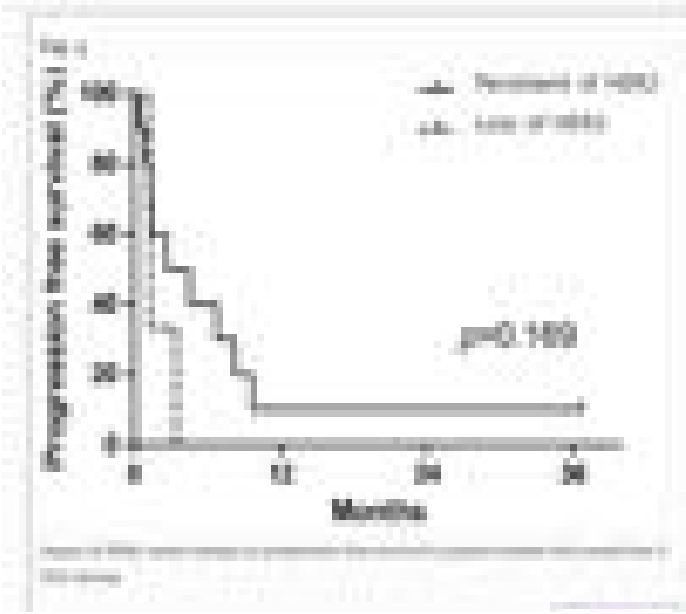
Changes in HER2 after Treatment



T-ACT second line exploratory analyses, HER2 positivity of tumor tissues was lost after first-line chemotherapy

Makiyama A, et al. *J Clin Oncol*.2018;36(15_suppl):4011.

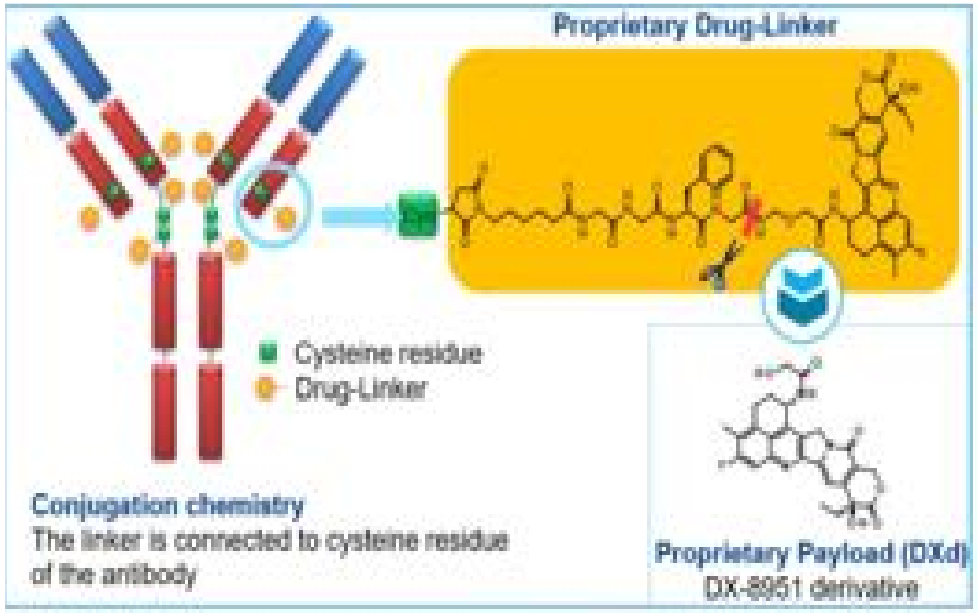
- Mechanism of resistance
- HER2-negative clones
- 15-70% of patients no longer expressing or amplified

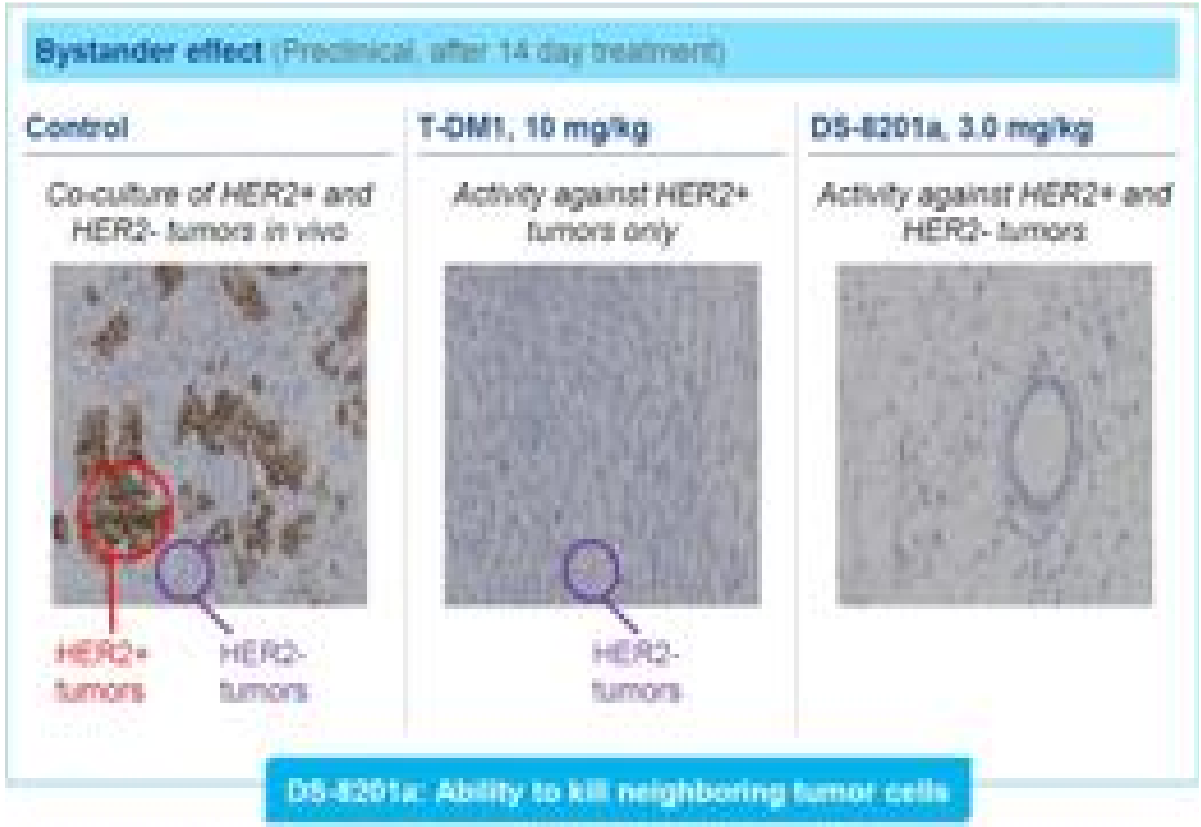


GASTHER3: 43 pts, 14 with loss of HER2 treatment TDM1

Seo et al., GASTHER3 Gastric Cancer, 2019

Trastuzumab Deruxtecan

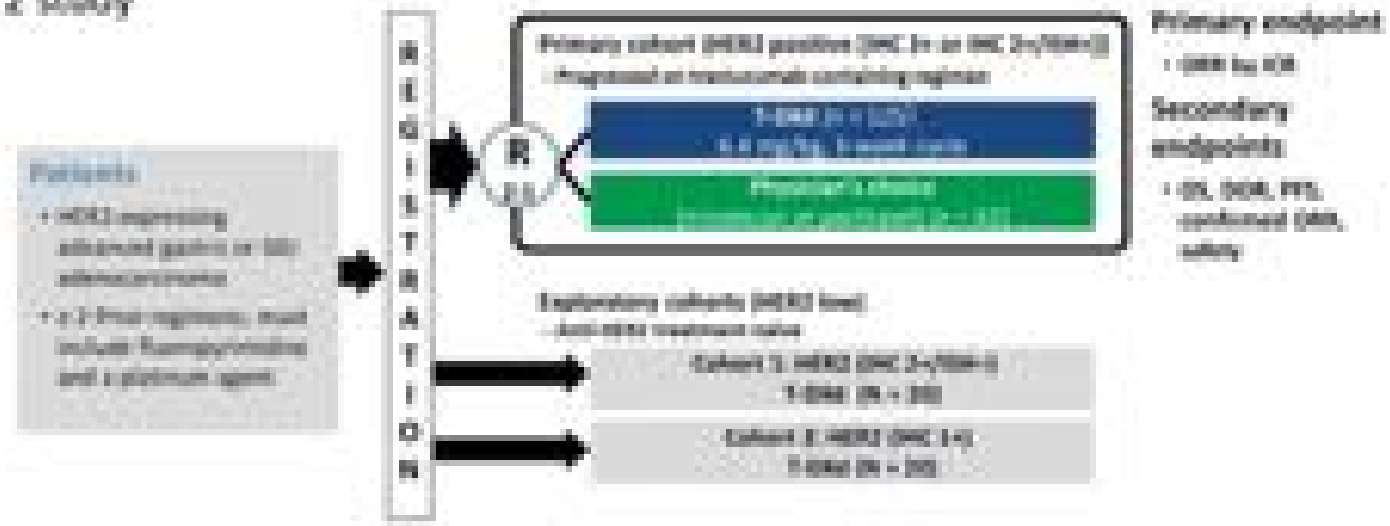




DESTINY-Gastric01

An open-label, multicenter, randomized phase 2 study

- T-DXd is an antibody-drug conjugate consisting of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and topoisomerase I inhibitor payload
- Previously, T-DXd 5.4 or 6.4 mg/kg in a phase 1 study demonstrated an ORR of 43.2% and median PFS of 5.6 months in 44 patients with HER2-positive gastric or GEJ cancer previously treated with trastuzumab (NCT02564900)[1]
- We present the results for the primary cohort of DESTINY-Gastric01 (NCT03329690)



