2021 ESMO congress

Mini Oral Discussion: LBA52, LBA53, LBA 54, and LBA55

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Friday, 17 September 2021
15 Minutes

DECLARATION OF INTERESTS

Consulting fees and travel funding from

Bristol-Myers Squibb
Merck Serono, RGENIX
Eli Lilly
Daiichi—Sankyo
Pfizer, Bayer
Imugene
Merck
Zymeworks Inc.
Seagen
Basilea Pharmaceutica
AstraZeneca
Michael J Hennessy Associates
Paradigm Medical Communications

Funds for research support from

NCI

Department of Defense

Cycle For Survival

Fred's team

RGENIX

Bayer

Genetech/Roche,

Bristol-Myers Squibb

Eli Lilly

Merck

Immunotherapy and HER2 Inhibition

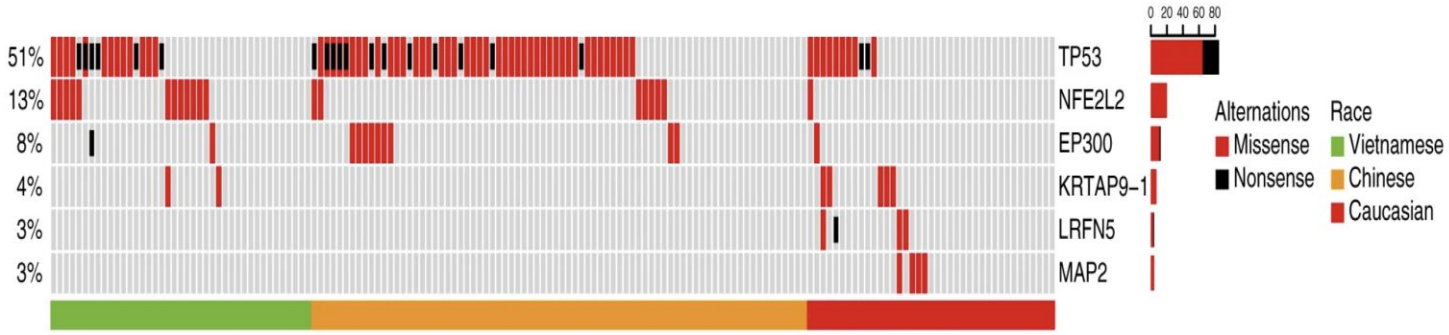
- Randomized Phase III first-line studies of sintilimab (anti-PD-1)/chemotherapy
  - Orient 15-- esophageal SCC
  - Orient 16-- gastric/GEJ adenocarcinoma
- HER2-positive gastric/GEJ adenocarcinoma
  - Phase II first-line study nivolumab/trastuzumab/chemo vs. nivolumab/ipilimumab/trastuzumab
  - Phase II second-line study of T-Dxd in Western patients

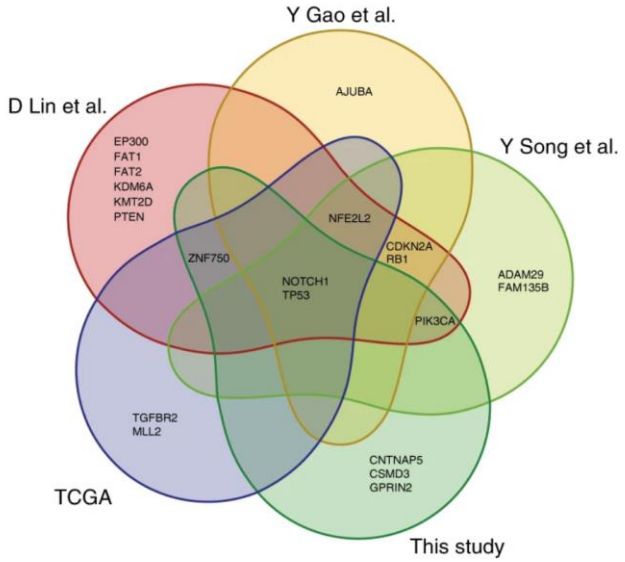
Immunotherapy in Esophageal Squamous Cancer

- First-line pembrolizumab/fluorouracil/platinum FDA approved irrespective of PDL-1
- Nivolumab with ipilimumab or fluorouracil/platinum improves OS vs chemo
- Second-line or beyond FDA approved
  - Pembrolizumab in CPS $\geq$10
  - Nivolumab irrespective of PDL-1

Kojima et al, J Clin Oncol 2020; Kato et al, Lancet Onc 2019; Sun et al, Lancet 2021

Distinct biology of ESCC in East and West





- *TP53*, *EP300*, and *NFE2L2* alterations more common in patients from China
- CSMD3 mutations more common among Chinese patients and associated with better prognosis

