Updates in the Treatment of Esophagogastric Cancer

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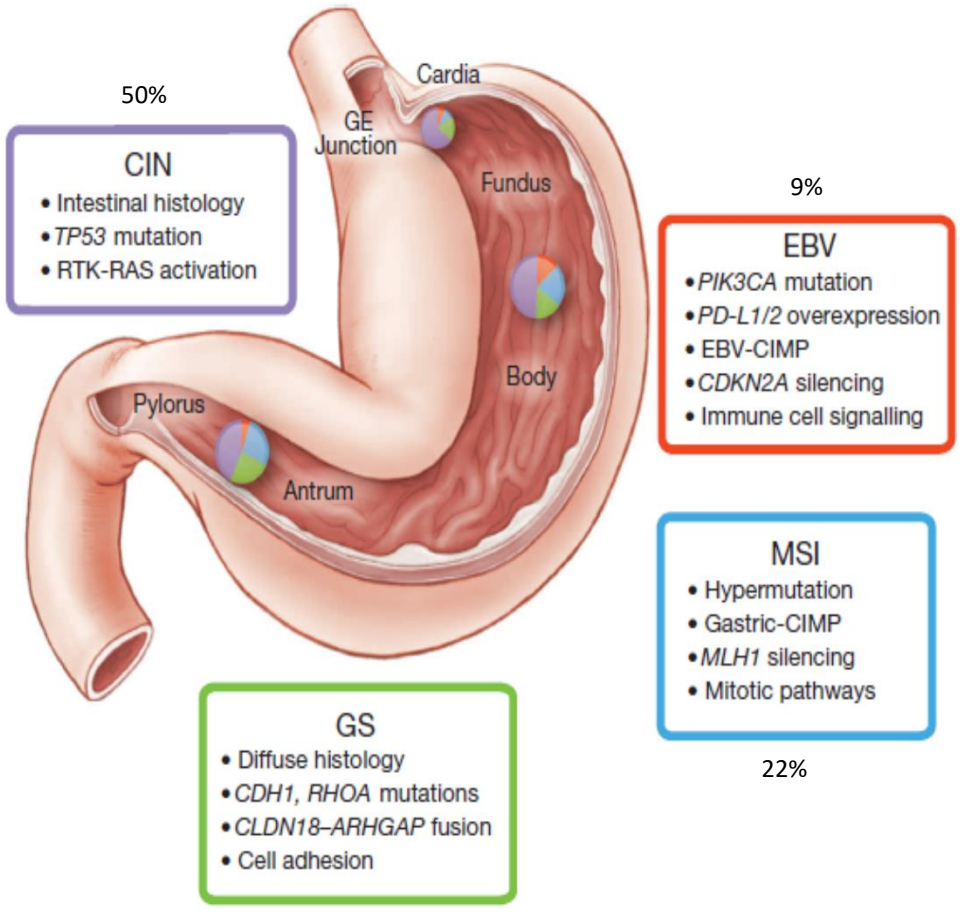
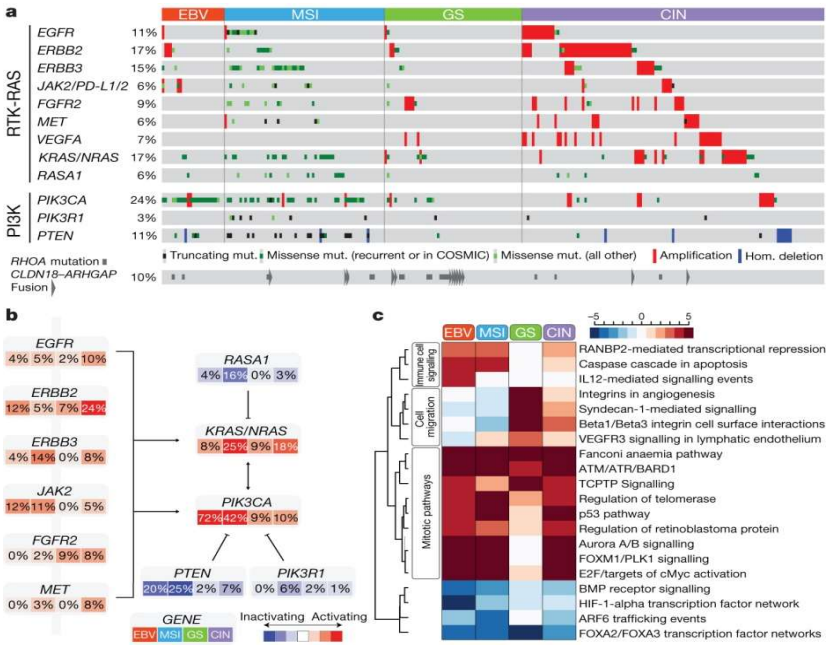
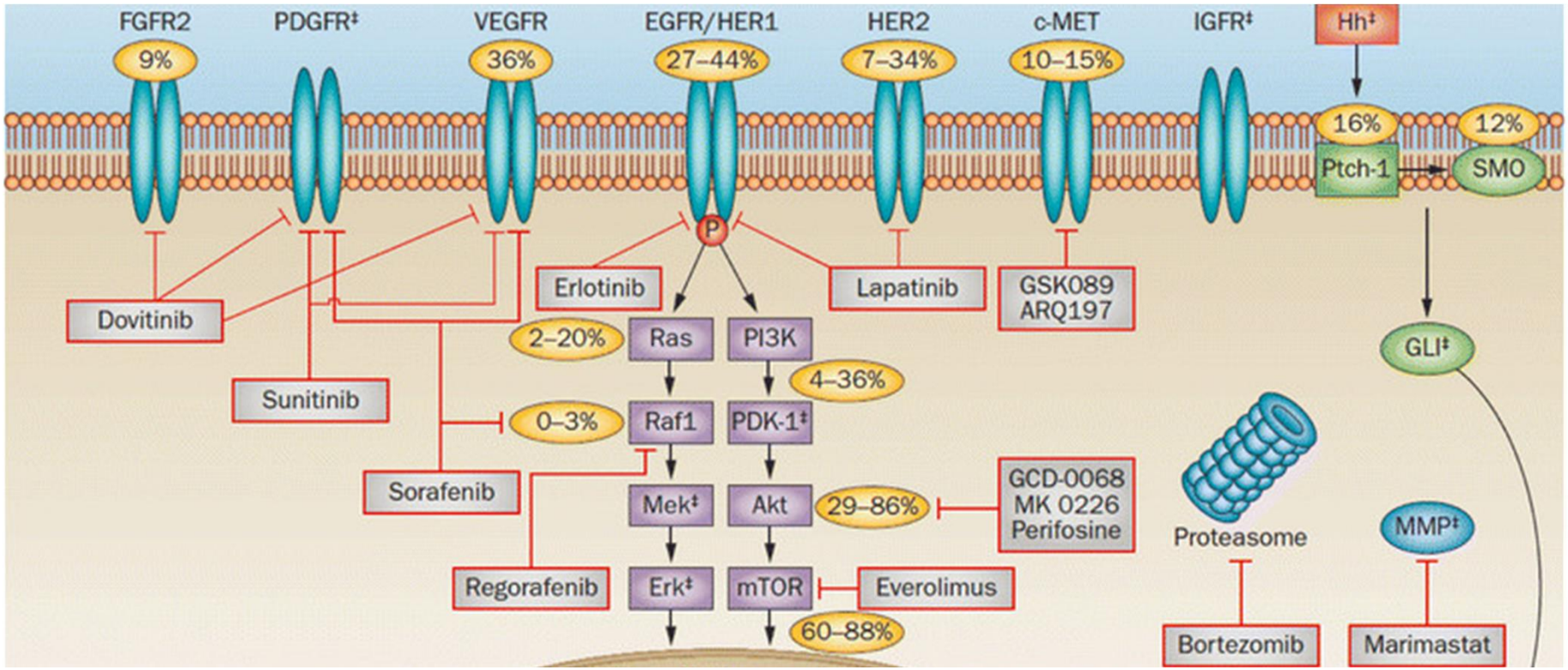
TCGA





Bass AJ, et al The Cancer Genome Atlas Research Network. Nature. 2014, 513: 202-207.

Signaling Pathways and Targeted therapy in Gastric Cancer



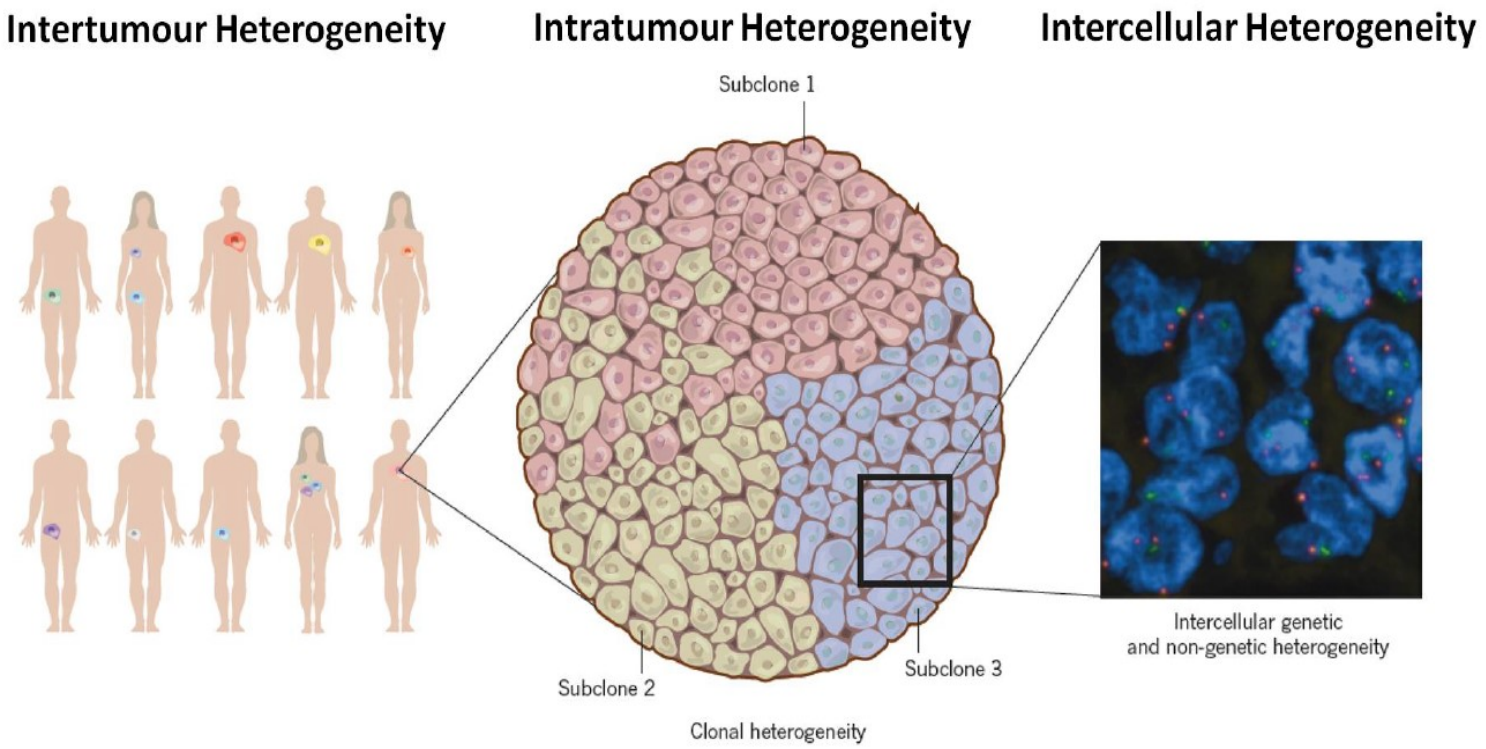
Wadhwa, R. et al. Nat. Rev. Clin. Oncol. 10, 643–655 (2013) [181])

Randomized phase III trials of HER2 negative targeted therapies in metastatic gastric cancer

Target	Drug	Trial	Line of therapy	Treatment groups	OS benefit	Reference
Angiogenesis	Apatinib	HENGRUI 20101208	Third or more	Apatinib versus placebo	Yes	Li and colleagues
	Bevacizumab	AVAGAST	First	Bevacizumab versus placebo, in combination with chemotherapy (cisplatin and fluoropyrimidine)	No	Ohtsu and colleagues[1]
		AVATAR	First	Bevacizumab versus placebo, in combination with chemotherapy (cisplatin and capecitabine)	No	Shen and colleagues
	Ramucirumab	RAINBOW	Second	Ramucirumab versus placebo, in combination with chemotherapy (paclitaxel)	Yes	Wilke and colleagues
		REGARD	Second	Ramucirumab versus placebo	Yes	Fuchs and colleagues
		RAINFALL	First	Ramucirumab, in combination with cisplatin and fluropyrimidine vs. placebo	No	Fuchs and colleagues
EGFR	Cetuximab	EXPAND	First	Chemotherapy (cisplatin and capecitabine) with or without cetuximab	No	Lordick and colleagues
	Gefitinib	COG	Second	Gefitinib versus placebo	No	Dutton and colleagues
	Panitumumab	REAL-3	First	Chemotherapy (epirubicin, oxaliplatin and capecitabine) with or without panitumumab	No	Waddell and colleagues
MET	Onartuzumab	METGastric	First	Onartuzumab versus placebo, in combination with chemotherapy (FOLFOX)	No	Shah and colleagues
	Rilotumumab	RILOMET-1	First	Rilotumumab versus placebo, in combination with chemotherapy (epirubicin, cisplatin and capecitabine)	No	Cunningham and colleagues
mTOR	Everolimus	GRANITE-1	Second or more	Everolimus versus placebo	No	Ohtsu and colleagues