- 187 patients were randomized (T-DXd, n = 125; PC, n = 62)
- 70% of patients had HER2 IHC 3+
- The median number of prior systemic therapies was 2 (range, 2-9)
- 86% previously received taxanes, 72% ramucirumab, and 33% anti-PD1/-PD-L1
- At data cut-off (November 8, 2019), 22.4% and 4.8% of patients in the T-DXd and PC arms remained on treatment

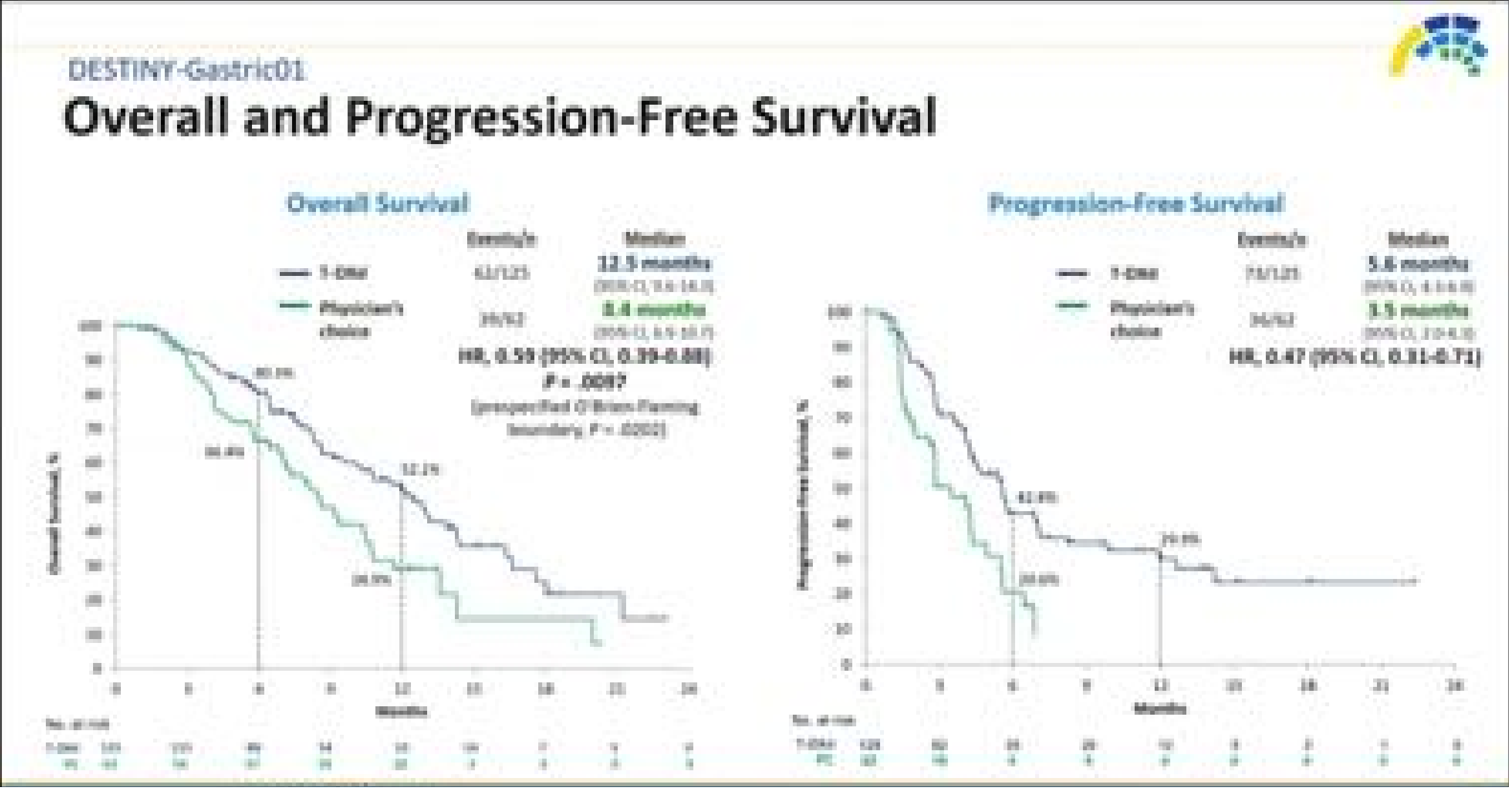
1. Shitara K, et al. *Lancet Oncol*. 2018;19:1437-48.

GEJ = gastroesophageal junction.

Shitara K, et al. *Lancet Oncol*. 2018;19:1437-48.

DESTINY-Gastric01

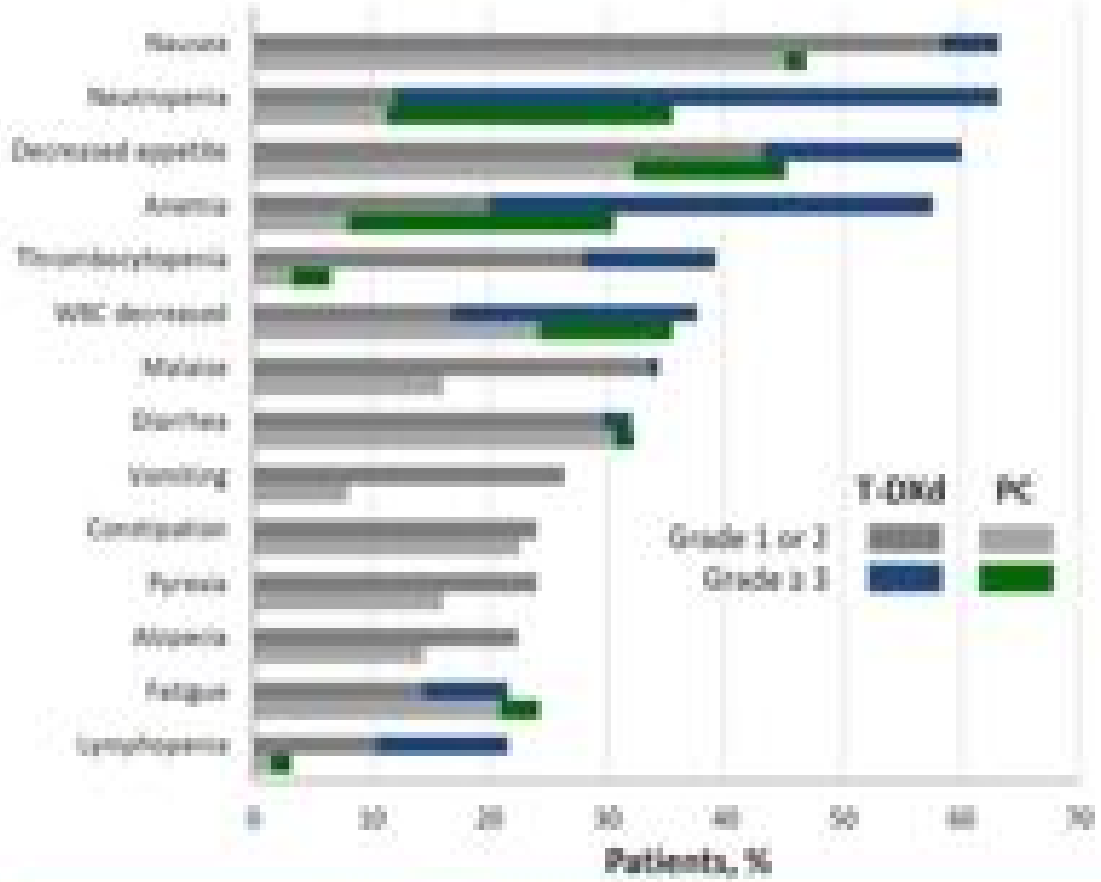
Overall and Progression-Free Survival



Shitara K, et al. *Lancet Oncol*. 2018;19:1437-48.

DESTINY-Gastric01

Safety Summary



TEAEs associated with:	T-DXd (n = 125)	PC (n = 62)
Drug discontinuation	15.2%	6.5%
Dose reduction	32.0%	33.9%
Dose interruption	62.4%	37.1%

- There was 1 drug-related death due to pneumonia with T-DXd and none with PC
- 12 patients (9.6%) had T-DXd-related ILD/pneumonitis as determined by an independent adjudication committee
  - Median time to first onset, 84.5 days (range, 36-638 days)
  - Most were grade 1 or 2 (grade 1, n=3; grade 2, n=6; grade 3, n=2; grade 4, n=1; no grade 5 events)

T-DXD = trastuzumab deruxtecan; TEAEs = treatment-emergent adverse events; PC = physician's choice.

Shitara K, et al. *Lancet Oncol*. 2018;19:1437-48.