Deng J et al. Nature Communications, 2017

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Sintilimab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced or metastatic esophageal squamous cell cancer: First Results of the Phase 3 ORIENT-15 study

Lin Shen[1], Zhihao Lu[2], Junye Wang[3], Yongqian Shu[4], Li Kong[5], Lei Yang[6], Buhai Wang[7], Zhiwu Wang[8], Yinghua Ji[9], Guochun Cao[10], Hu Liu[11], Tongjian Cui[12], Na Li[13], Wensheng Qiu[14], Zhuo Ma[15], Yuling Chen[15], Haoyu Li[15], Xing Sun[15], Yan Wang[15], Hui Zhou[15]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital and Institute, Beijing, China, [2]Department of Gastrointestinal Oncology, Peking University Cancer Hospital & Institute, Beijing, China, [3]Department of Oncology, The Affiliated Hospital of Jining Medical College, Jining, China, [4]Department of Medical Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China, [5]Special Needs Ward, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, [6]Department of Medical Oncology, Nantong Cancer Hospital, Nantong, China, [7]Department of Medical Oncology, Northern Jiangsu People's Hospital, Affiliated Hospital to Yangzhou University, Yangzhou, China, [8]Department of Radiotherapy and Chemotherapy, Tangshan People Hospital, Tangshan, China, [9]Department of Medical Oncology, The First Affiliated Hospital of Xinxiang Medical University, Xinxiang, China, [10]Department of Oncology, Jiangsu Cancer Hospital, Nanjing Medical University, Nanjing, China, [11]Department of Medical Oncology, Anhui provincial Cancer Hospital, University of Science and Technology of China, Hefei, China, [12]Department of Oncology, Fujian Provincial Hospital, Fuzhou, China, [13]Department of Medical Oncology, Suining Central Hospital, Suining, China, [14]Department of Medical Oncology, The Affiliated Hospital of Qingdao University, Qingdao, China, [15]Medical Oncology, Innovent Biologics, Inc., Suzhou, China, [16]Biostatistics, Innovent Biologics, Inc., Suzhou, China

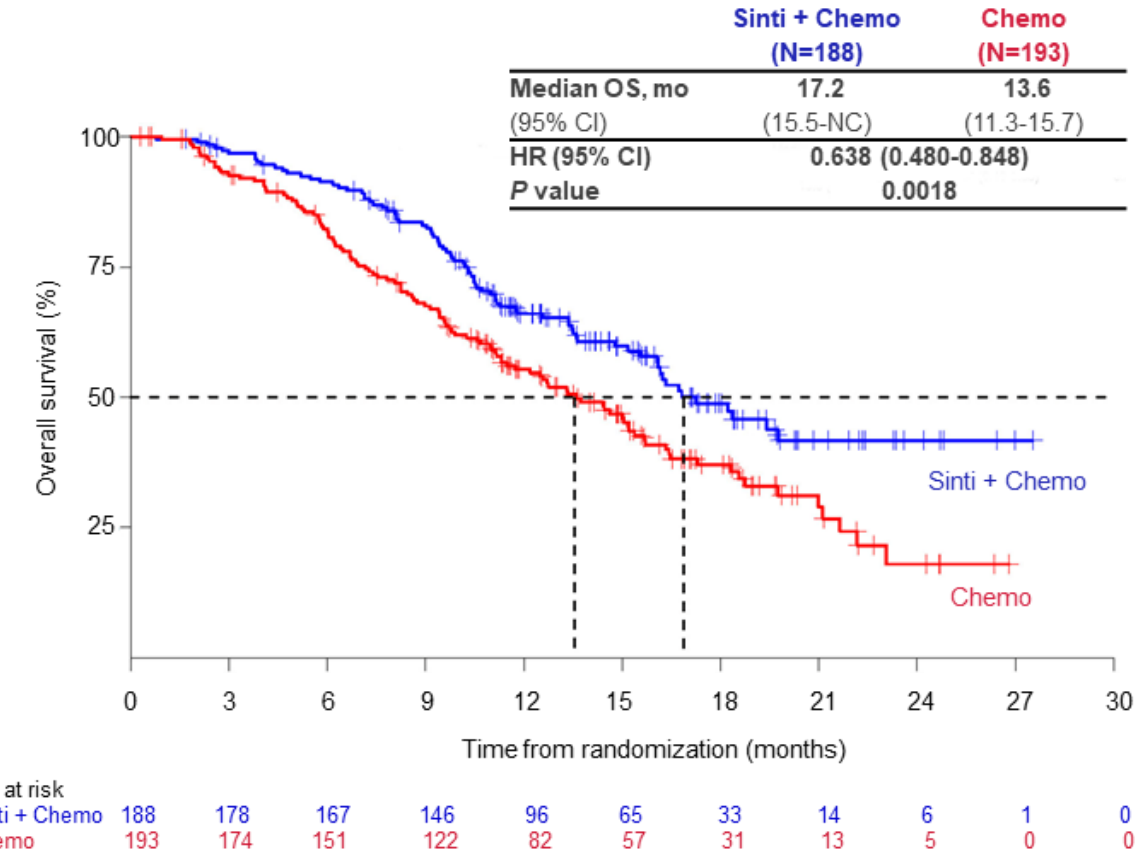
ORIENT-15 notable facts

- SCC patients from China-paclitaxel/cisplatin (PC)
- TPS ≥10 36% ; CPS ≥10 (22C3 clone) 57% similar OS HR
- Dual primary endpoints OS in CPS ≥10 and ITT- both met
- No new safety signals 59% Grade 3-4 AEs w/ Sinti/PC