Therap Adv Gastroenterol. 2018

(Moving) Targets in EG Cancer



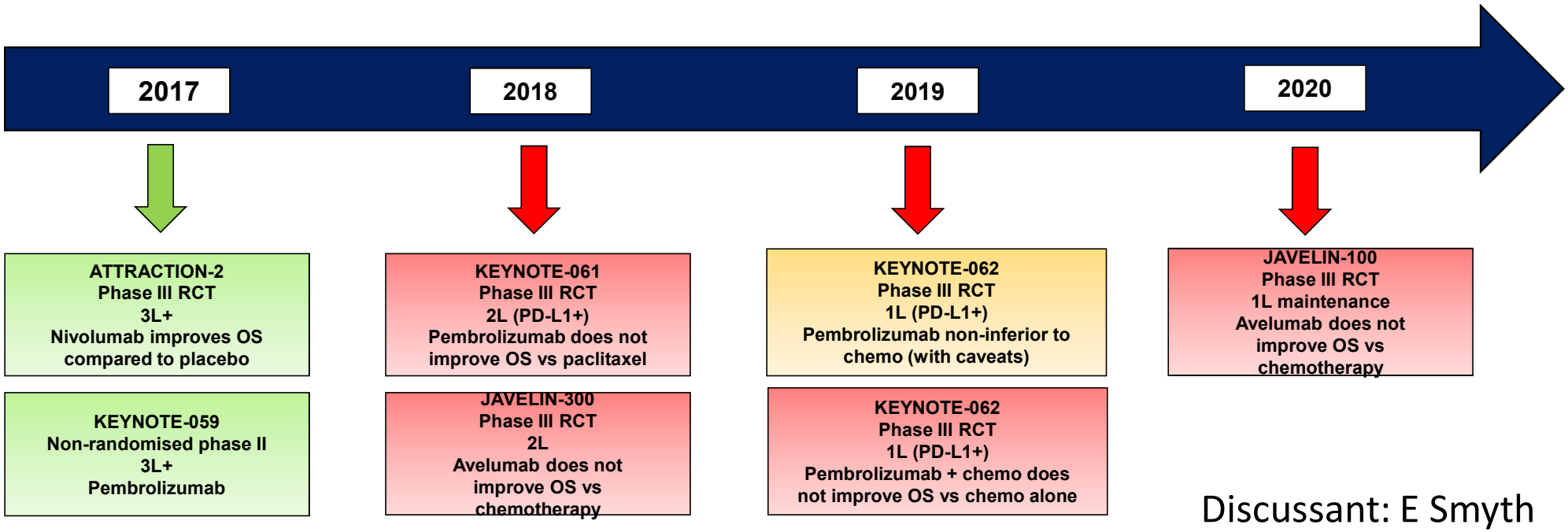
Gastric Cancer is **NOT** a monogenic single disease

Burrell et al., Nature 2013

Courtesy Sam Klempner

• Immune checkpoint inhibitors in GEA

- Successes and failures



KEY LEARNING

Most GEA do not benefit from anti-PD-(L)1 monotherapy

PD-L1 expression modestly sensitises (ORR 15% PD-L1 CPS ≥ 1, 25% CPS ≥ 10)

MSI (<5%) and high TMB (~18%) have good outcomes (ORR >50% to 30-40%)

CPS, combined proportion score; MSI, microsatellite unstable; ORR, overall response rate; OS, overall survival, PD-L1, programmed death-ligand-1; TMB, tumour mutational burden.

Discussant: E Smyth

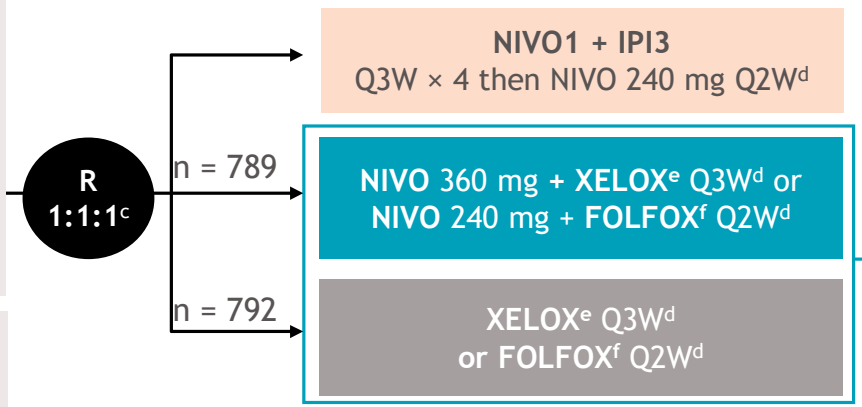
1. Kang et, *Lancet* . 2017 Dec 2;390(10111):2461-2471.
2. Fuchs CS et al. *JAMA Oncol*. 2018;4:e180013.
3. Shitara K et al. *Lancet*. 2018;392:123–133.
4. Bang et al, *Ann Oncol*. 2018 Oct 1;29(10):2052-2060.
4.Shitara et al, .*JAMA Oncol* . 2020 Sep 3. Online ahead of print.
5. Moehler et al, *JCO*.2020.38.4_suppl.278.
6. 1. Shitara K et al. Presented at ASCO 2020; poster 4537.
2. Fuchs CS et al. Presented at ASCO 2020; poster 4512.

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)



N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

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

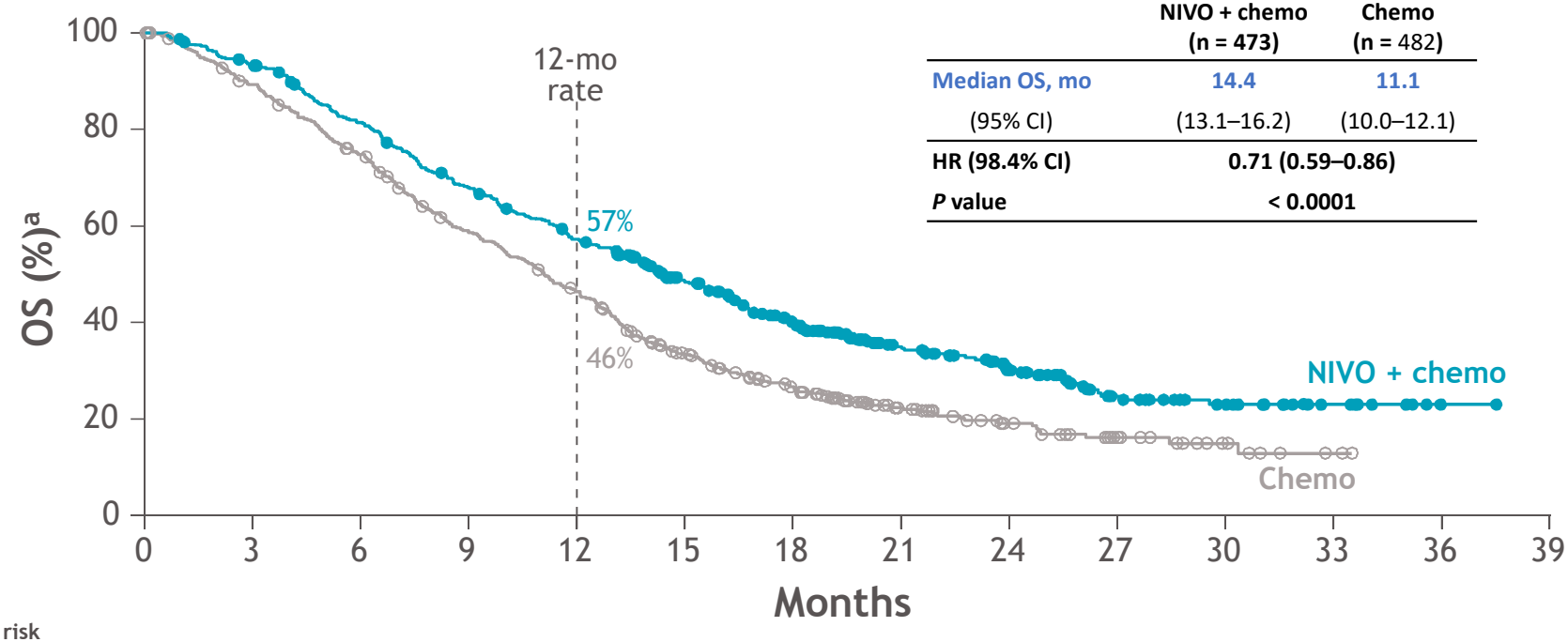
Secondary endpoints:
- **OS** (PD-L1 CPS ≥ 1 or all randomized)
- **OS** (PD-L1 CPS ≥ 10)
- **PFS**[g] (PD-L1 CPS ≥ 10, 1, or all randomized)
- **ORR**[g]

- 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.

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**	

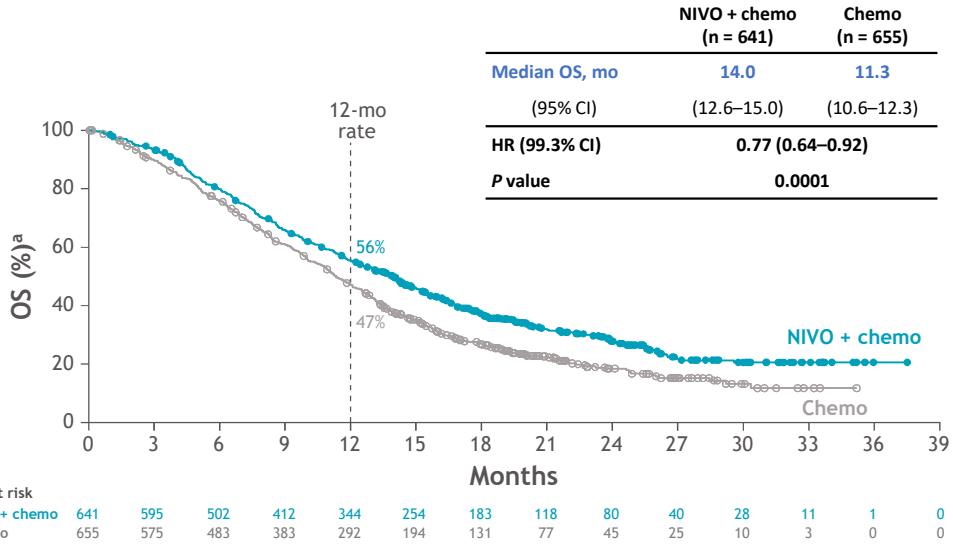
- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

[a]Minimum follow-up 12.1 months.

- CheckMate 649

Overall survival

PD-L1 CPS ≥ 1

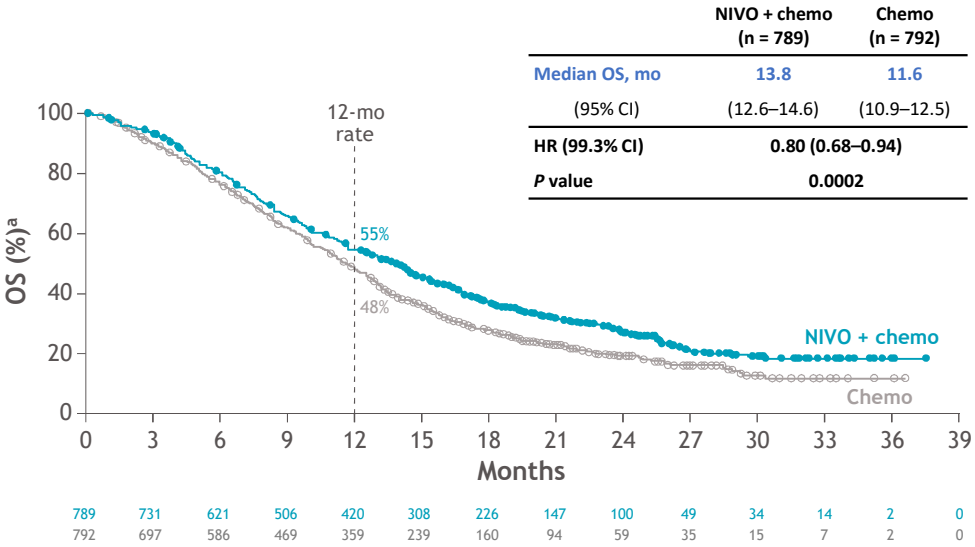


	NIVO + chemo (n = 641)	Chemo (n = 655)
Median OS, mo	14.0	11.3
(95% CI)	(12.6–15.0)	(10.6–12.3)
HR (99.3% CI)	0.77 (0.64–0.92)	
P value	0.0001	

No. at risk

NIVO + chemo	641	595	502	412	344	254	183	118	80	40	28	11	1	0
Chemo	655	575	483	383	292	194	131	77	45	25	10	3	0	0

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6–14.6)	(10.9–12.5)
HR (99.3% CI)	0.80 (0.68–0.94)	
P value	0.0002	

NIVO + chemo	789	731	621	506	420	308	226	147	100	49	34	14	2	0
Chemo	792	697	586	469	359	239	160	94	59	35	15	7	2	0

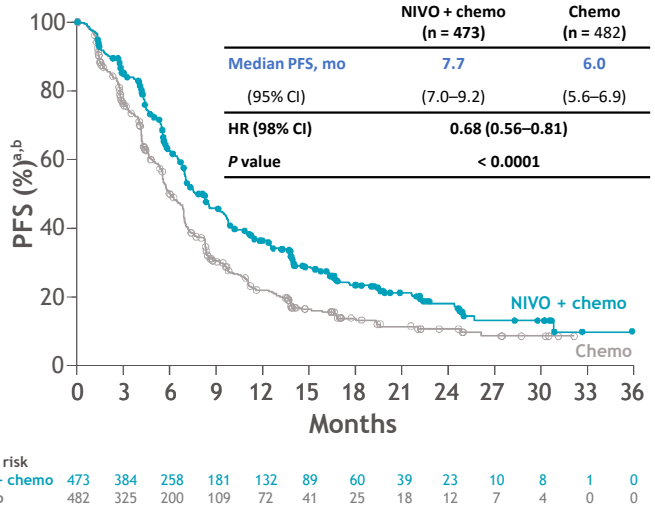
- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

[a]Minimum follow-up 12.1 months.