DESTINY-Gastric01 Exploratory Cohorts

Primary Endpoint: ORR

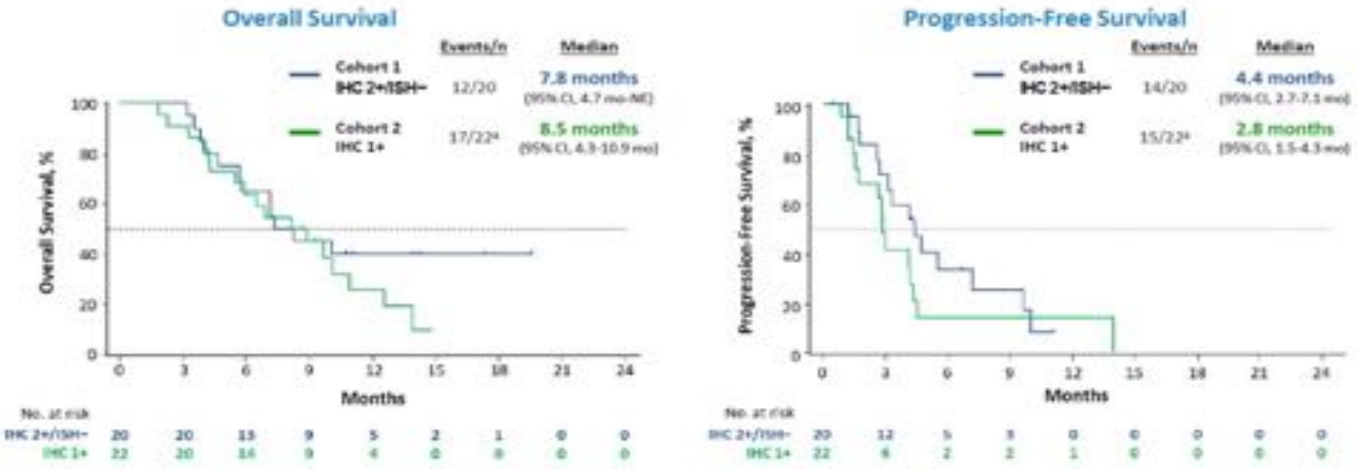
	Primary Cohort[1]		Exploratory Cohorts	
	T-DXd (n = 113)	PC Overall (n = 56)	Cohort 1 IHC 2+/ISH− (n = 19)	Cohort 2 IHC 3+ (n = 21)
ORR by ICR (CR + PR)	51.3% (n = 61) 95% CI, 41.9-60.5; *P* < .0001*	14.3% (n = 8) 95% CI, 6.4-26.2	36.8% (n = 7) 95% CI, 16.3%-61.6%	19.0% (n = 4) 95% CI, 5.4%-41.9%
Confirmed ORR by ICR (CR + PR)	42.9% (n = 51) 95% CI, 33.8-52.3	12.5% (n = 7) 95% CI, 5.2-24.1	26.3% (n = 5) 95% CI, 9.1%-51.2%	9.5% (n = 2) 95% CI, 1.2%-30.4%
CR	8.4% (n = 10)	0	0	0
PR	34.5% (n = 41)	12.5% (n = 7)	26.3% (n = 5)	9.5% (n = 2)
SD	42.9% (n = 51)	50.0% (n = 28)	63.2% (n = 12)	61.9% (n = 13)
PD	11.8% (n = 14)	30.4% (n = 17)	10.5% (n = 2)	28.6% (n = 6)
NE	2.5% (n = 3)	7.1% (n = 4)	0	0
Confirmed DCR (CR + PR + SD)	85.7% (n = 102) 95% CI, 78.1-91.5	62.5% (n = 35) 95% CI, 48.5-75.1	89.5% (n = 17) 95% CI, 66.9%-98.7%	71.4% (n = 15) 95% CI, 47.8%-88.7%
Median confirmed DOR	11.3 months 95% CI, 5.6 months-NE	3.9 months 95% CI, 3.0-4.9 months	7.6 months 95% CI, 4.1 months-NE	12.5 months 95% CI, NE-NE

Includes data for the response-evaluable set: all randomized (for primary cohort) patients who received ≥ 1 dose of study drug and had measurable tumors based on independent central review at baseline.
*Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region.

1. Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

DESTINY-Gastric01 Exploratory Cohorts

Overall and Progression-Free Survival

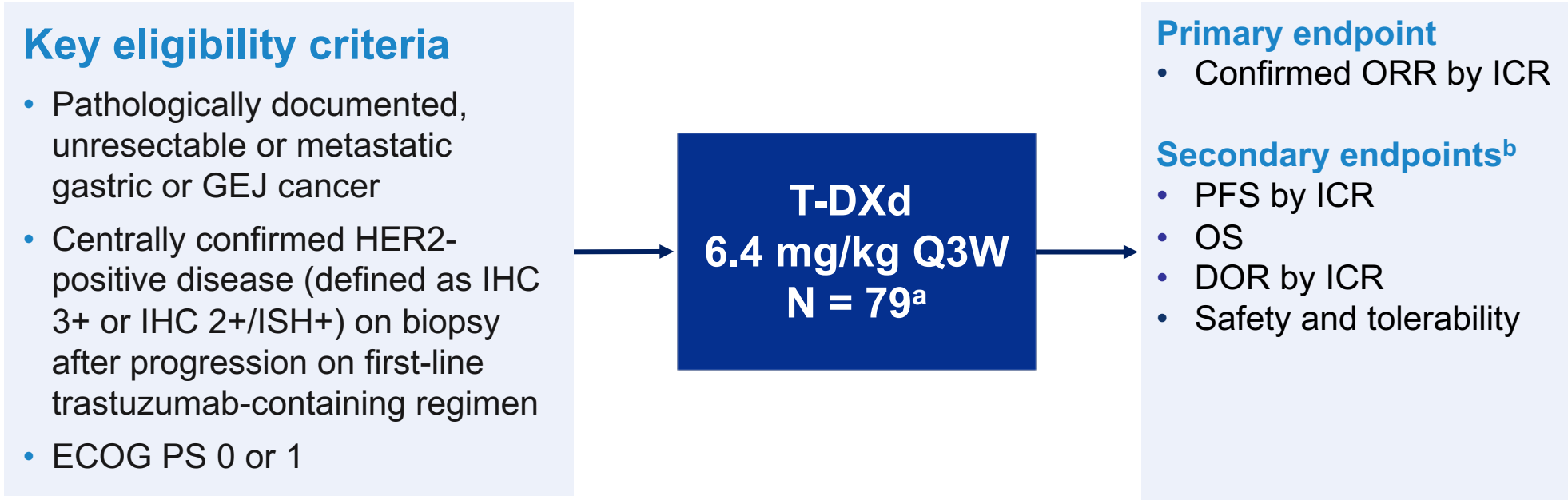


*Two patients were excluded from analysis due to a missing HER2 status by central laboratory.

Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.
al. *Ann Oncol*. 2020;31(suppl_4):S841-S873.

DESTINY-Gastric02 Study Design

- An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer (NCT04014075)



- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

[a]Enrollment of 80 patients was planned; actual enrollment was 79 patients.
[b]Other secondary endpoints were ORR, PFS, and DOR by investigator assessment, pharmacokinetics, anti-drug antibodies, and patient-reported outcomes.
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; Q3W, every 3 weeks
Shitara K, et al. *N Engl J Med*. 2020;382:2419-30. Van Cutsem E, et al. ***Ann Oncol*. 2021;32(suppl_5):S1283-S1346.**

Efficacy Endpoints

	Patients (N = 79)
Confirmed ORR[a], n (%)	**30 (38)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%)	
CR	**3 (3.8)**
PR	**27 (34.2)**
SD	**34 (43.0)**
PD	**13 (16.5)**
Not evaluable	**2 (2.5)**
Median DOR,[b] months	8.1 (95% CI, 4.1-NE)
Confirmed DCR[c], n (%)	64 (81.0) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.6)
Median PFS,[d] months	5.5 (95% CI, 4.2-7.3)
Median follow up, months	5.7 (range, 0.7-15.2)

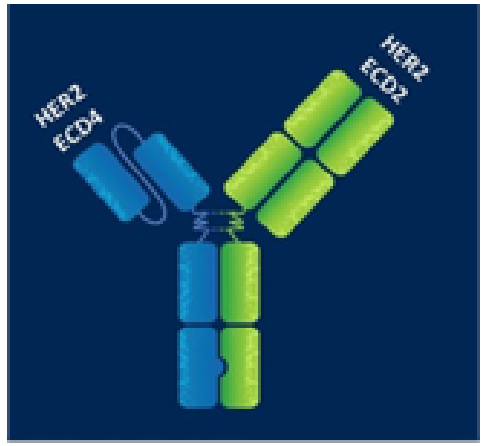
Cutoff date: April 9, 2021.

[a]Primary endpoint. [b]Secondary endpoint analysis based on responders (n=30); 21 patients were censored (reasons: initiating new anticancer therapy, adequate tumor assessment no longer available, and ongoing without occurrence of progressive disease or death). [c]Exploratory endpoint. [d]Secondary endpoint analysis in the full analysis set based on 42 events (36 PD, 6 deaths).

BOR, best overall response; CR, complete response; DCR, disease control rate; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

Van Cutsem E, et al. *Ann Oncol*. 2021;32(suppl_5):S1283-S1346.