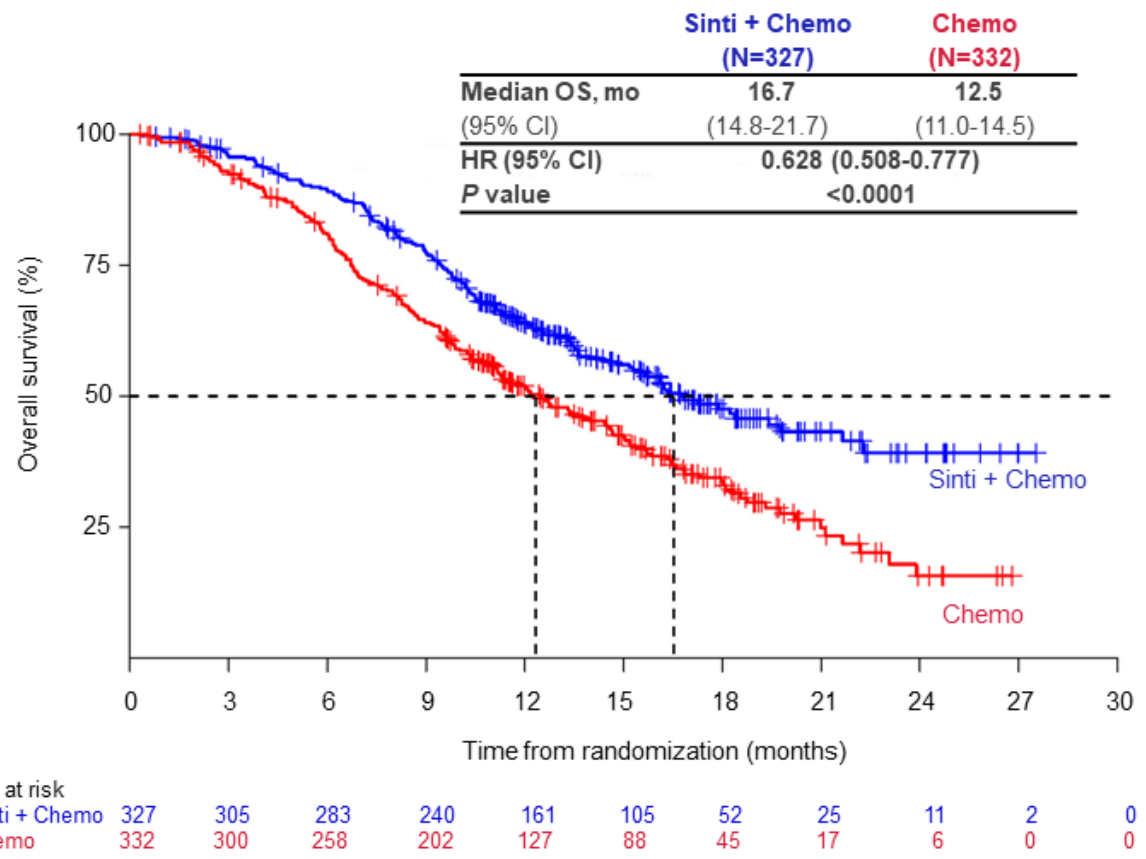
Category	Subgroup	No. events/patients		HR (95% CI)
		Sinti+ Chemo	Chemo	
PD-L1 expression	CPS <10	66/139	90/139	0.617 (0.448-0.849)
	CPS ⩾10	82/188	113/193	0.638 (0.480-0.848)
	TPS <10%	96/208	124/213	0.675 (0.516-0.882)
	TPS ⩾10%	52/119	79/119	0.547 (0.384-0.778)