Progression-free survival

- CheckMate 649

Primary endpoint (PD-L1 CPS ≥ 5)

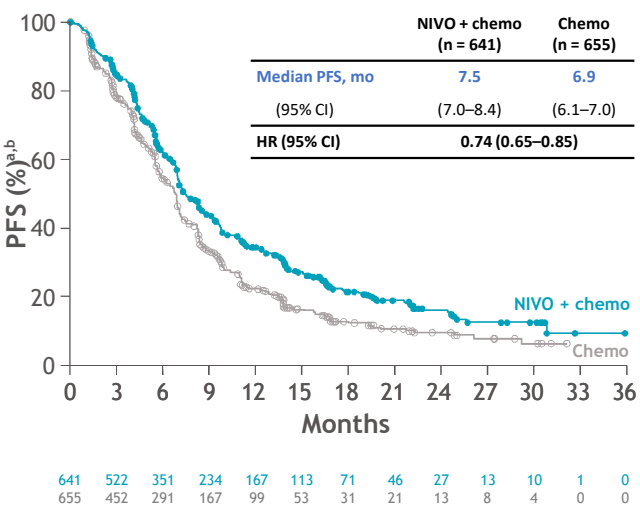


	NIVO + chemo (n = 473)	Chemo (n = 482)
Median PFS, mo	7.7	6.0
(95% CI)	(7.0–9.2)	(5.6–6.9)
HR (98% CI)	0.68 (0.56–0.81)	
P value	< 0.0001	

No. at risk													
NIVO + chemo	473	384	258	181	132	89	60	39	23	10	8	1	0
Chemo	482	325	200	109	72	41	25	18	12	7	4	0	0

12-mo rate: NIVO + chemo, 36%; chemo, 22%

PD-L1 CPS ≥ 1

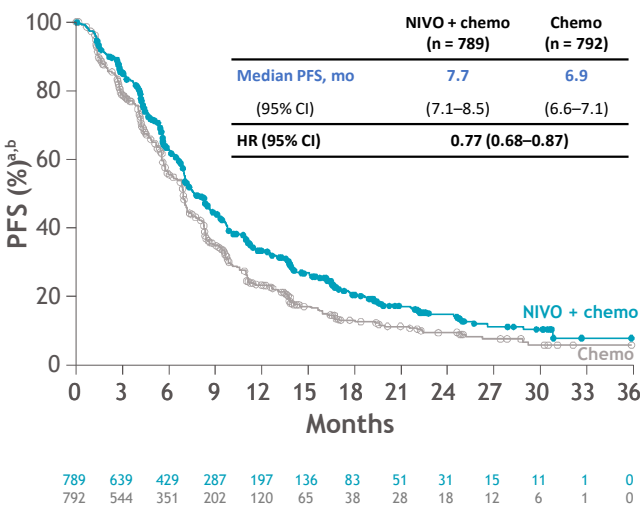


	NIVO + chemo (n = 641)	Chemo (n = 655)
Median PFS, mo	7.5	6.9
(95% CI)	(7.0–8.4)	(6.1–7.0)
HR (95% CI)	0.74 (0.65–0.85)	

	641	522	351	234	167	113	71	46	27	13	10	1	0
	655	452	291	167	99	53	31	21	13	8	4	0	0

NIVO + chemo, 34%; chemo, 22%

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS, mo	7.7	6.9
(95% CI)	(7.1–8.5)	(6.6–7.1)
HR (95% CI)	0.77 (0.68–0.87)	

	789	639	429	287	197	136	83	51	31	15	11	1	0
	792	544	351	202	120	65	38	28	18	12	6	1	0

NIVO + chemo, 33%; chemo, 23%

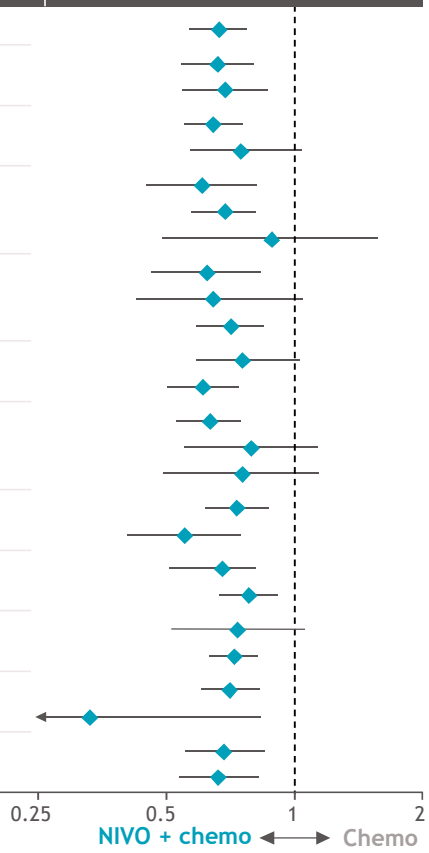
- Superior PFS, 32% reduction in the risk of progression or death with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5
- PFS benefit with NIVO + chemo versus chemo in PD-L1 CPS ≥ 1 and all randomized patients

[a]Per BICR assessment; [b]Minimum follow-up 12.1 months.

- CheckMate 649

Overall survival subgroup analysis

Category (PD-L1 CPS ≥ 5)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 955)		14.4	11.1	0.70
Age, years	< 65 (n = 552)	14.8	11.0	0.69
	≥ 65 (n = 403)	14.3	11.2	0.72
Sex	Male (n = 680)	14.4	10.8	0.67
	Female (n = 275)	14.4	12.1	0.78
Race	Asian (n = 236)	16.1	11.5	0.63
	White (n = 655)	14.0	11.1	0.71
	Other (n = 64)	9.8	10.6	0.93
Region	Asia (n = 228)	15.6	11.8	0.64
	US/Canada (n = 137)	16.8	12.6	0.67
	ROW (n = 590)	13.6	10.4	0.74
ECOG PS[a]	0 (n = 397)	17.6	13.8	0.79
	1 (n = 557)	12.6	8.8	0.63
Primary tumor location	GC (n = 667)	15.0	10.5	0.66
	GEJC (n = 170)	14.2	13.1	0.84
	EAC (n = 118)	11.2	11.3	0.78
Tumor cell PD-L1[b] expression	< 1% (n = 724)	14.2	11.6	0.75
	≥ 1% (n = 230)	16.2	8.8	0.56
Liver metastases	Yes (n = 408)	13.1	9.8	0.63
	No (n = 518)	15.5	12.0	0.76
Signet ring cell carcinoma	Yes (n = 141)	12.1	9.0	0.71
	No (n = 814)	15.1	11.3	0.69
MSI status[c]	MSS (n = 846)	14.4	11.1	0.73
	MSI-H (n = 34)	Not reached	8.8	0.33
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.71
	XELOX (n = 454)	15.0	11.0	0.69



- OS consistently favored NIVO + chemo versus chemo across multiple pre-specified subgroups

[a]Not reported, n = 1; [b]Unknown, n = 1; [c]Not reported/invalid, n = 75.

Conclusions

- NIVO is the first PD-1–inhibitor to demonstrate superior OS and PFS in combination with chemo versus chemo alone in previously untreated patients with advanced GC/GEJC/EAC
  - Statistically significant and clinically meaningful OS benefit in patients whose tumors expressed PD-L1 CPS ≥ 5 and ≥ 1 and in all randomized patients
  - Survival benefit across multiple pre-specified subgroups (assessed in primary population)
  - PFS benefit in PD-L1 CPS ≥ 5 (statistically significant), PD-L1 CPS ≥ 1, and all randomized patients
- No new safety signals were identified with NIVO + chemo
- **NIVO + chemo represents a new potential standard 1L treatment for patients with advanced GC/GEJC/EAC**

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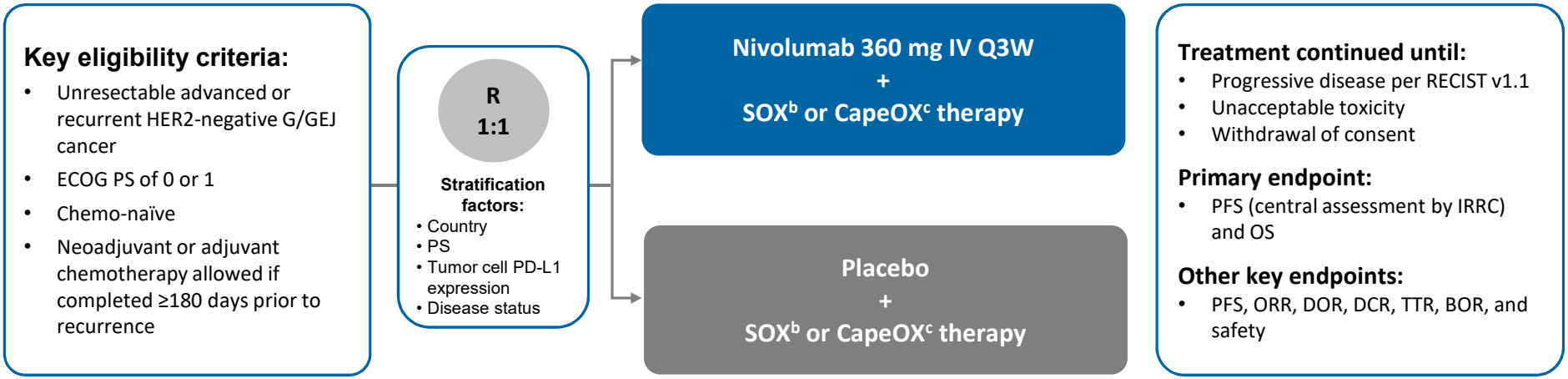
Phase 3 part of ATTRACTION-4: Study Design

- Phase 3 part of ATTRACTION-4 is a double-blind, randomized (1:1) controlled study conducted at 130 centers in **Japan, Korea, and Taiwan** from Mar 2017[a]



- At data cutoff for interim analysis of PFS (31 Oct 2018), the median follow-up period was 11.6 months
- At data cutoff for final analysis of OS (31 Jan 2020), the median follow-up was 26.6 months
- A total of 724 patients were randomized

[a]ClinicalTrials.gov Identifier: NCT02746796,
[b]SOX : S-1 (tegafur-gimeracil-oteracil potassium) 40 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w
[c]CapeOX : Capecitabine 1000 mg/m^2 orally twice daily (days 1–14) and Oxaliplatin 130 mg/m^2 IV (day 1), q3w

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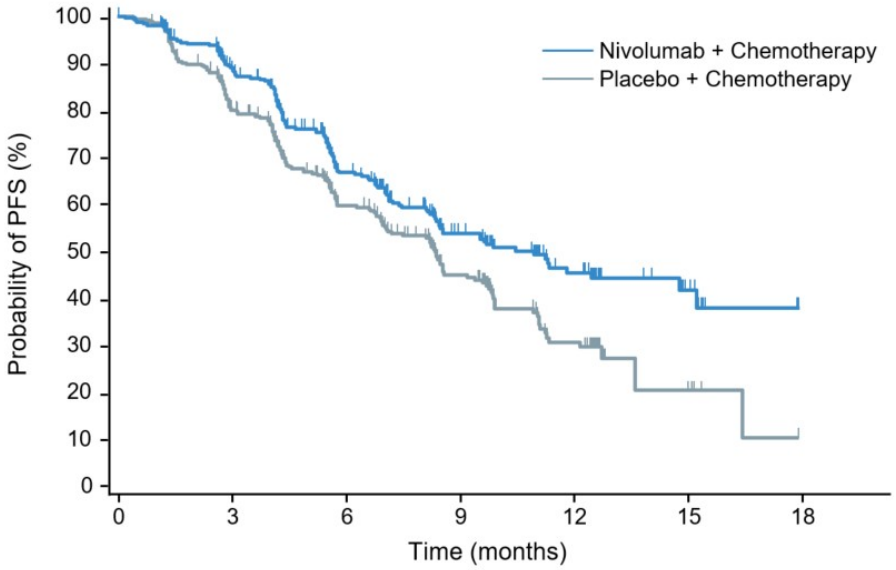
Progression-Free Survival (Interim Analysis)