Phase II Study of Zanidatamab + Chemotherapy in First-line HER2 Expressing Gastroesophageal Adenocarcinoma



Simultaneously binds two HER2 epitopes:

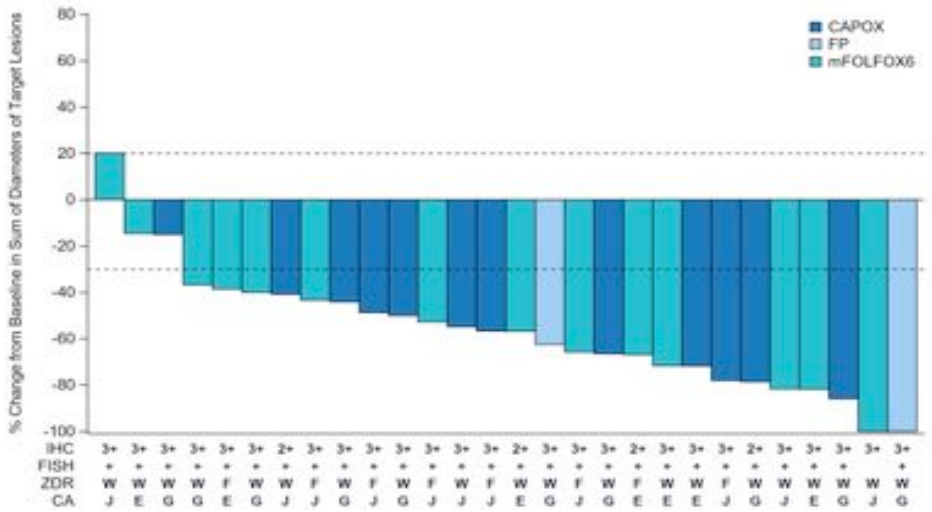
- ECD4 - trastuzumab binding domain
- ECD2 - pertuzumab binding domain

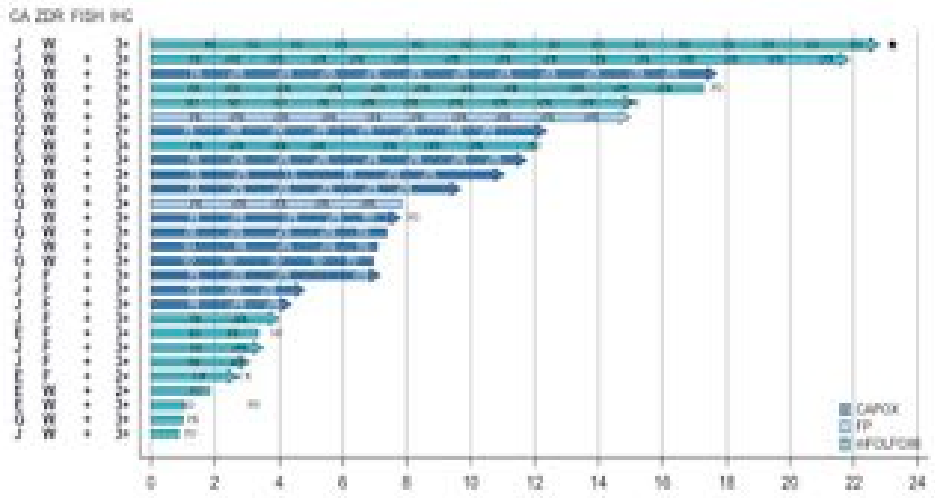
Multiple mechanisms of action:

- improved binding, clustering and receptor internalization
- Inhibition of ligand-depending and independent proliferation
- Potent activation of antibody dependent cellular cytotoxicity

Ku G, et al. Presented at: ESMO; September 16-21, 2021; Virtual. Abstract 1380P.

Phase II Study of Zanidatamab + Chemotherapy in First-line HEr2 Expressing Gastroesophageal Adenocarcinoma





Toxicity: Diarrhea

Ku G, et al. Presented at: ESMO;

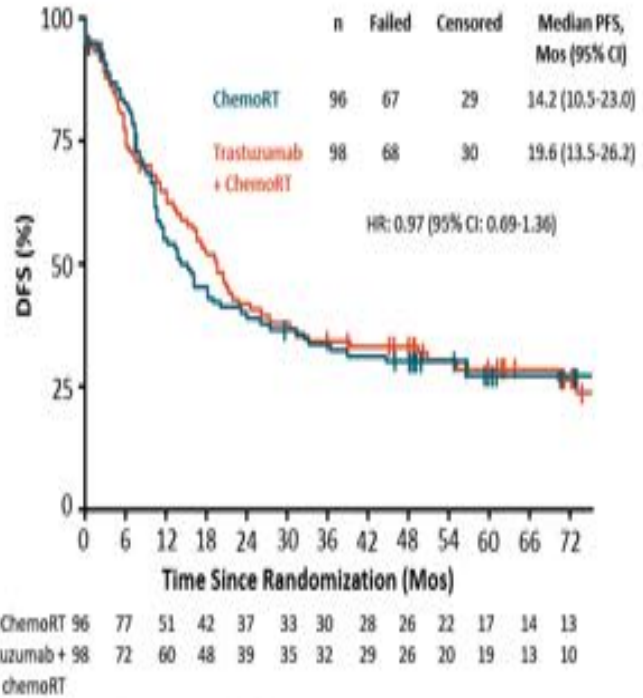
September 16-21, 2021; Virtual. Abstract 1380P.

Selected Ongoing Phase III Trials for Advanced Gastroesophageal Cancer

Trial	Regimen	Population	Phase
MOUNTAINEER-02 (NCT04499924)	Tucatinib + trastuzumab vs placebo (both with ramucirumab + paclitaxel)	2L+, GC/GEJC, HER2+	II/III
MAHOGANY (NCT04082364)	Margetuximab + PD-1 inhibitor ± CT or margetuximab + CT ± dual checkpoint inhibitor or trastuzumab + CT	1L, GC/GEJC, HER2+	II/III
DESTINY-Gastric04 (NCT04704934)	Trastuzumab deruxtecan vs ramucirumab + paclitaxel	2L+, GC/GEJC, HER2+	III

Perioperative HER2 inhibition

RTOG 1010: DFS (Primary Endpoint) and OS



Safran. ASCO 2020. Abstr 4500. Reproduced with permission.

- Median OS, trastuzumab + chemoRT vs chemoRT: 38.5 vs 38.9 mos; HR 1.01 (95% CI: 0.69-1.47)

Slide credit: clinicaloptions.com

Treatment of Resectable HER2-positive GC

PETRARCA Trial – randomized Phase II

ypT-stage	FLOT N = 41	FLOT + Tras / Per N = 40	P-value
≤T1	11 (27%)	17 (43%)	
T2	9 (22%)	8 (20%)	
T3	17 (41%)	14 (29%)	
T4	3 (7%)	0 (0%)	
N0	16 (39%)	27 (68%)	
Margin-free (R0)-resection (ITT)	37 (90%)	37 (93%)	
pCR	5 (12%)	14 (35%)	P = 0.02

Al-Batran SE, et al. ESMO 2020; #1421

HER2 + EGC Summary

- Beyond immunotherapy, new agents in HER+

- Evaluation of HER2
  - Hitting the target, heterogeneity

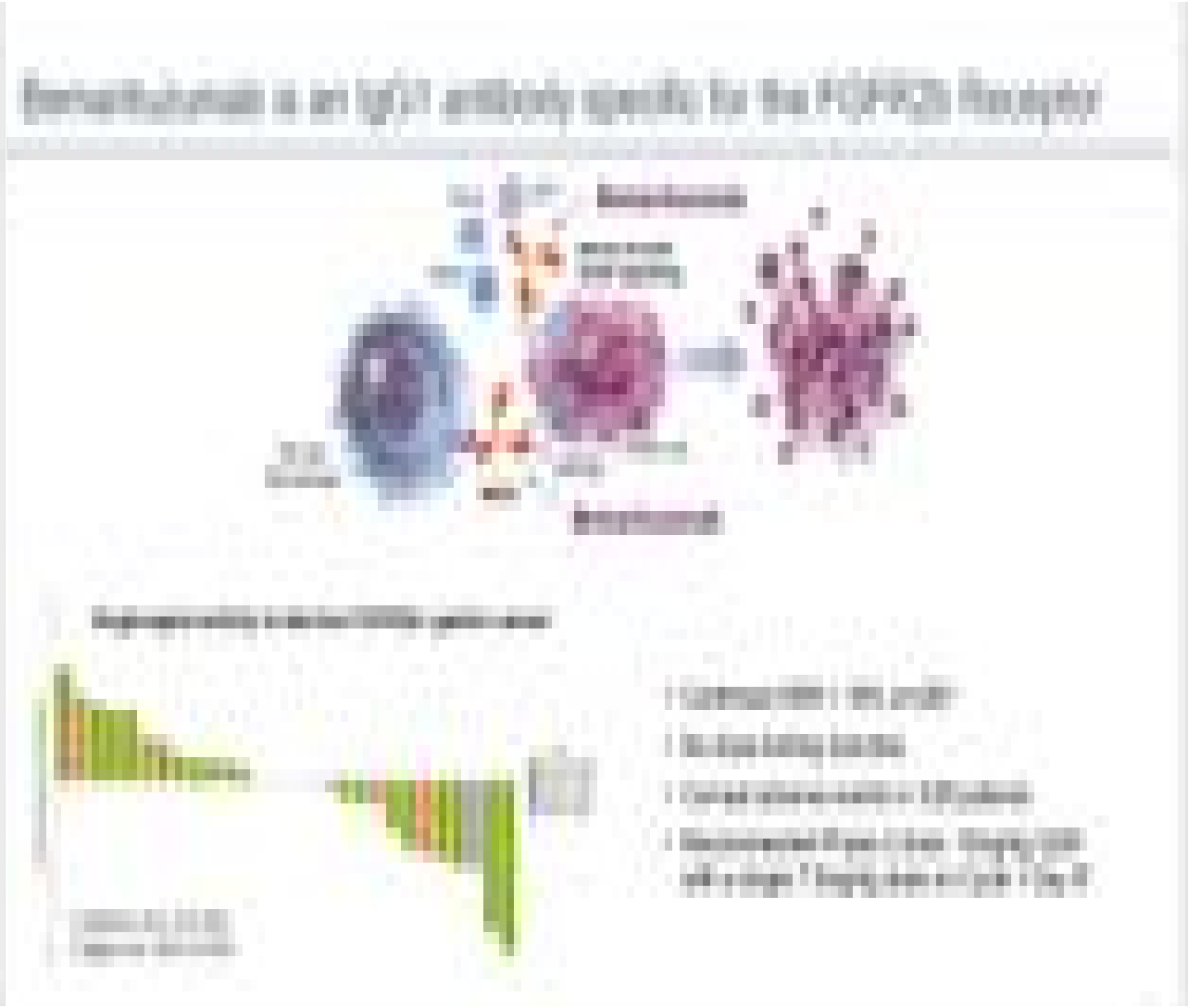
- Trastuzumab deruxtecan demonstrates second-line activity in advanced/metastatic HER2+ EGC (and beyond)
  - FDA approval
  - Ongoing studies