ORIENT-15 Overall survival

PD-L1 CPS ≥10



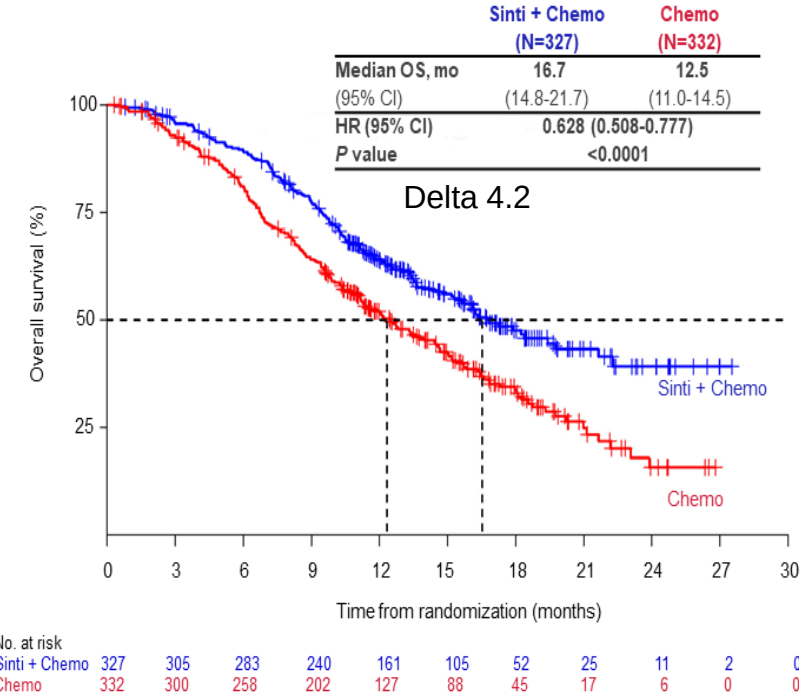
All patients



- Superior OS benefit with Sinti + Chemo versus Chemo in PD-L1 CPS≥10 and all randomized patients.

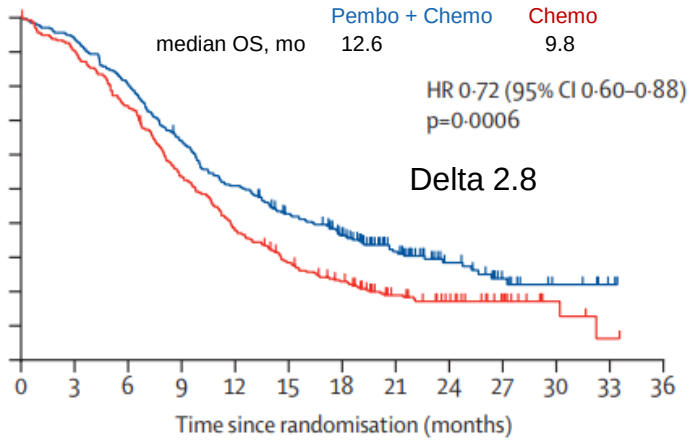
Overall survival ORIENT-15, KN 590 and CM 648

ORIENT-15 ITT



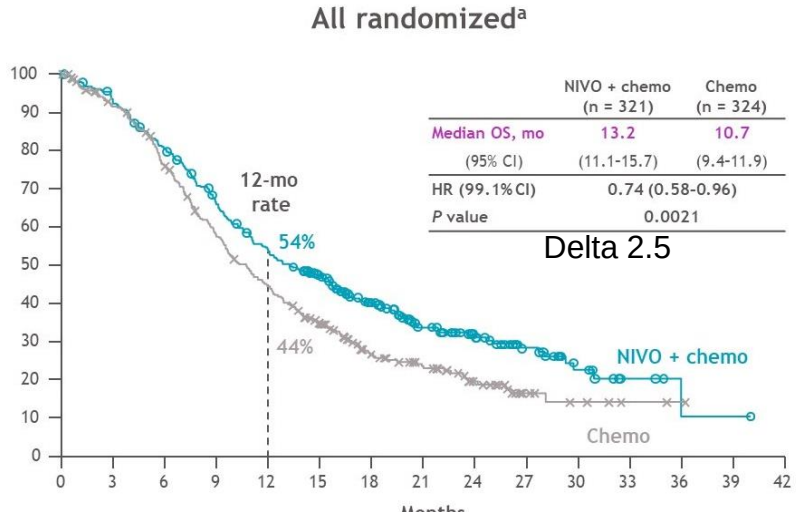
- Control arm 2 mos better
- Larger delta
- Irrespective of PDL1?