At Risk							
Nivolumab + Chemotherapy	362	274	168	94	46	13	0
Placebo + Chemotherapy	362	259	160	80	30	5	0

	Nivolumab + chemotherapy N = 362	Placebo + chemotherapy N = 362
Median PFS, months (95% CI)	10.45 (8.44-14.75)	8.34 (6.97-9.40)
Hazard ratio (98.51% CI)	0.68 (0.51 – 0.90)	
P value	0.0007	
1yr PFS rate (%)	45.4	30.6

Cut off : 31 Oct 2018 for Interim analysis

- PFS was continuously longer in NIVO + Chemo than in Chemo at the final analysis (NIVO+Chemo vs. Chemo: HR 0.70; mPFS 10.9 vs. 8.4 mo)

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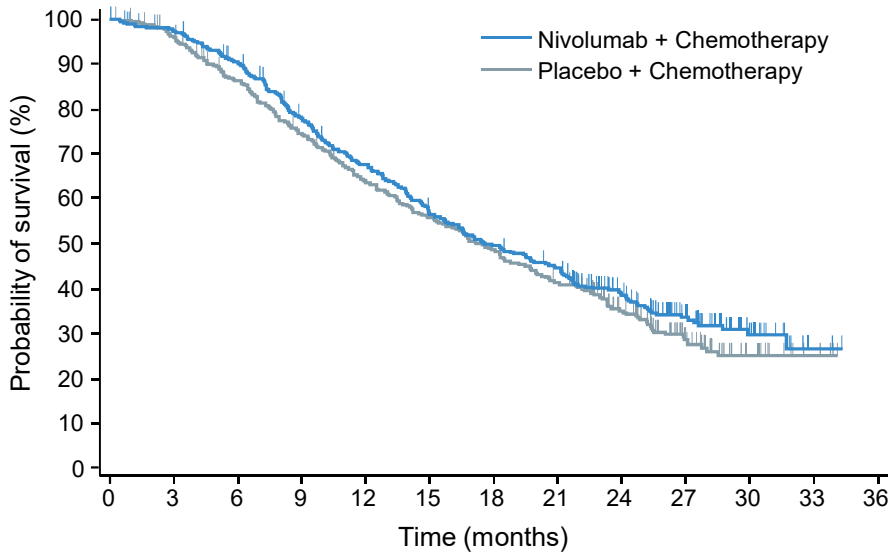
Overall Survival (Final Analysis)



At Risk													
Nivolumab + Chemotherapy	362	346	318	269	232	193	169	150	102	58	23	2	0
Placebo + Chemotherapy	362	342	301	259	219	192	167	141	97	48	16	5	0

	Nivolumab + chemotherapy N = 362	Placebo + chemotherapy N = 362
Median OS, months (95% CI)	17.45 (15.67-20.83)	17.15 (15.18-19.65)
Hazard ratio (95% CI)	0.90 (0.75 – 1.08)	
P value	0.257	

Cut off : 31 Jan 2020 for final analysis

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Summary and Conclusion

- NIVO + Chemo demonstrated the significant improvement in PFS, but not in OS.
  - Superior response rates and longer response duration

- The pre-specified objective of Phase 3 part of ATTRACTION-4 was achieved, showing clinical meaningful efficacy.

- NIVO + Chemo was manageable in safety.

- NIVO + Chemo could be considered as new first-line treatment option in unresectable advanced or recurrent G/GEJ cancer.

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• CheckMate 649 & ATTRACTION-4

- Similarities and distinctions

	CheckMate 649 PD-L1 CPS ≥ 5	ATTRACTION-4 Biomarker agnostic
Trial design	Phase III RCT Open label	Phase III RCT Placebo controlled
Region	Global 25% Asian	Asia (Japan, Korea, Taiwan)
Chemotherapy	CAPOX (50%) FOLFOX (50%)	CAPOX (36%) Oxaliplatin - S1 (64%)
Site of disease	Gastric (70%) GEJ/Eso (30%)	Gastric* (89%) GEJ* (11%)
Primary endpoint	OS and PFS **CPS ≥ 5**	OS and PFS

CheckMate 649
↑PFS and ↑OS

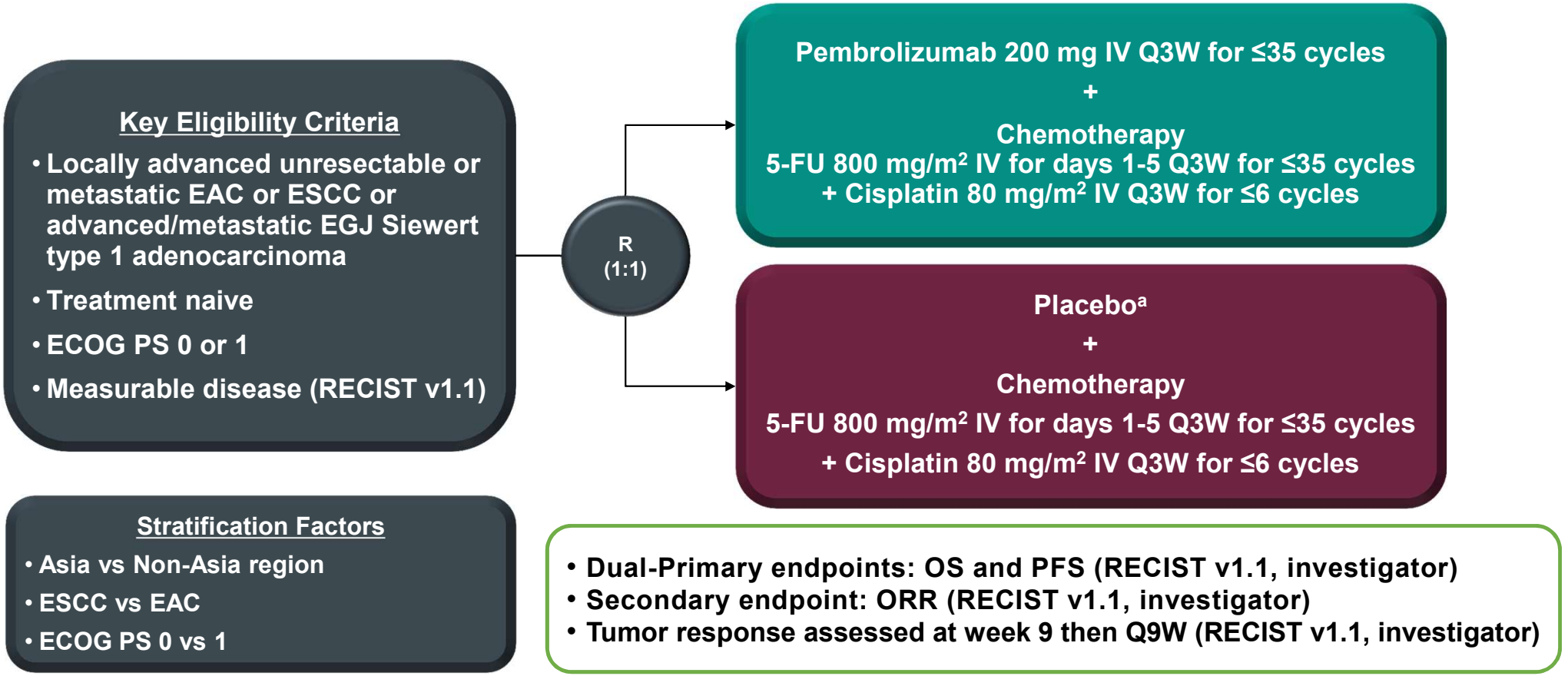
ATTRACTION-4
↑PFS but not OS

Both trials meet primary endpoints

Discussant: E Smyth

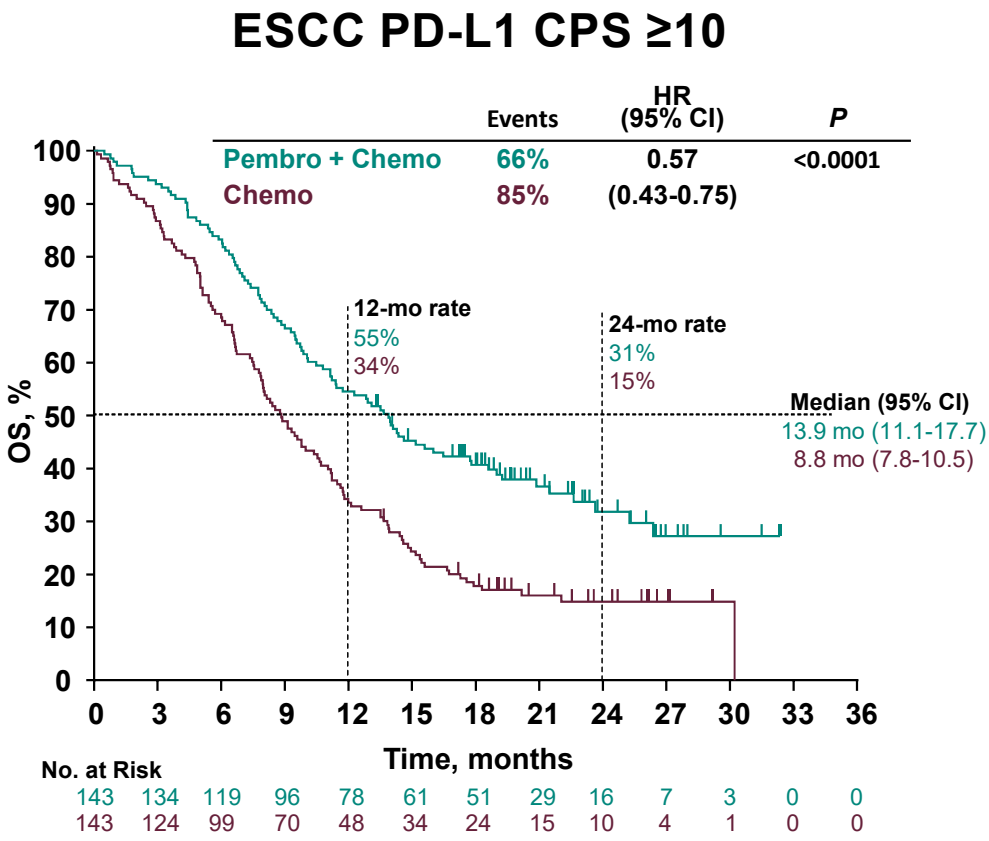
CAPOX, capecitabine/oxalipatin; Eso, esophagus; FOLFOX, infusional 5-FU/oxaliplatin; GEJ, gastroesophageal junction; OS, overall survival; PFS, progression free survival; RCT, randomised controlled trial. *of patients with known tumour site

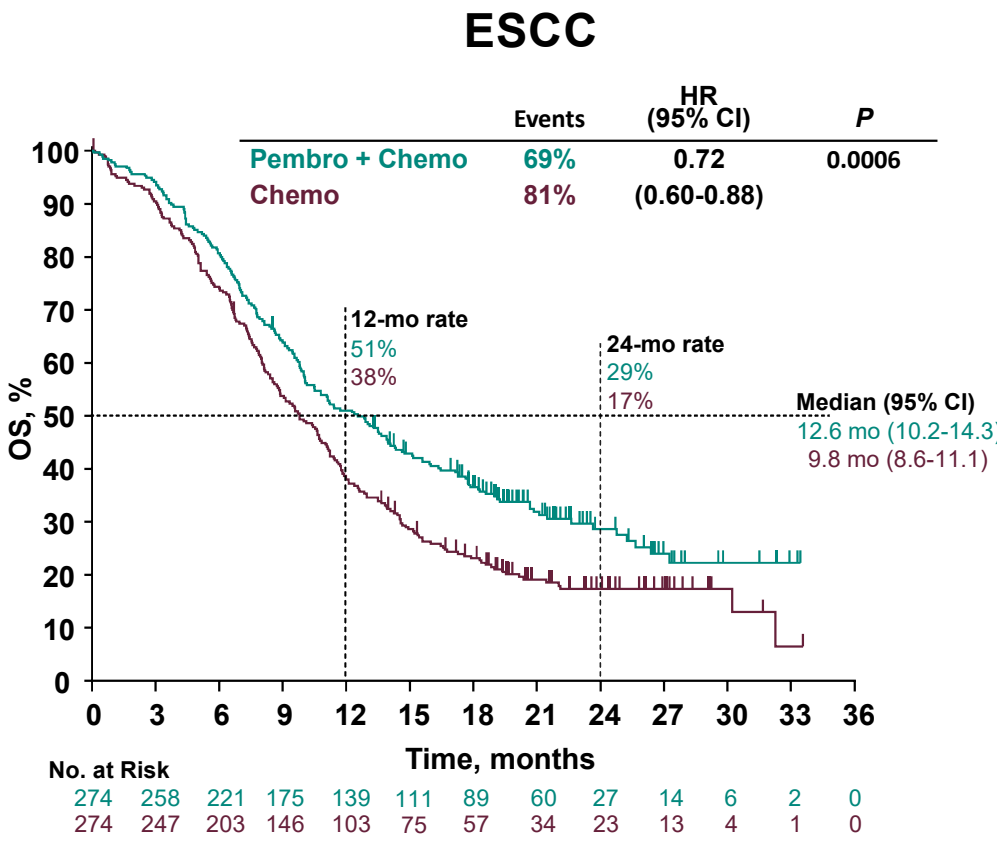
KEYNOTE-590 Study Design (NCT03189719)