- HER2 positive – multiple agents with promising activity after several failed trials
  - zanidatimab, margetuximab, tucatinib

- Perioperative studies negative thus far

Other Novel Targets

Fibroblast Growth Factor Receptor



Wainberg, GI ASCO 2021

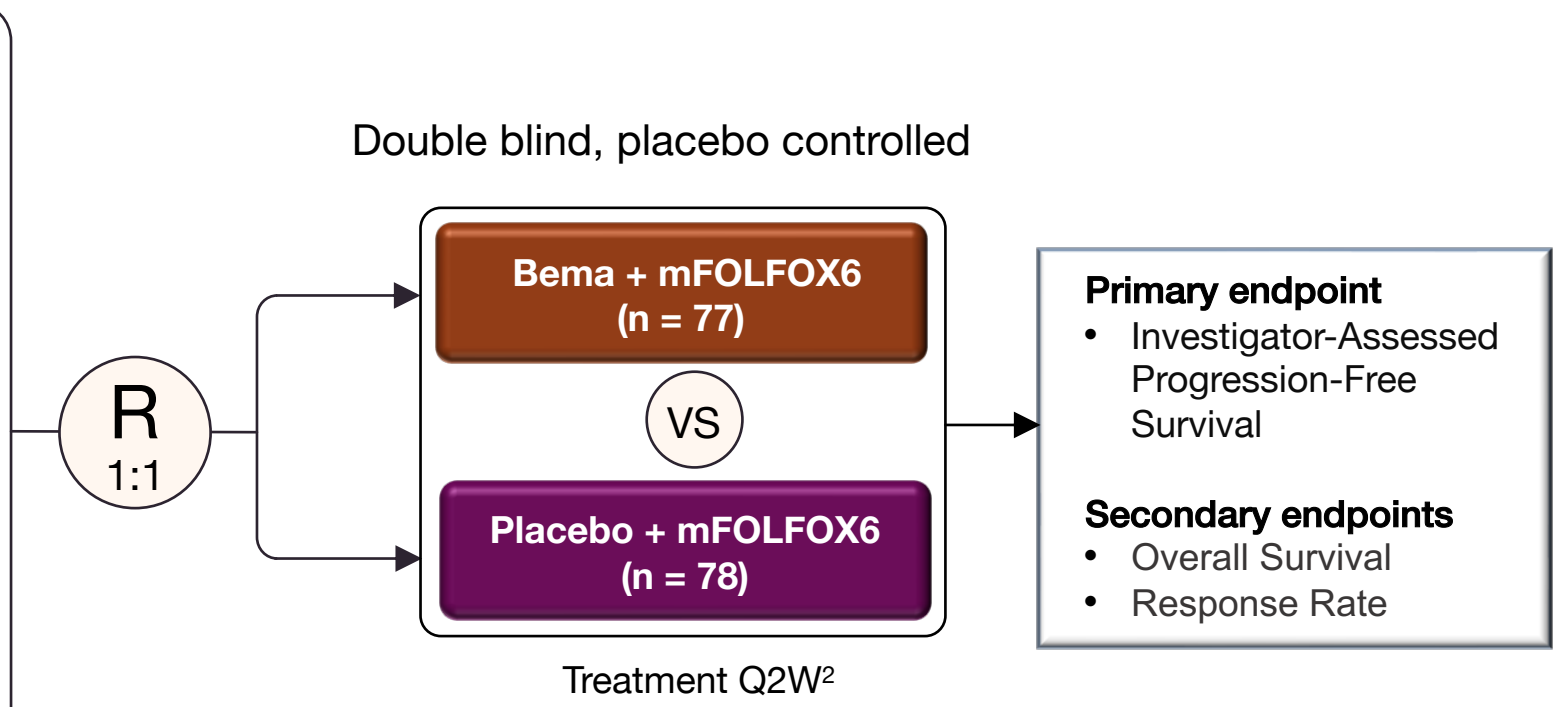
FIGHT Trial Design

Key Eligibility Criteria

- No prior therapy for unresectable locally advanced or metastatic gastric/GEJ adenocarcinoma
- RECIST v1.1 evaluable disease
- FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by ctDNA[1]
- ECOG 0/1
- HER2 not positive
- May receive 1 dose of mFOLFOX6

Stratification Factors

- Geographic region
- Single dose of mFOLFOX6 during screening
- Prior adjuvant or neo-adjuvant chemotherapy



Statistical Plan

Trial initially designed as registrational Phase 3 (n=548) with 2-sided α 0.05
Amended after enrolling n = 155 to a proof-of-concept Phase 2 with pre-specified statistical assumptions of:

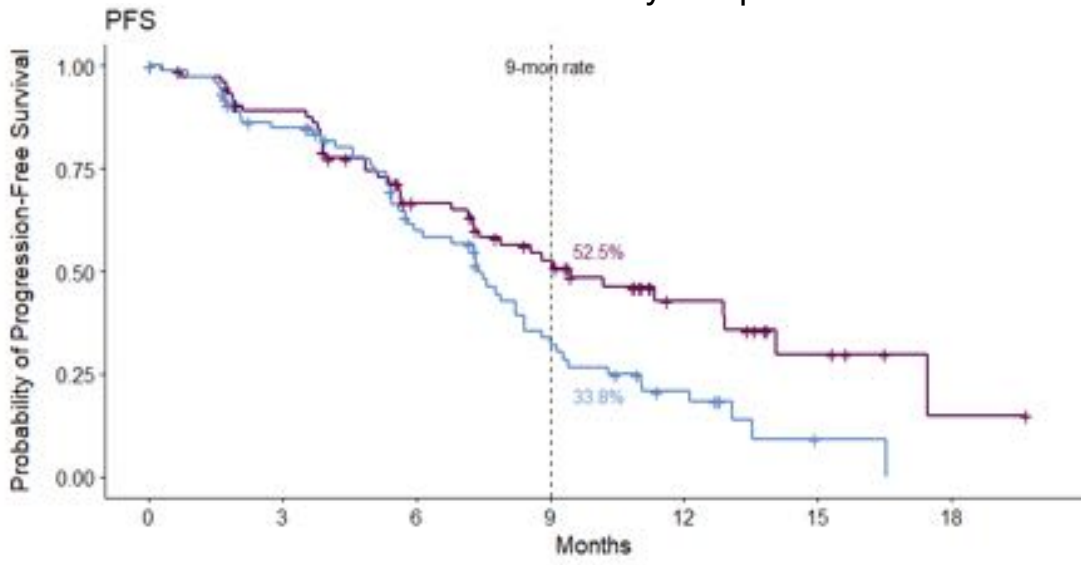
- Hierarchical sequential testing: PFS, then OS/ORR
- ≥84 events to demonstrate benefit at a HR≤0.76 for PFS at 2-sided α of 0.2

1 Central testing: Immunohistochemical stain (Ventana): cut-off any 2+/3+; circulating tumor DNA (PGDx): cut-off 1.5X
2 15mg/kg Q2W with a single 7.5mg/kg dose on Cycle 1 Day 8[2]

Wainberg, GI ASCO 2021

Progression-Free Survival and Overall Survival: Intent to Treat

PFS Primary Endpoint

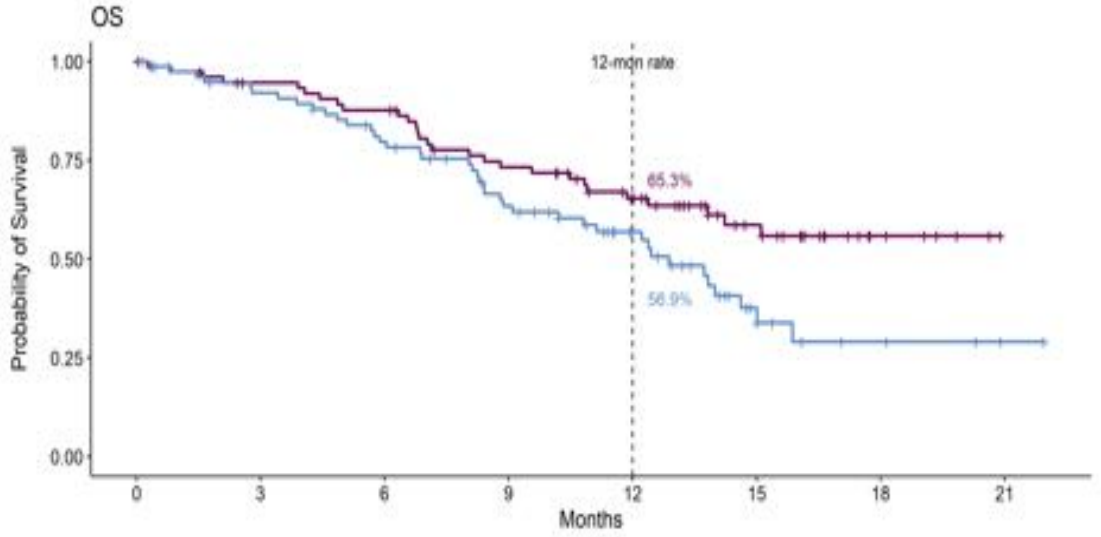


Number at risk

BEMA + mFOLFOX6	77	62	40	28	12	5	1
PLACEBO + mFOLFOX6	78	59	37	19	9	1	0

	Bema N = 77	Placebo N = 78
Median PFS, mo (95% CI)	9.5 (7.3, 12.9)	7.4 (5.8, 8.4)
	P=0.0727	
HR (95% CI)	0.68 (0.44, 1.04)	