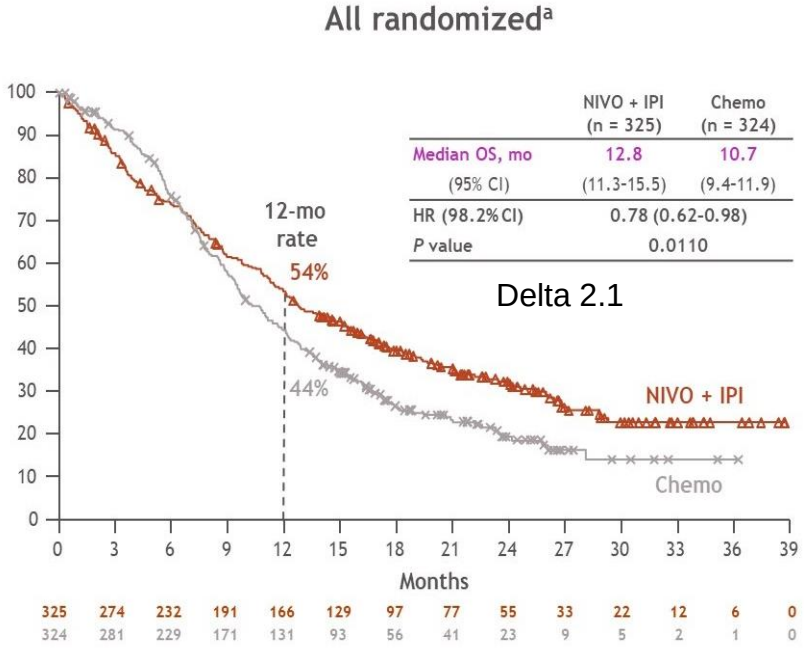
KN 590 ITT SCC patients



Subgroup	Overall Survival N, median OS* (95% CI), mo HR (95% CI)†	
	P + C	C
ESCC CPS <10	N = 121 10.5 (9.2-13.5)	N = 126 11.1 (9.1-12.4)
	0.99 (0.74-1.32)	

CM 648 ITT





Sen L et al.LBA52, ESMO 2021; Jong Mu Sum et al. Lancet, 2021; Chau I et al. LBA 4001, ASCO 2021

Immunotherapy in Esophageal SCC

	Keynote 590	Checkmate 648	Orient 15	ESCORT-1st
Design	FU/cis /PD-1 vs FU/Cis	PD-1/CTLA-4 vs FU/Cis; FU/Cis/PD-1 vs FU/Cis	Paclitaxel/cis /PD-1 vs paclitaxel/cis	paclitaxel/cis/PD-1 vs paclitaxel/cis
Major enrollment	53% Asian	70% Asian	China	China
PDL1 testing	CPS ≥10 51%	CPS ≥10 NA/ TPS ≥10 30%	CPS ≥10 58%/ TPS ≥10 36%	TPS ≥10 34%
OS HR ITT; CPS ≥10; CPS <10	0.73; 0.62; 0.86	TPS ITT : 0.78; and 0.74	0.62; 0.61; 0.63	TPS 0.70*; 0.52*; 0.78*
ITT PFS	0.65	1.26; and 0.81	0.55	0.56
ITT ORR	45% vs 29%	28% vs 27% and 47% vs 27%	66% vs 45%	72% vs 62%
Grade 3-5 SAE	86% vs 83%	34% vs 37% and 49% vs 37%	60% vs 54%	63% vs 68%

Sun JM et al. Lancet 2021. Chau I et al. LBA 4001, ASCO 2021; Shen L et al.LBA52, ESMO 2021; Xu R et al. LBA4000, ASCO 2021.

Immunotherapy in EG adenocarcinoma

- Nivolumab with chemotherapy approved in the United States for 1st-line treament irrespective of PD-L1 status[1]
- Pembrolizumab, trastuzumab, and chemotherapy approved in the United States for HER2-positive disease[2]
- Nivolumab approved in Asia irrespective of PD-L1 status for ≥ 3rd-line treament[3]
- Pembrolizumab approval for ≥ 3rd-line treatment in the United States to be withdrawn (announced in July 2021)[4]
- Pembrolizumab approved in TMB ≥ 10 mut/Mb (United States) or MSI-H tumors (United States and Japan)[2,5]

1. OPDIVO (nivolumab) [package insert]. Princeton, NJ: Bristol Myers Squibb; 2021. 2. KEYTRUDA (pembrolizumab) [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2021. 3. Högner A, Thuss-Patience P. *Pharmaceuticals (Basel).* 2021;14:151. 4. Merck (press release, July 1, 2021). Accessed July 20, 2021. 5. Merck (press release, August 24, 2020). Accessed July 20, 2021.

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Sintilimab plus chemotherapy (chemo) versus chemo as the first-line treatment for advanced gastric or gastroesophageal junction (G/GEJ) adenocarcinoma (ORIENT-16)

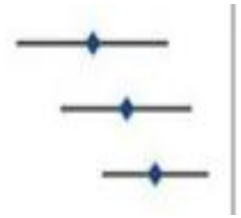
Jianming Xu*, Haiping Jiang, Yueyin Pan, Kangsheng Gu, Sundong Cang, Lei Han, Yongqian Shu, Jiayi Li, Junhui Zhao, Hongming Pan, Suxia Luo, Yanru Qin, Qunyi Guo, Yuxian Bai, Yang Ling, Yingmei Guo, Ziran Li, Ying Liu, Yan Wang, Hui Zhou