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

Overall Survival

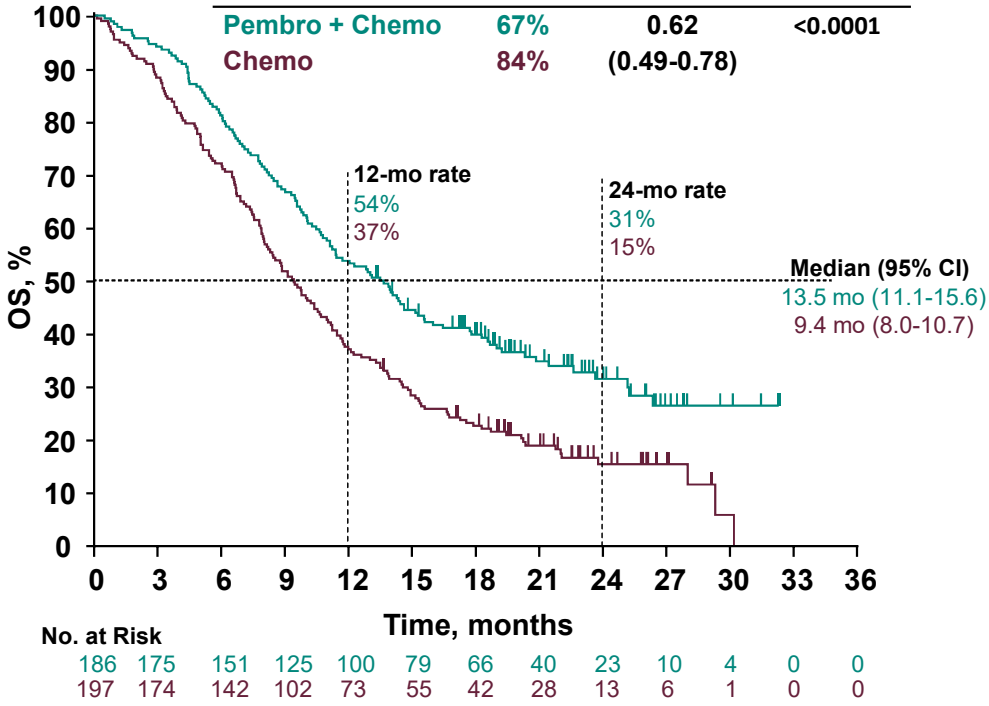




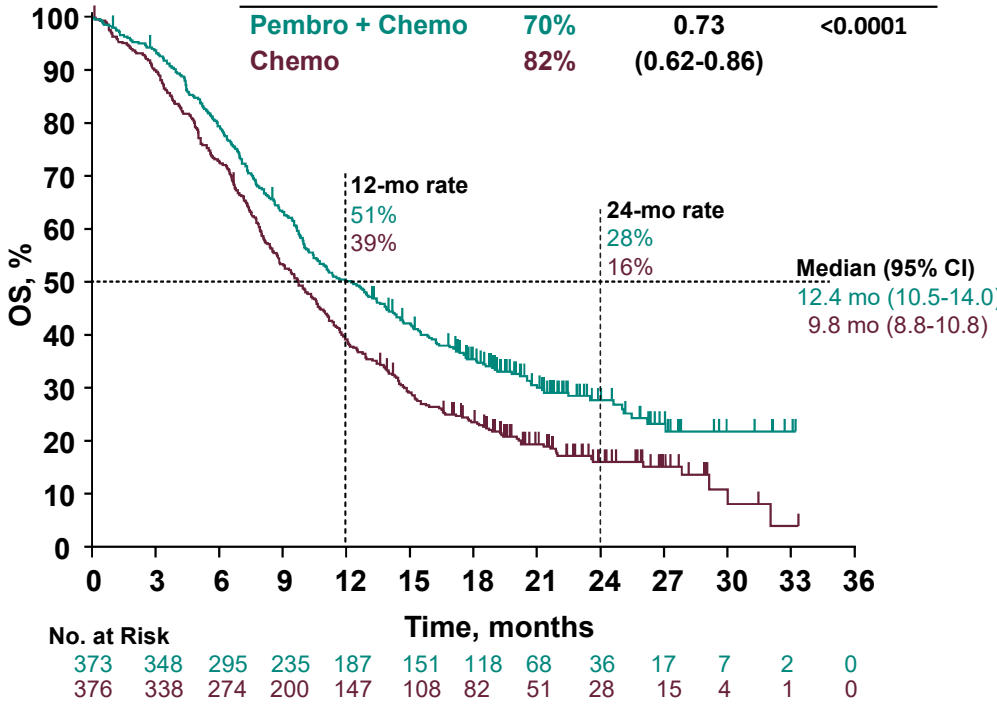
Data cut-off: July 2, 2020.

Overall Survival

PD-L1 CPS ≥10



All Patients



Data cut-off: July 2, 2020.

Summary and Conclusions

- First-line pembrolizumab plus chemotherapy vs chemotherapy plus placebo provided a statistically significant and clinically meaningful improvement in OS, PFS, and ORR in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma
  - Superior OS: ESCC CPS ≥10 (HR 0.57, *P*<0.001), ESCC (HR 0.72, *P*=0.006), CPS ≥10 (HR 0.62, *P*<0.001), all patients (HR 0.73, *P*<0.001)
  - Superior PFS: ESCC (HR 0.65), CPS ≥10 (HR 0.51), all patients (HR 0.65), all *P*<0.001
  - Superior ORR: all patients (45.0% vs 29.3%, Δ15.8%, *P*<0.001)
- Comparable safety profile between the two treatment groups
  - No new safety signals detected
- Pembrolizumab plus chemotherapy should be a new standard-of-care as first-line therapy in patients with locally advanced and metastatic esophageal cancer including EGJ adenocarcinoma

CheckMate 577 study design

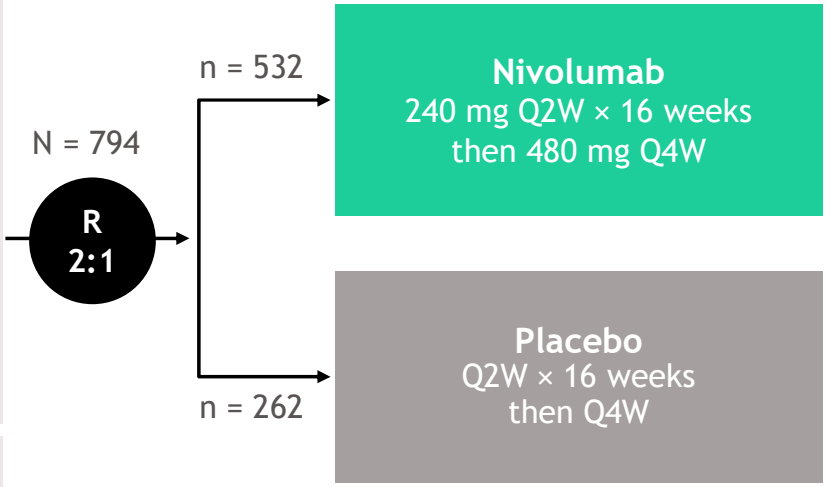
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

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:

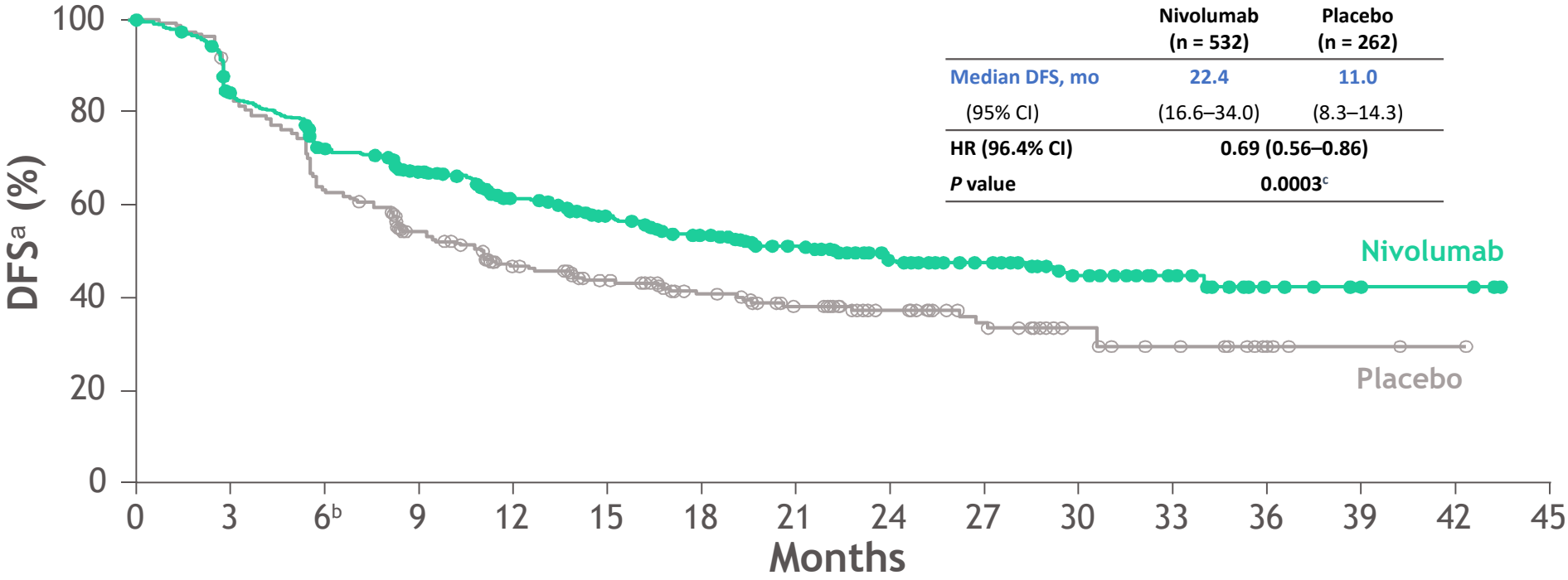
- OS[f]
- OS rate at 1, 2, and 3 years

- 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).

Disease-free survival

- CheckMate 577



	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

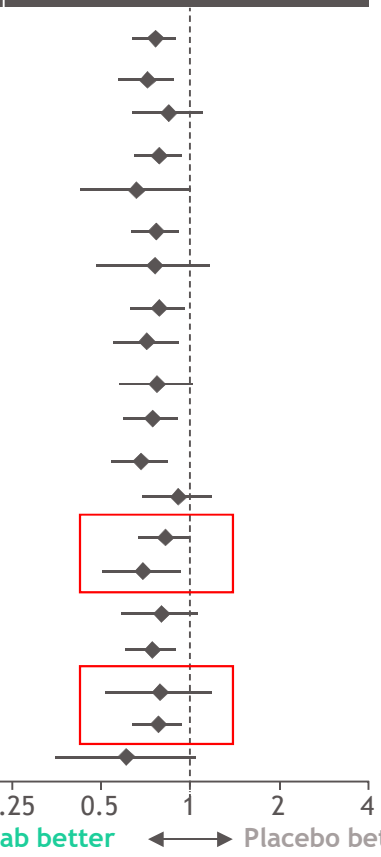
- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[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.