OS Key Secondary Endpoint



Number at risk

BEMA + mFOLFOX6	77	68	63	50	38	21	6	0
PLACEBO + mFOLFOX6	78	68	57	42	27	10	4	1

	Bema N = 77	Placebo N = 78
Median OS, mo (95% CI)	NR (13.8, NR)	12.9 (9.1, 15.0)
	P=0.0268	
HR (95% CI)	0.58 (0.35, 0.95)	

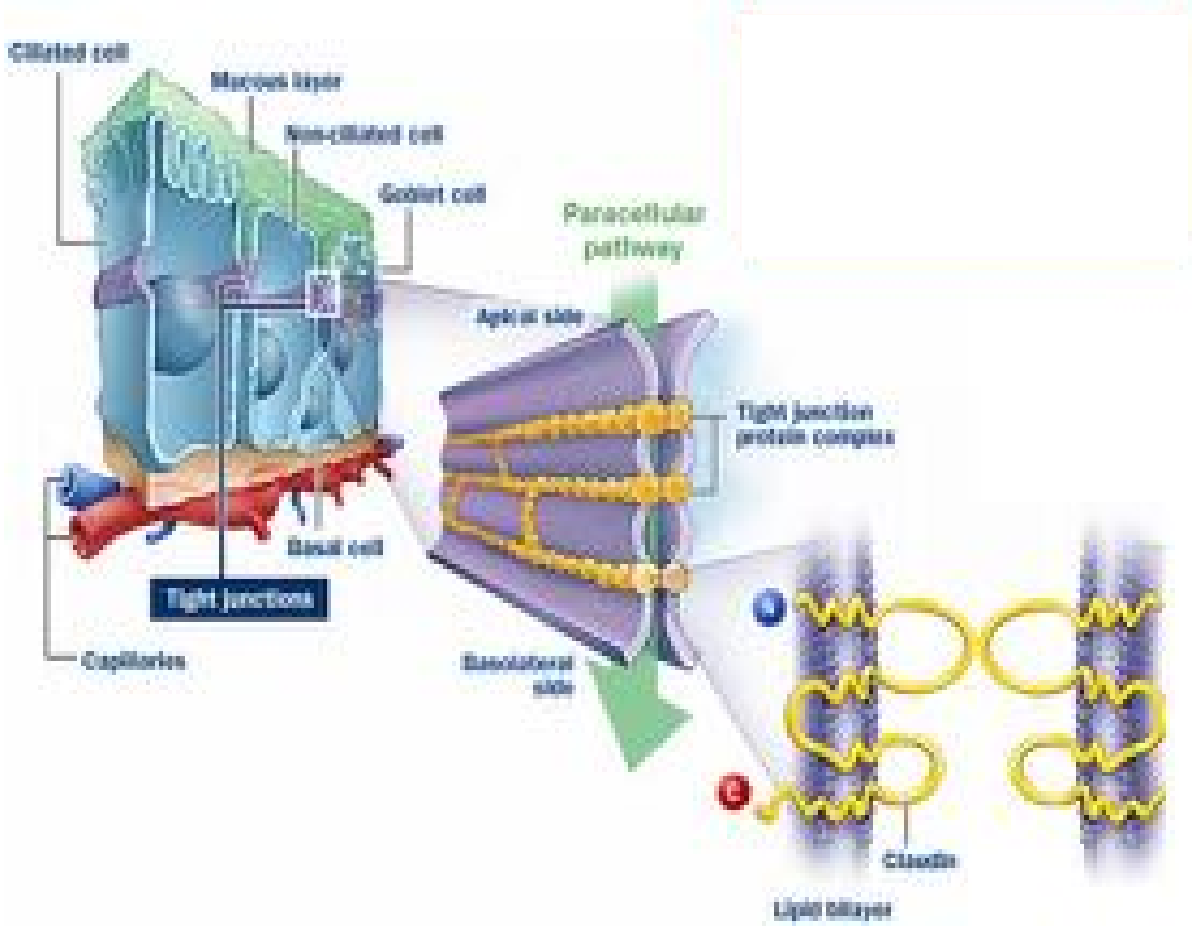
Wainberg, GI ASCO 2021

Summary of Selected Treatment-Emergent Adverse Events

Selected Adverse Events	Any Grade		Grade ≥ 3	
	Bema (N = 76)	Placebo (N = 77)	Bema (N = 76)	Placebo (N = 77)
Preferred Term	76 (100.0%)	76 (98.7%)	63 (82.9%)	57 (74.0%)
Nausea	36 (47.4%)	41 (53.2%)	0	3 (3.9%)
Vomiting	22 (28.9%)	24 (31.2%)	2 (2.6%)	2 (2.6%)
Diarrhoea	31 (40.8%)	24 (31.2%)	2 (2.6%)	1 (1.3%)
Stomatitis	24 (31.6%)	10 (13.0%)	7 (9.2%)	1 (1.3%)
Peripheral sensory neuropathy	15 (19.7%)	15 (19.5%)	4 (5.3%)	3 (3.9%)
Neutrophil count decreased	31 (40.8%)	33 (42.9%)	23 (30.3%)	27 (35.1%)
Platelet count decreased	14 (18.4%)	21 (27.3%)	1 (1.3%)	0
Aspartate aminotransferase increased	23 (30.3%)	15 (19.5%)	4 (5.3%)	2 (2.6%)
Alanine aminotransferase increased	22 (28.9%)	11 (14.3%)	2 (2.6%)	1 (1.3%)
Dry eye	20 (26.3%)	5 (6.5%)	2 (2.6%)	0

Wainberg, GI ASCO 2021

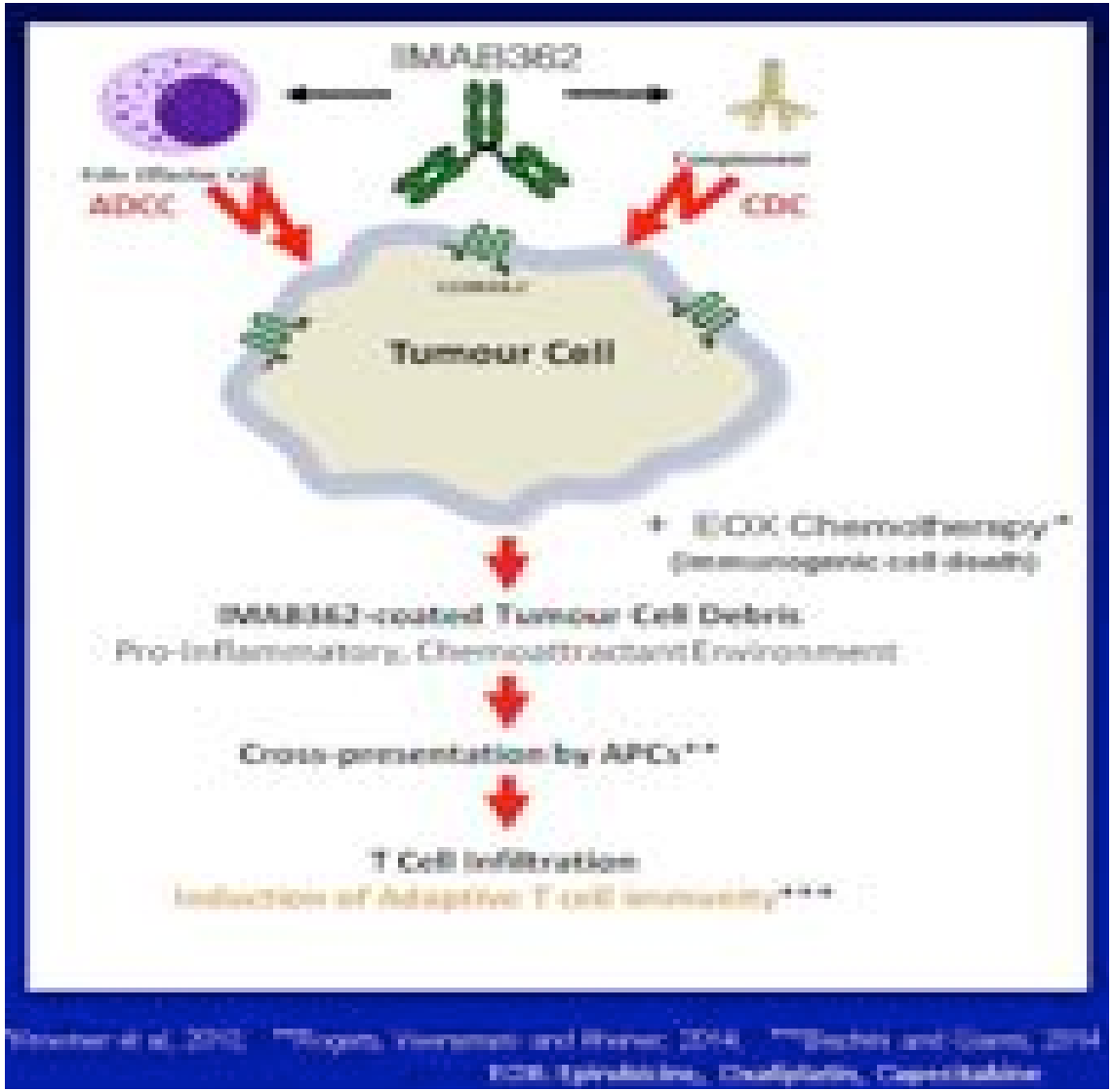
The Target: Claudin 18.2



- Member of the claudin (CLDN) family
- Major structural component of tight junctions
  - Seals intercellular space in epithelial sheets
- Broadly expressed in various cancer types
  - ~70-90% biliary duct, pancreatic, gastric, and mucinous ovarian cancer
  - ~10% ovarian cancer and NSCLC
- Not expressed in any healthy tissues, except for stomach mucosa, with limited accessibility to the antibody