*, presenting author, MD, The Fifth Medical Center, Chinese PLA General Hospital

ORIENT-16 notable facts

- Gastric/GEJ, no esophagus adeno (Gastric do better than GEJ/esophagus)
- Dual primary endpoints OS in CPS ≥5 and ITT - both met
- XELOX/Sinti ITT mOS 15.2 mos HR .76; mPFS 7.1 HR .63; ORR 58%
- No new safety signals 59% Grade 3-4 AEs w/ XELOX/Sinti

Category	Subgroup	Sin + Chemo (N)	Chemo (N)	HR (95% CI)	HR (95% CI)
PD-L1 expression	CPS ≥10	146	142	0.56 (0.41-0.77)	
	CPS ≥5	197	200	0.64 (0.49-0.84)	
	CPS ≥1	275	271	0.73 (0.58-0.90)	



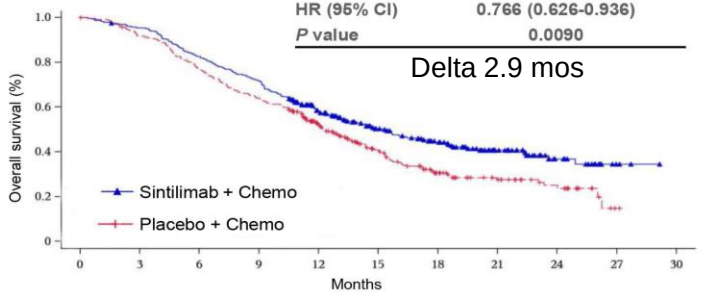
Overall Survival ORIENT-16 and CM 649

ORIENT-16 ITT

All Randomized

	Sin + Chemo (N=327)	Chemo (N=323)
Median OS, mo (95% CI)	15.2 (12.9-18.4)	12.3 (11.3-.13.8)
HR (95% CI)	0.766 (0.626-0.936)	
P value	0.0090	

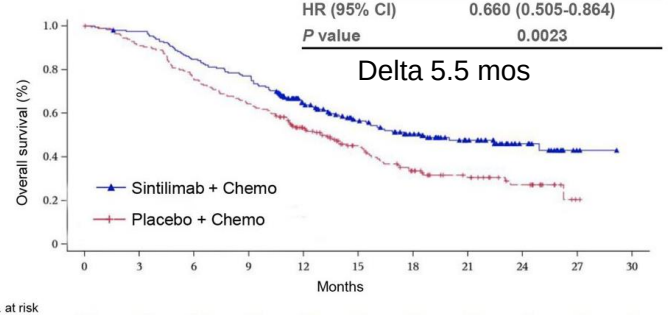
Delta 2.9 mos



PD-L1 CPS ≥5

	Sin + Chemo (N=197)	Chemo (N=200)
Median OS, mo (95% CI)	18.4 (14.6-NC)	12.9 (11.1-.15.4)
HR (95% CI)	0.660 (0.505-0.864)	
P value	0.0023	

Delta 5.5 mos



No. at risk

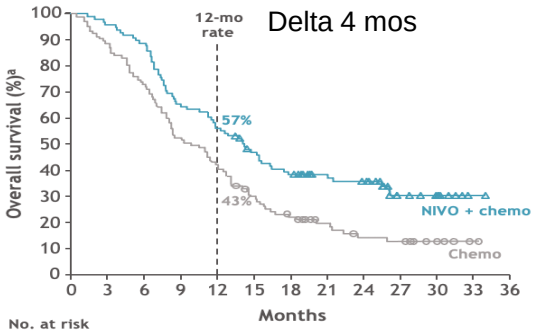
Sin + chemo	197	191	166	151	106	79	61	39	18	2	0
Chemo	200	181	150	128	91	60	39	26	16	1	0

CM 649 CHINA

All randomized

	NIVO + chemo (n = 99)	Chemo (n = 109)
Median OS, mo	14.3	10.3
(95% CI)	(11.5-17.5)	(8.1-12.1)
HR (95% CI)	0.61 (0.44-0.85)	

Delta 4 mos



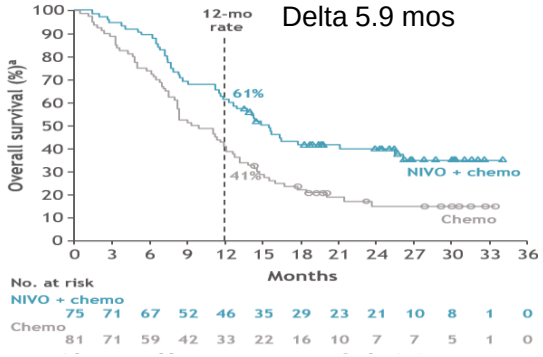
No. at risk

NIVO + chemo	99	95	88	65	56	44	36	29	26	12	9	1	0
Chemo	109	96	79	57	46	31	22	15	10	9	5	1	0