- CheckMate 577

Disease-free survival by subgroups

Subgroup		Median DFS, months		Unstratified HR
		Nivolumab	Placebo	
Overall (N = 794)		22.4	11.0	0.70
Age, years	< 65 (n = 507)	24.4	10.8	0.65
	≥ 65 (n = 287)	17.0	13.9	0.80
Sex	Male (n = 671)	21.4	11.1	0.73
	Female (n = 123)	Not reached	11.0	0.59
Race	White (n = 648)	21.3	10.9	0.71
	Asian (n = 117)	24.0	10.2	0.70
ECOG PS	0 (n = 464)	29.4	11.1	0.73
	1 (n = 330)	17.0	10.9	0.66
Disease stage at initial diagnosis	II (n = 278)	34.0	13.9	0.72
	III (n = 514)	19.4	8.5	0.68
Tumor location	EC (n = 462)	24.0	8.3	0.61
	GEJC (n = 332)	22.1	20.6	0.87
Histology	Adenocarcinoma (n = 563)	19.4	11.1	0.75
	Squamous cell carcinoma (n = 230)	29.7	11.0	0.61
Pathologic lymph node status	ypN0 (n = 336)	Not reached	27.0	0.74
	≥ ypN1 (n = 457)	14.8	7.6	0.67
Tumor cell PD-L1 expression	≥ 1% (n = 129)	19.7	14.1	0.75
	< 1% (n = 570)	21.3	11.1	0.73
	Indeterminate/nonevaluable (n = 95)	Not reached	9.5	0.54

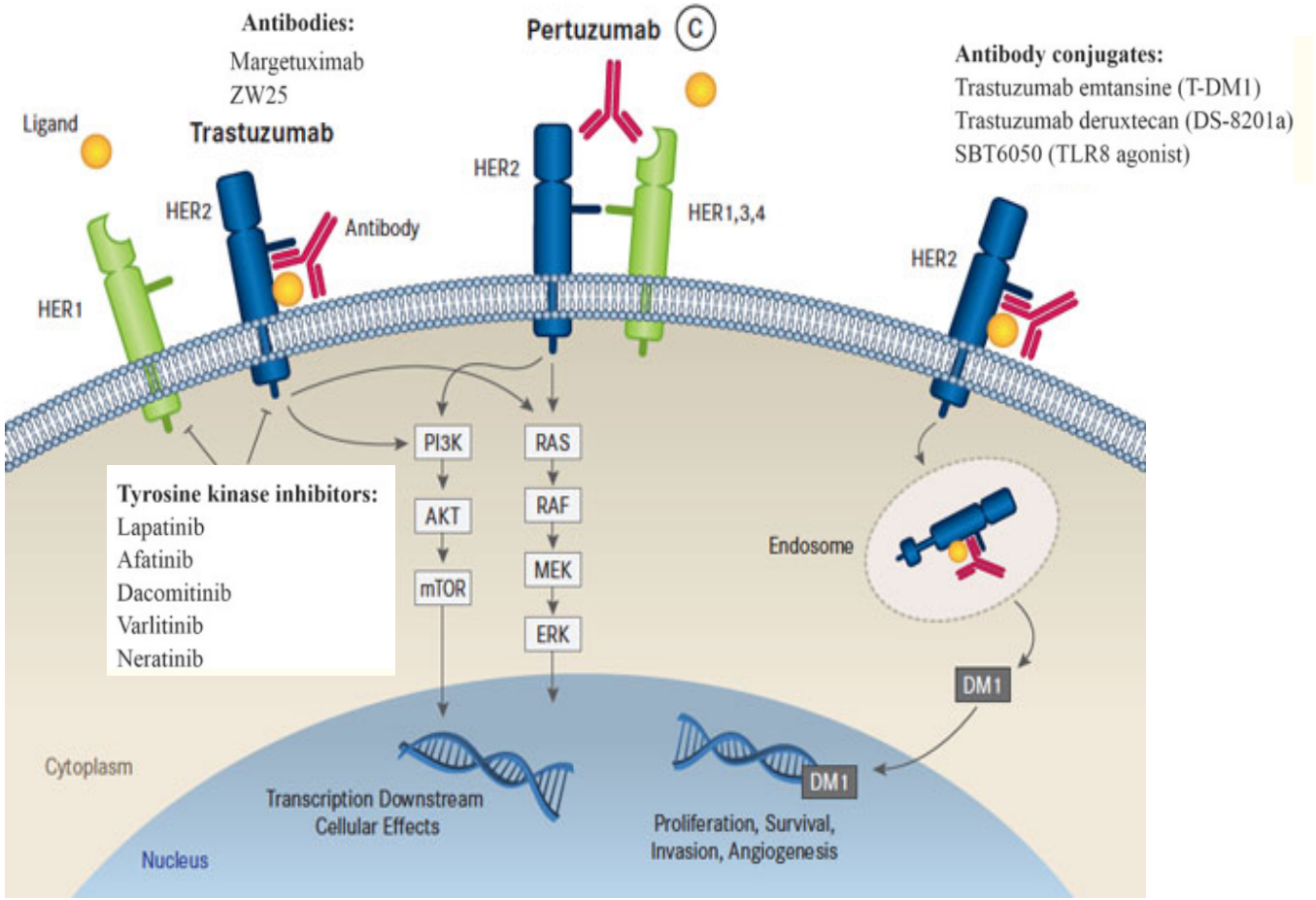


- DFS favored nivolumab versus placebo across these pre-specified subgroups

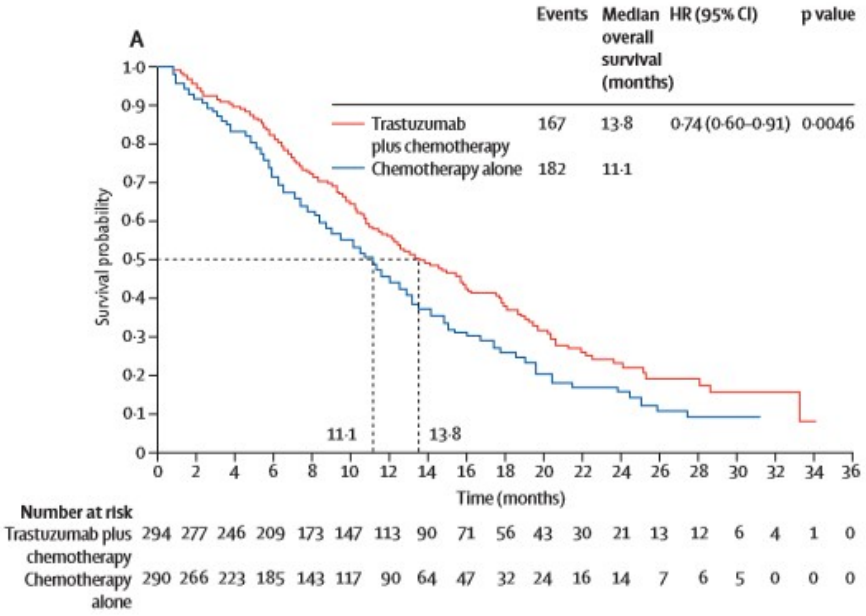
Summary

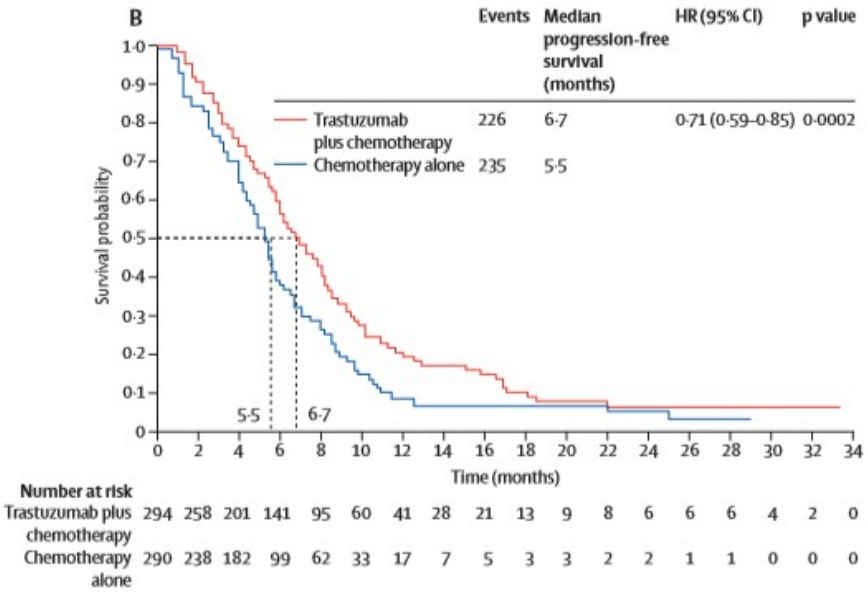
- Nivolumab is the first adjuvant therapy to provide a statistically significant and clinically meaningful improvement in DFS versus placebo in resected EC/GEJC following neoadjuvant CRT
  - 31% reduction in the risk of recurrence or death and a doubling in median DFS
  - DFS benefit across multiple pre-specified subgroups
- Nivolumab was well tolerated with an acceptable safety profile
  - Incidence of serious TRAEs and TRAEs leading to discontinuation were ≤ 9% with nivolumab and 3% with placebo
- These results represent the first advance in years for this group of patients, potentially establishing adjuvant nivolumab as a new standard of care

Anti-Her2 agents



ToGA phase III study





Bang et al. Lancet 2010

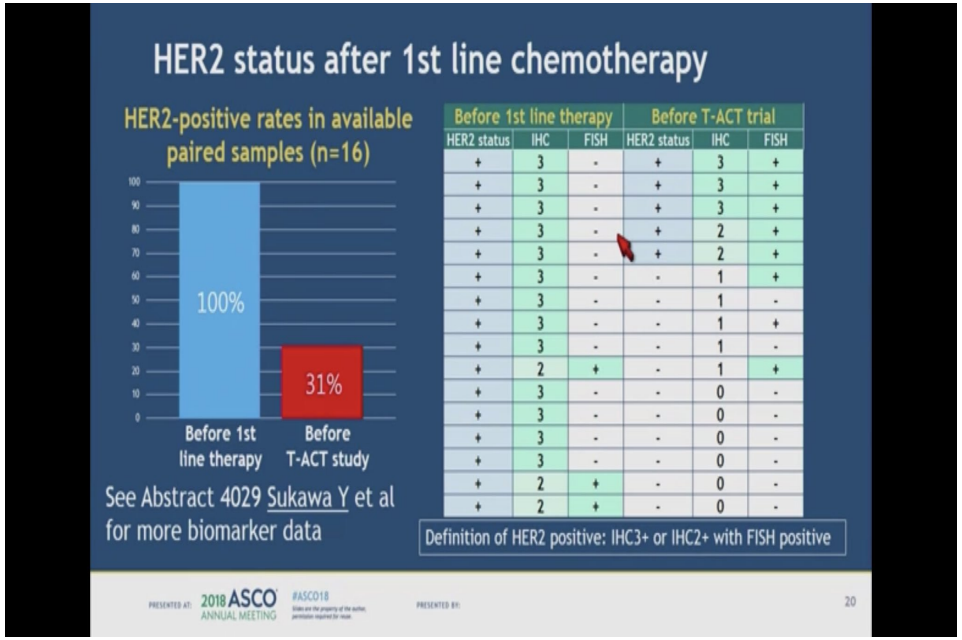
Landmark clinical trials of HER2-positive gastric cancer

Trials	Patients	Line of therapy	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/m^2 twice daily on days 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, $P = 0.199$).

Zhao et al. Journal of Hematology & Oncology (2019) 12:50

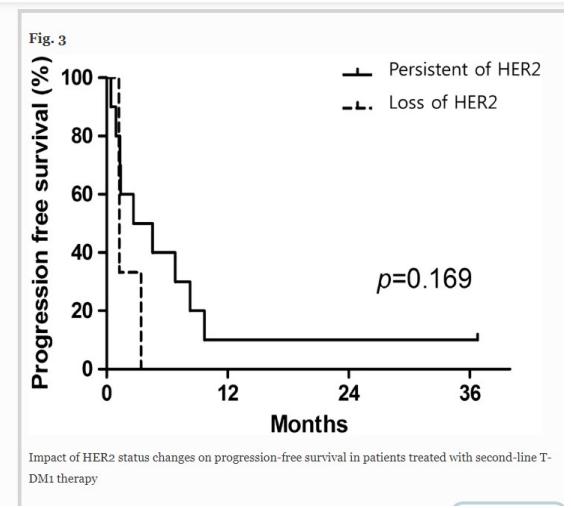
Changes in HER2 after treatment

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



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

Makiyama et al., ASCO 2018



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

Seo et al., GASTHER3 Gastric Cancer, 2019

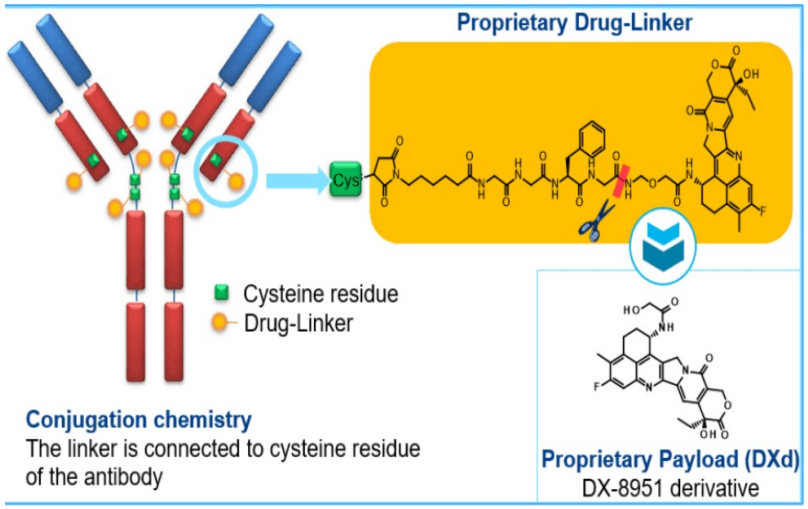
Anti-HER2 2L Treatment in G/GE Cancers

- Initially 10-20% GC have HER2 gene amplification
- ToGA showed 26% ↑ OS with trastuzumab (35% for IHC2+/FISH+ or IHC3+)
- 2L trials negative[2-4]: Unselected for HER2+ prior to 2L treatment

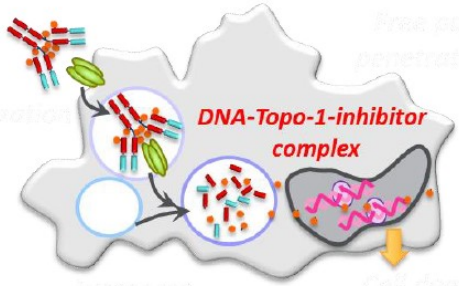
Trial	Test	Treatments	OS (mos)	
TyTAN 2014[2]	HER2:CEP17 ratio ≥ 2	2nd line Paclitaxel +/- Lapatinib	11.0 vs 8.9	HR 0.84, p 0.10
	IHC 0/1+		9.7 vs 8.1	HR 1.07, p 0.80
	IHC 2+		10.2 vs 10.7	HR 0.88, p 0.78
	IHC 3+		14.0 vs 7.6	HR 0.59, p 0.01
GATSBY 2017[3]	HER2+ IHC or FISH	2nd line Taxane vs TDM-1	8.6 vs 7.9	HR 1.15, p 0.08
T-ACT 2018[4]	HER2+ IHC or FISH	2nd line Paclitaxel +/- Trastuzumab	10.2 vs 9.9	HR 1.23, p 0.20