Al-Batran SE, et al. ASCO 2016 (LBA4001)

IMAB362 Antibody - Zolbetuximab



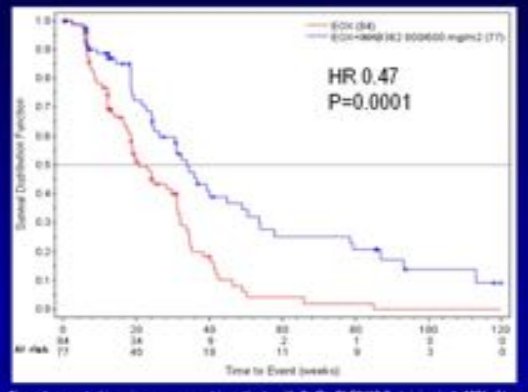
- Chimeric IgG1 backbone antibody
- Highly specific for CLDN18.2
- Modes of Action
  - ADCC – Antibody dependent cellular cytotoxicity
  - CDC -- Complement dependent cytotoxicity
  - In combination with chemotherapy
    - Enhances T-cell infiltration
    - Induces pro-inflammatory cytokines

Al-Batran SE, et al. ASCO 2016 (LBA4001)

FAST Results

Progression-free Survival (primary endpoint)

Progression-free survival*



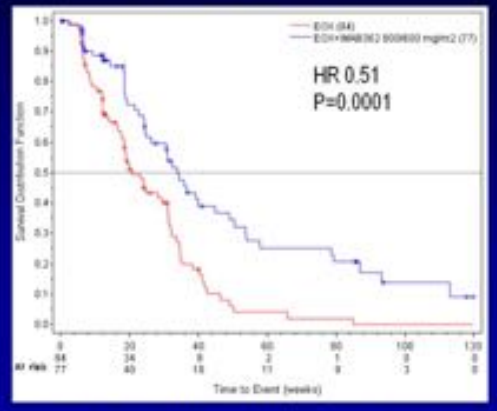
Patient disposition	Arm 1 EOX (N=84)	Arm 2 EOX + IMAB362 (N=77)
Patients with event N (%)	66 (78.6)	45 (58.4)
PFS [median (95% CI), months]	4.8 (4.1; 7.2)	7.9 (5.7; 10.4)
Hazard ratio (95% CI)		0.47 (0.31, 0.70)
p-value (1-sided, stratified Cox model)		0.0001

*based on central imaging assessment in patients with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells (Total population) Updated data!

Al-Batran SE, et al. ASCO 2016 (LBA4001)

Overall Survival

Overall Survival*



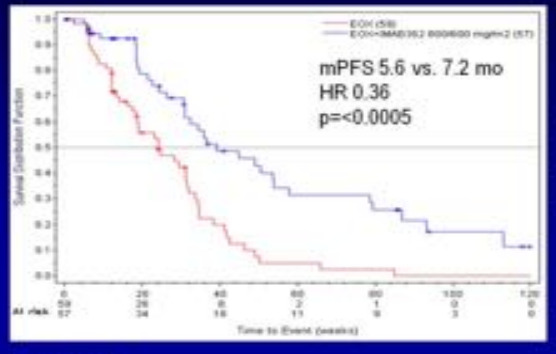
Patient disposition	Arm 1 EOX (N=84)	Arm 2 EOX + IMAB362 (N=77)
Patients with event N (%)	75 (89.3)	53 (68.8)
OS [median (95% CI), months]	8.4 (7.0; 10.3)	13.2 (9.7; 18.9)
Hazard ratio (95% CI)		0.51 (0.36; 0.73)
P-Value		0.0001

*in patients with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells (Total population); Updated data!

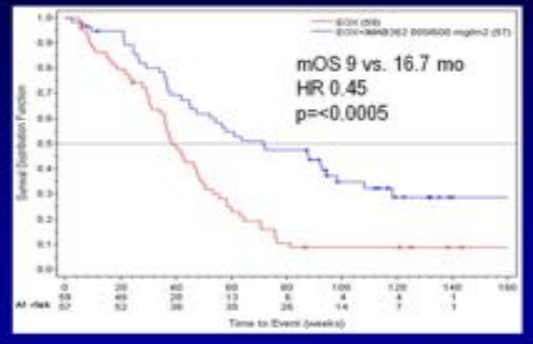
Al-Batran SE, et al. ASCO 2016 (LBA4001)

PFS and OS in patients with 2+/3+ CLDN18.2 staining in ≥ 70% of tumor cells (high expressors)

Progression-free survival



Overall Survival



Updated data!

Al-Batran SE, et al. ASCO 2016 (LBA4001)

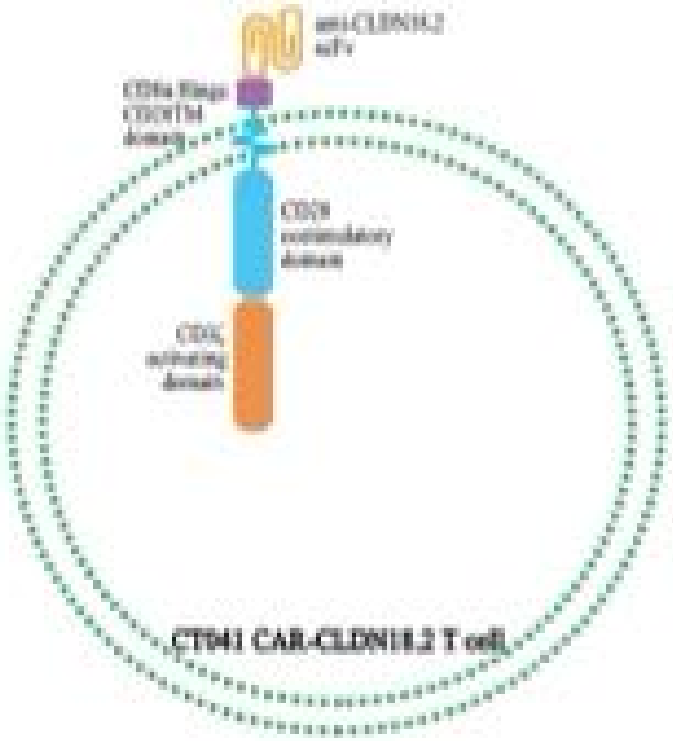
- Toxicities - Nausea/vomiting, neutropenia and anemia
- The addition of zolbetuximab to EOX increased PFS and OS vs EOX alone

- Awaiting GLOW and SPOTLIGHT

Al Batran et al., JCO. 2016

Background

- **Claudin18.2 (CLDN18.2)** has emerged as a promising therapeutic target in gastric/gastroesophageal junction (G/GEJ) cancers.
- **CT041** (CLDN18.2-redirected CAR T-cell therapy) showed promising anti-tumor activity in preclinical studies.
- Results of a phase I study demonstrated that CT041 was well tolerated and had encouraging efficacy in patients with previously treated, CLDN18.2-positive advanced G/GEJ adenocarcinoma.



nature medicine
ARTICLES

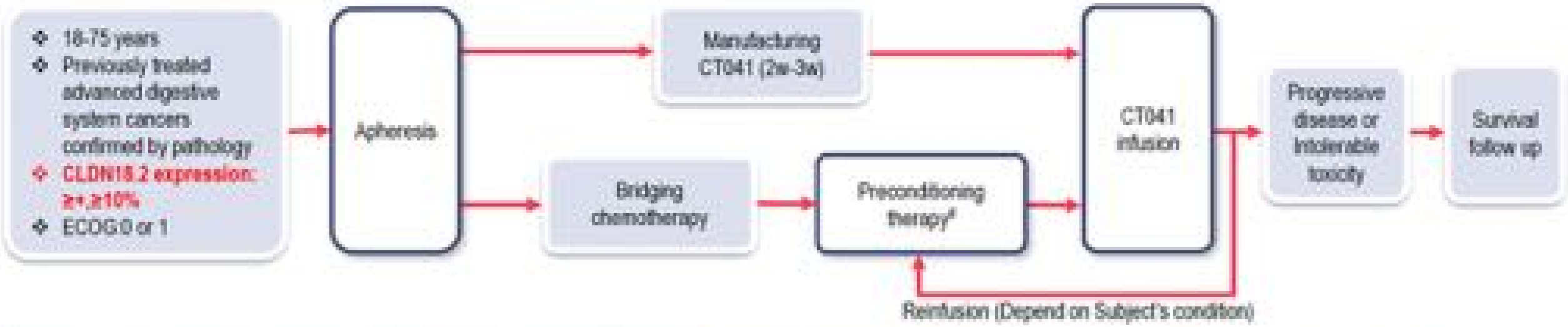
OPEN

Claudin18.2-specific CAR T cells in gastrointestinal cancers: phase 1 trial interim results

Changsong Qi[1], Jifang Gong[1], Jian Li[1], Dan Liu[2], Yanru Qin[2], Sai Ge[2], Miao Zhang[2], Zhi Peng[2], Jun Zhou[2], Yanshuo Cao[2], Xiaotian Zhang[2], Zhihao Lu[2], Ming Li[2], Jiajia Yuan[2], Zhenghang Wang[3], Yakun Wang[3], Xiaohui Peng[4], Huiping Gao[4], Zhen Liu[4], Huamao Wang[4], Daqing Yuan[4], Jun Xiao[4], Hong Ma[4], Wei Wang[4], Zonghai Li[4] and Lin Shen[1]✉

Study Design

A multicenter, open-label, phase I ongoing study.