PD-L1 CPS ≥ 5

	NIVO + chemo (n = 75)	Chemo (n = 81)
Median OS, mo	15.5	9.6
(95% CI)	(11.9-25.5)	(8.0-12.1)
HR (95% CI)	0.54 (0.36-0.79)	

Delta 5.9 mos



No. at risk

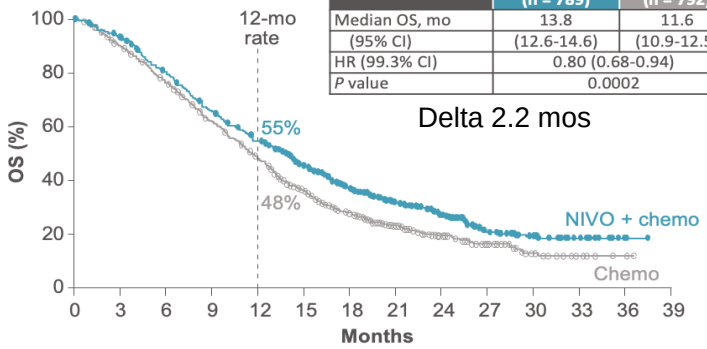
NIVO + chemo	75	71	67	52	46	35	29	23	21	10	8	1	0
Chemo	81	71	59	42	33	22	16	10	7	7	5	1	0

CM 649 ITT

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	

Delta 2.2 mos

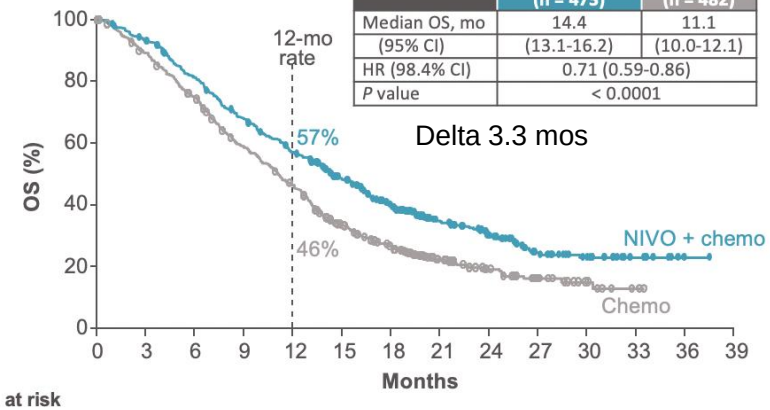


789	731	621	506	420	308	226	147	100	49	34	14	2	0
792	697	586	469	359	239	160	94	59	35	15	7	2	0

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	

Delta 3.3 mos



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

Xu et al, ESMO 2021; Shen et al, AACR 2021; Janjigian et al, Lancet 2021

Immunotherapy in EG adenocarcinoma

	Keynote 62	Checkmate 649	Orient 16
Design	Chemo/PD-1 vs chemo PD-1 vs chemo	Chemo/PD-1 vs chemo	Chemo/PD-1 vs chemo
Major enrollment	US/ Europe/ Australia 58%	US 17%, Asia 23%, rest 60%	China
CPS ≥ 5	NA (37% CPS ≥ 10)	60%	62%
OS HR ITT; CPS ≥ 5; CPS ,<5	NA; CPS ≥1 0.85*; NA; NA and 0.91; NA;NA	0.80; 0.71; 0.94	0.76; 0.66; NA
ITT PFS	0.84* and 1.66*	0.77	0.63
ITT ORR	49% vs 37% and 15% vs 37%	58% vs 46%	58%/vs 48%
Grade 3-5 AEs	73% vs 69% and 17% vs 69%	60% vs 44%	60% vs 52%

Shitara K et al. JAMA Oncol, 2020.; Janjigian Y et al. Lancet, 2021. Xuet al. ESMO 2021, LBA53.

Conclusions: Sintilimab studies

- Well-executed large multicenter randomized phase III studies
- Solidifies the importance of anti-PD-1/chemo in first-line setting
- PDL1 CPS preferred over TPS in SCC and adenocarcinoma
- The role for Sinti in first-line setting globally is TBD
- Intriguing data w/ paclitaxel/cisplatin backbone in SCC