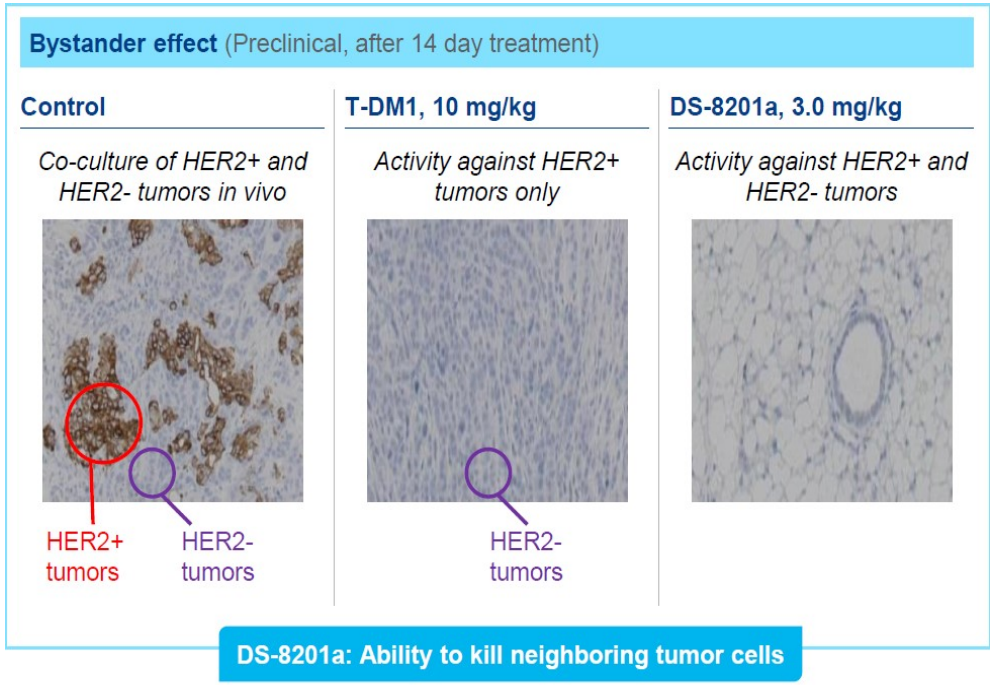
[1]Kashiwada T, et al ASCO 2018 abstr
[2]Satoh T, et al. J Clin Oncol 2014; 32:2039-2049
[3]Thuss-Patience PC, et al Lancet Oncol 2017; 18: 640-653
[4]Makiyama A, et al J Clin Oncol 2018; 36 suppl; abstr 4011
[5]Sukawa Y, et al J Clin Oncol 2018; 36 suppl abstr 4029

Trastuzumab Deruxtecan



https://www.adcreview.com/trastuzumab-deruxtecan-drug-description/

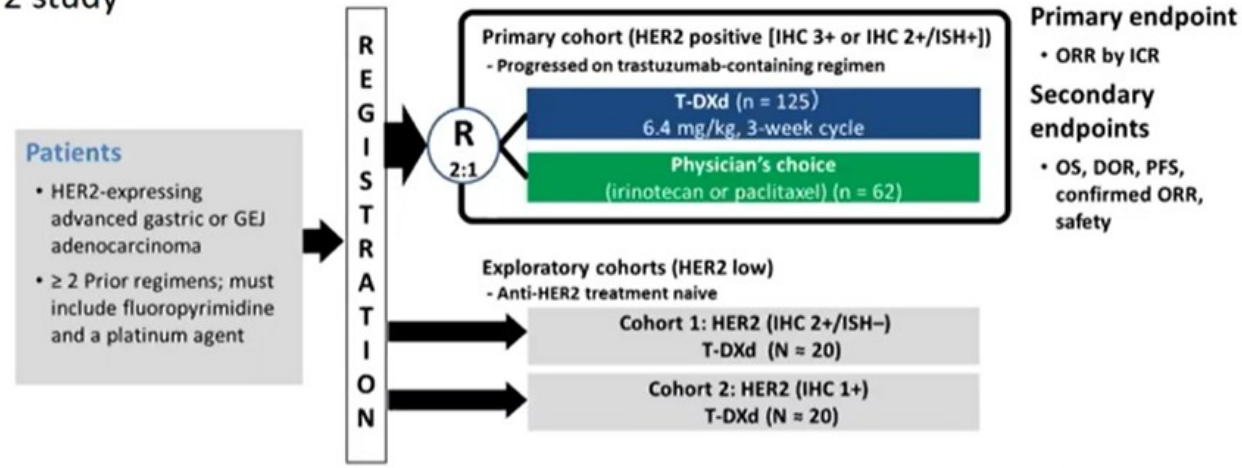




DESTINY-Gastric01

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)



*OS was a key secondary endpoint to be statistically evaluated hierarchically if the primary endpoint was statistically significant (Familywise type I error was controlled at 0.05 for ORR and OS)

- 187 patients were randomized (T-DXd, n = 125; PC, n = 62)
- 76% 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.

PRESENTED BY: Dr Kohei Shitara; National Cancer Center Hospital East, Chiba, Japan; kshitara@east.ncc.go.jp

DESTINY-Gastric01 Exploratory Cohorts

Primary Endpoint: ORR

	Primary Cohort[1]		Exploratory Cohorts	
	T-DXd (n = 119)	PC Overall (n = 56)	Cohort 1 IHC 2+/ISH− (n = 19)	Cohort 2 IHC 1+ (n = 21)
ORR by ICR (CR + PR)	**51.3% (n = 61)** 95% CI, 41.9-60.5; *P* < .0001[a]	**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

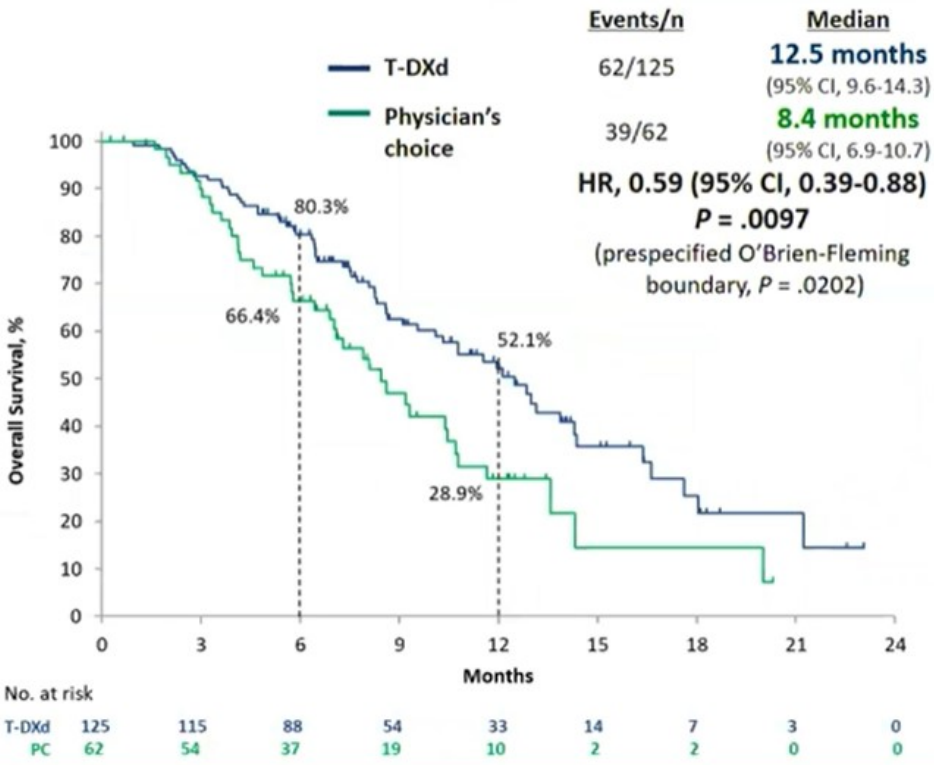
Includes data for the response-evaluable set: all randomized (for primary cohort) patients who received ≥ 1 dose of study drug and had measurable tumors based on independent central review at baseline.
[a]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region.

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

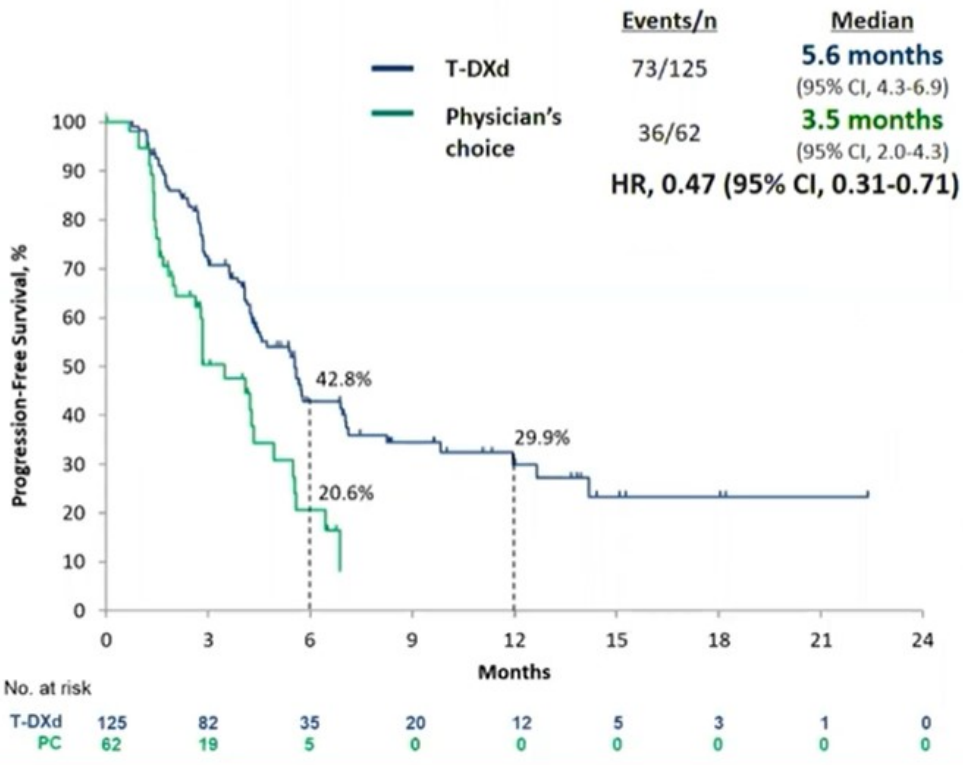
DESTINY-Gastric01

Overall and Progression-Free Survival

Overall Survival



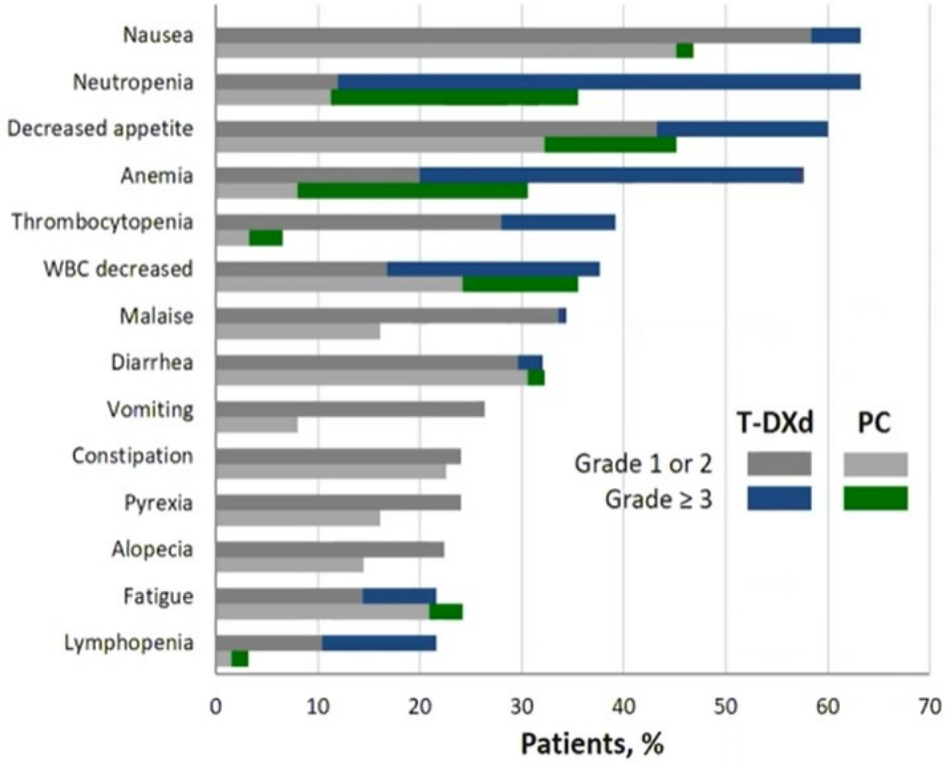
Progression-Free Survival



PRESENTED BY: Dr Kohei Shitara; National Cancer Center Hospital East, Chiba, Japan; kshitara@east.ncc.go.jp