Primary Objectives: Safety and tolerability

Secondary Objectives : Efficacy, Pharmacokinetics

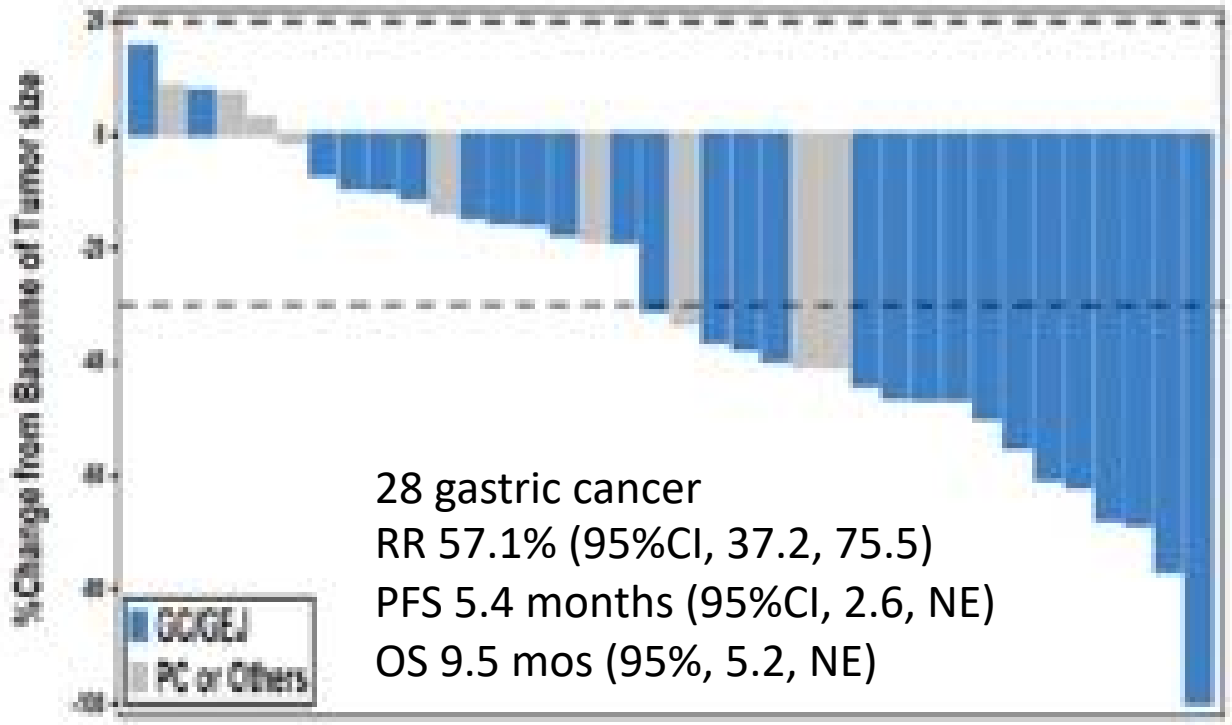
Explorative Objectives : Influence factor of Efficacy, Distribution of CT041

#Fludarabine 25 mg/m²/day(D-4~D-3)+Cyclophosphamide 250 mg/m²/day (D-4~D-3)+Nab-paclitaxel 100mg or gemcitabine 1000mg (D-3)

*One patient suffered gastrointestinal hemorrhage in D51 after reinfusion, which was considered to be caused by obvious tumor regression. After discussion among the investigators, DMC and partners, it was decided to lower the dose to 2.5× 10⁸ cells.

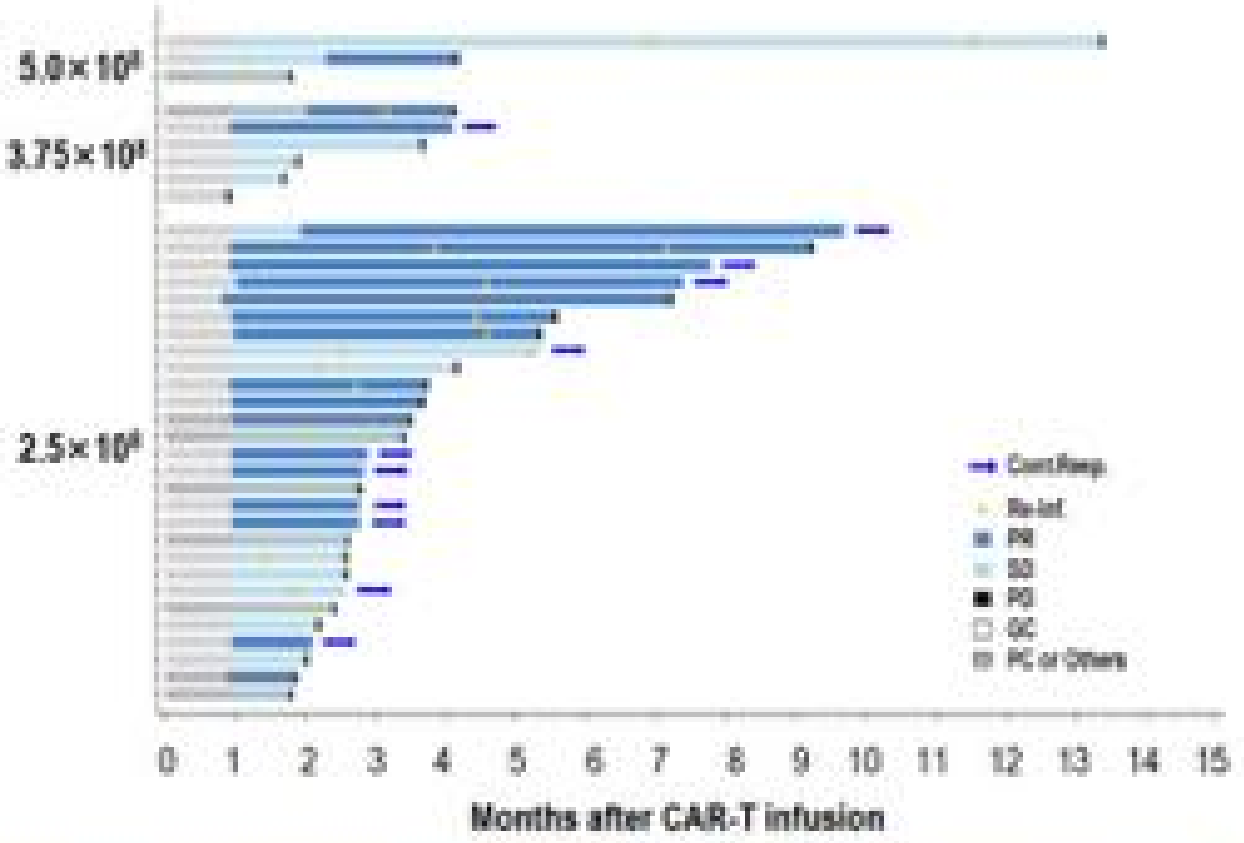
Efficacy : All patients

Thirty-six of the 37 subjects had target lesions. 31 subjects had different degrees of shrinkage of target lesions. According to RECIST 1.1, ORR and DCR reached **48.6%** (18/37) and **73.0%** (27/37) respectively.



28 gastric cancer
RR 57.1% (95%CI, 37.2, 75.5)
PFS 5.4 months (95%CI, 2.6, NE)
OS 9.5 mos (95%, 5.2, NE)

GC/GEJ : gastric carcinoma / gastroesophageal junction
PC : pancreatic adenocarcinoma



Summary

- Biomarker evaluation
  - MSI, PD-L1, HER2
  - Tumor agnostic – NTRK, TMB, MSI
  - Next-generation sequencing

- Incorporation of immunotherapy in EGC in metastatic in HER2+/- patients
  - Benefit for PD-L1 positive patients in HER2 –
  - Benefit for HER2 + patients

- Immunotherapy in adjuvant esophageal cancer, adeno and SCC with residual disease
  - Regardless of PD-L1 status

- Beyond trastuzumab, trastuzumab deruxtecan demonstrates activity in the second line

- Other Targets – FGFR2, Cldn 18.2, PARP inhibition, combination IO (PD1, LAG-3, TIGIT)

EGC = esophagogastric cancers.