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)

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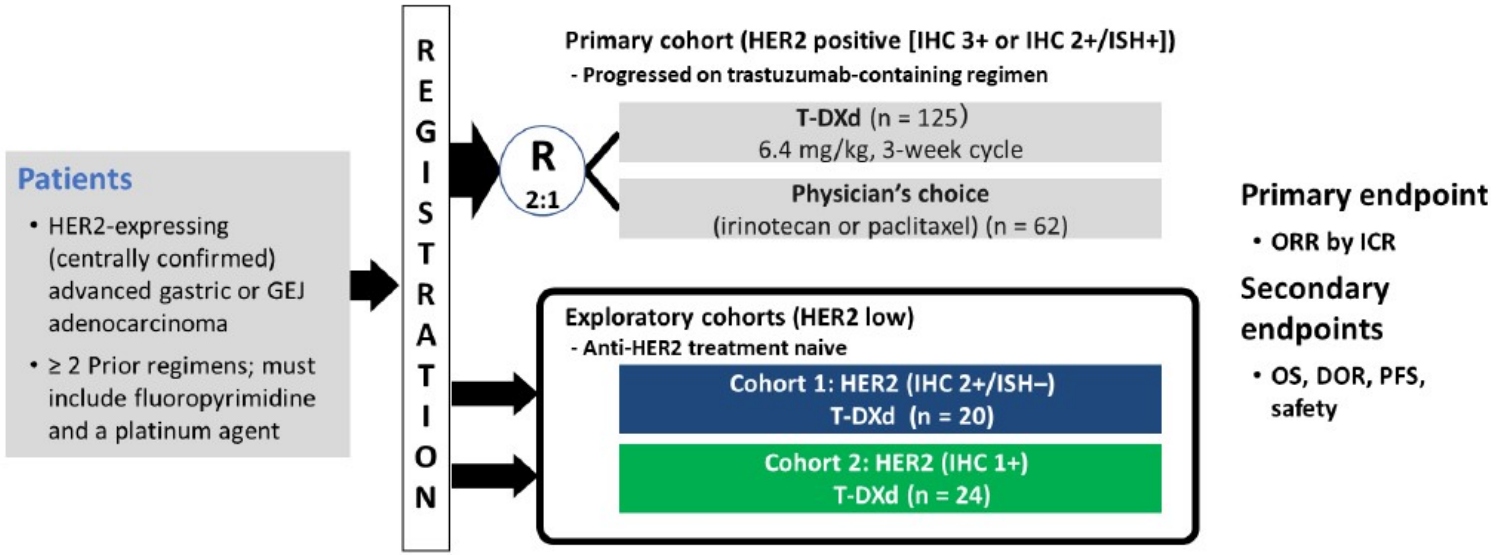
DESTINY-Gastric01

An open-label, multicenter, randomized, phase 2 study



- All patients received T-DXd 6.4 mg/kg q3w
  - Cohort 1 IHC 2+/ISH– (n = 20); cohort 2 IHC 1+ (n = 24)
- Patients had not previously received anti-HER2 treatment
- Median of 2 prior lines of therapy for advanced/metastatic disease
  - 18% had irinotecan, 84% had ramucirumab, 32% had anti–PD-1/PD-L1
- At data cutoff (8 November 2019), no patients in cohort 1 and 2 in cohort 2 (8.3%) remained on treatment

DESTINY-Gastric01 Exploratory Cohorts

Primary Endpoint: ORR

	Primary Cohort[1]		Exploratory Cohorts	
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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

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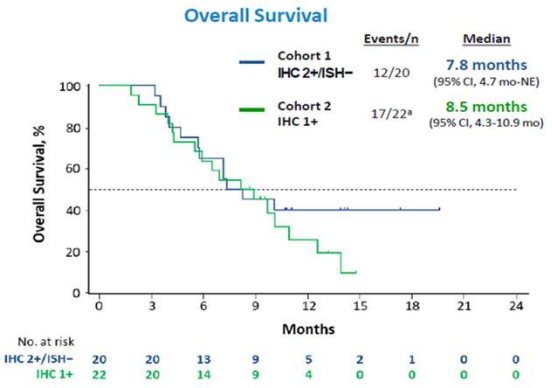
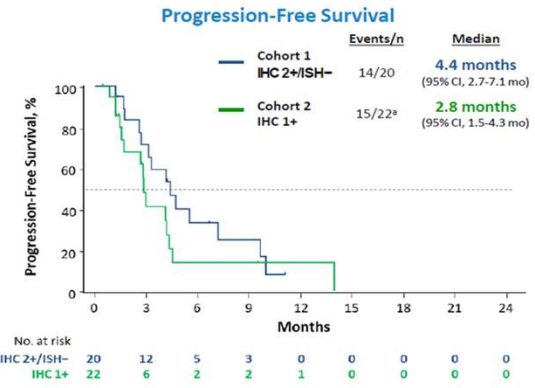
1. Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

VIRTUAL 2020 ESMO congress

DESTINY-Gastric01 Exploratory Cohorts

Overall and Progression-Free Survival





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

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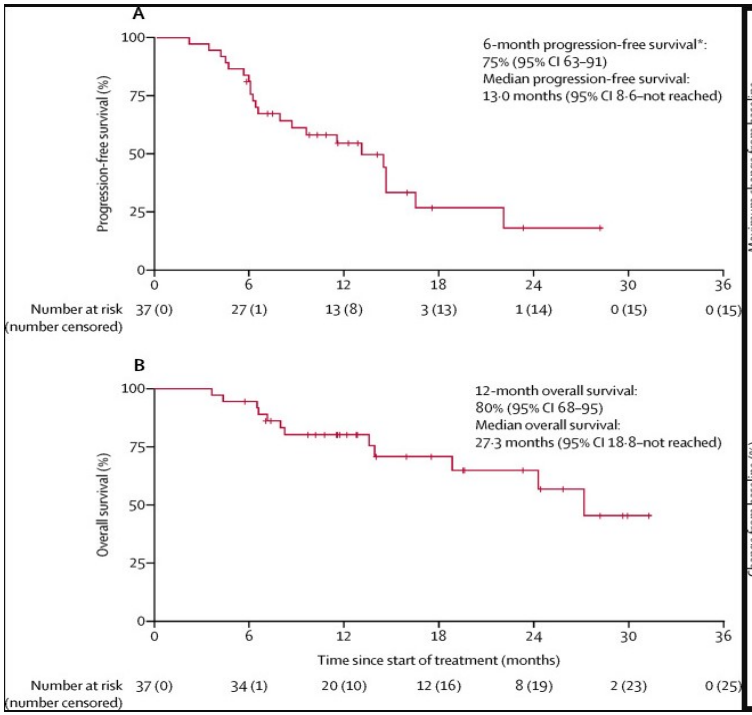
Summary - Trastuzumab-Deruxtecan

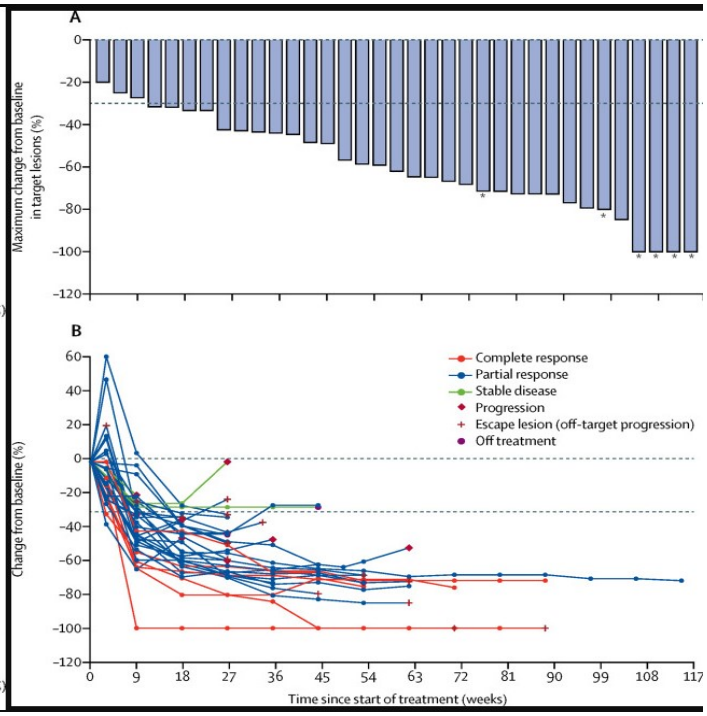
- There was a higher RR (51.3% vs. 14.3%) and longer OS (12.5 vs 8.4 mos) for patients receiving T-DXd
- Adverse events – GI, hematologic toxicities, ILD*
- Exploratory Data - Activity in HER2 IHC 2+/ISH-, IHC 1+
  - IHC2+/ISH- RR 26.3%, OS 7.8 mos, PFS 4.4 mos
  - IHC1+ RR 9.5%, OS 8.5 mos, PFS 2.4 mos
- Effective treatment option for patients after disease progression with Trastuzumab, including those with HER2 low tumors
- Data have been submitted to FDA as breakthrough therapy and orphan drug designation
  - DESTINY-Gastric02 study of 2nd-line DS8201a in US and Western Europe
  - DESTINY-Gastric03 study of novel combinations with DS8201a (chemo, ICI)
  - DESTINY-Gastric04 phase III study of 2nd-line DS8201a pending opening.

First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial

- 37 patients
- HER2 + advanced/met esophagogastric cancer
- Trastuxzumab + Pembro + FOLFOX
- Primary endpoint 6 mo PFS

- Promising results lead to KeyNote 811





RR 83%

Jangigian et al,.Volume 21, Issue 6, June 2020, Pages 821-831

HER2 Antibodies

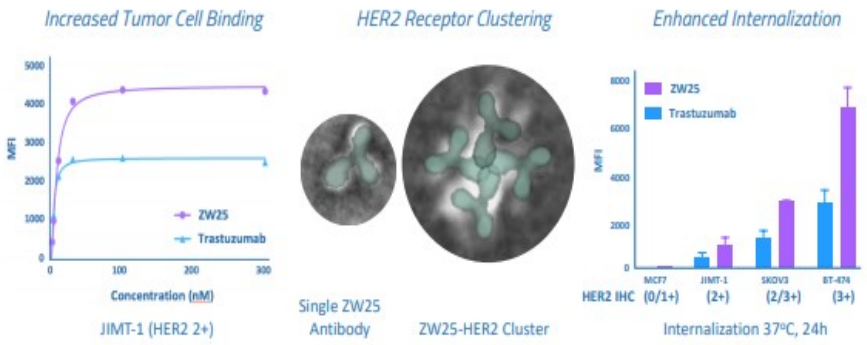
ZW25: Bispecific HER2-Targeted Antibody

- Designed using the Azymetric™ bispecific platform
- Biparatopic – simultaneously binds two HER2 epitopes
  - ECD4 (trastuzumab binding domain)
  - ECD2 (pertuzumab binding domain)
- Unique binding configuration results in multiple mechanisms of action
  - Improved binding, clustering, and receptor internalization and downregulation
  - Inhibition of ligand-dependent and independent proliferation
  - Potent activation of antibody-dependent cellular cytotoxicity

ECD=extracellular domain

ZW25: Unique Binding Configuration Drives Novel Mechanisms of Action

Enhanced tumor cell binding and internalization relative to trastuzumab



h=hour; IHC=immunohistochemistry; MFI=mean fluorescence intensity; nM=nanoMolar

Margetuximab Is a Novel, Immune-Optimized Anti-HER2 mAb Engineered to Enhance Immune System Engagement[1,2]

Trastuzumab

Fab portion

- Binds HER2 with high specificity
- Disrupts signaling that leads to cell proliferation and survival

Fc portion engages immune system

- Binds and activates immune cells

Margetuximab

Fab portion maintains trastuzumab antigen binding properties

- Binds HER2 with high specificity
- Disrupts signaling that leads to cell proliferation and survival

Fc portion engineered to enhance immune system engagement

- Binds and activates immune cells
- **Optimized in margetuximab**
  - **Increases ADCC activation via CD16A**
  - **Decreases immune inhibition via CD32B**

ADCC, antibody-mediated cellular dependent cytotoxicity; CD, cluster of differentiation; Fab, antigen-binding fragment; Fc, fragment crystallizable; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody.
1. Nordstrom JL, et al. *Breast Cancer Res*. 2011;13(6):R123. 2. Stavenhagen JB, et al. *Cancer Res*. 2007;67(18):8882-8890.

Meric-Bernstam et al., ASCO 2018

Conclusions

- Change in First line standard
  - Incorporation of nivolumab/pembrolizumab to chemotherapy
- Change in Adjuvant therapy
  - Nivolumab
- HER2 positive disease
  - Trastuzumab Deruxtecan-third line
- Multiple non-immunotx targets
  - Claudin, DKK, VEGF
- Hitting the target, tumor heterogeneity
- Serial biopsies, liquid biopsies, ctDNA, etc.