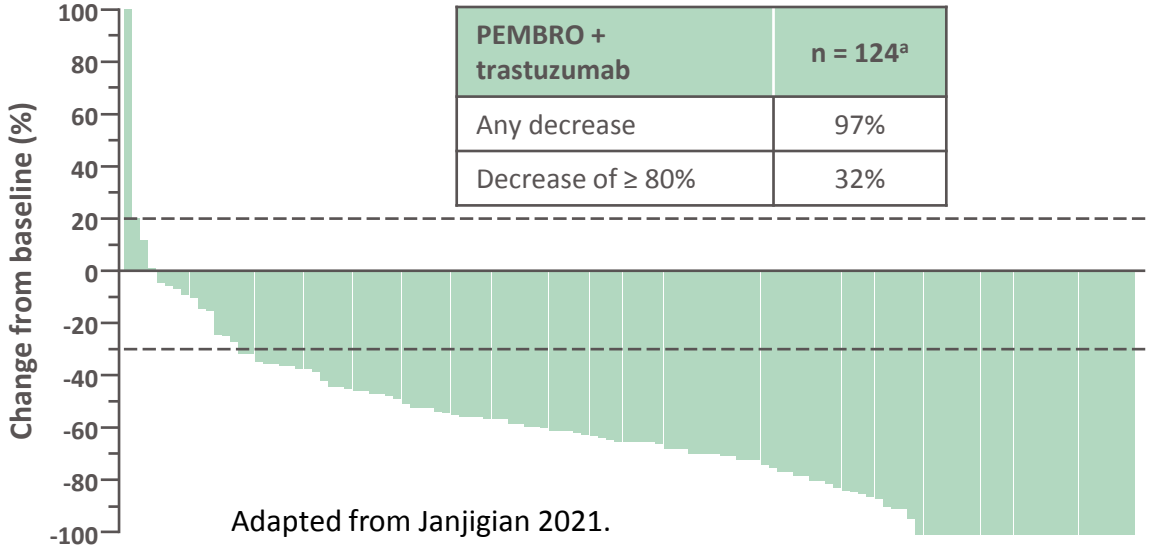
HER2 inhibition in EG adenocarcinoma

- Up to 20-30% HER2+ positive
- First-line trastuzumab/chemotherapy FDA approved mOS 13.8mos ORR 47%
- 30% of GEJ HER2+ tumors with co-alterations of the RTK/RAS/PI3K pathway– intrinsic resistance
- HER2 inhibition alone in 1st line insufficient to overcome intrinsic resistance- several negative studies (LOGIC, JACOB, HELOISE)
- Pembrolizumab/Trastuzumab/chemotherapy FDA approved in 1st line
- Trastuzumab deruxtecan (T-DXd) is FDA approved after trastuzumab failure based on Destiny Gastric 01

Bang Y et al. *Lancet*. 2010;376:687-697 ; Janjigian YY et al. *Cancer Discov.* 2018;8:49-58.*Hecht JR et al. J Clin Oncol, 2016. Tabernero J et al. Lancet Oncol, 2018. Shah MA et al. J Clin Oncol, 2017; Janjigian et al, ASCO 2021; Shitara et al. NEJM 2020*

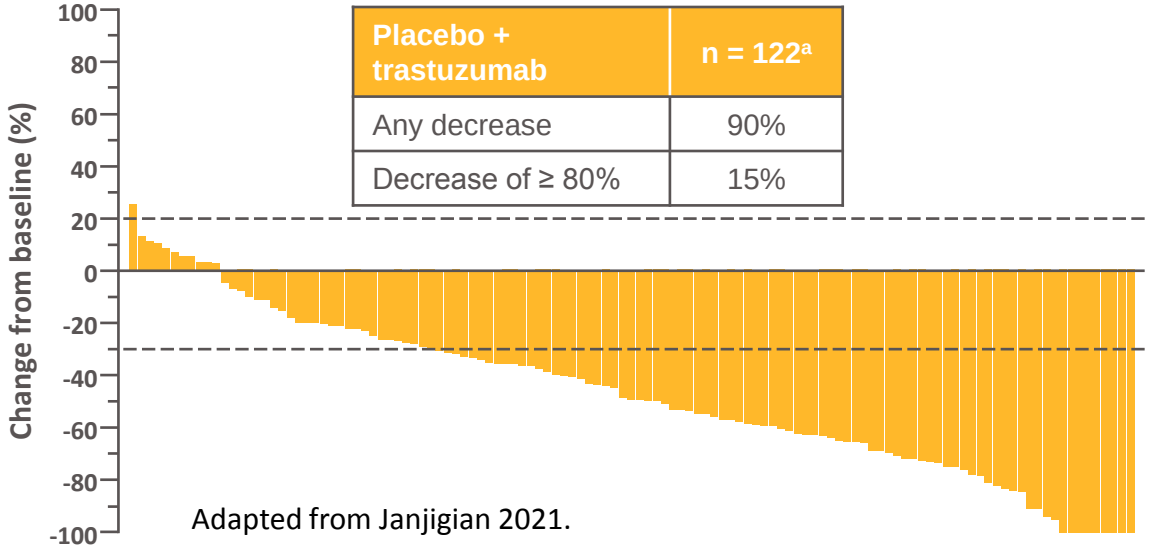
KEYNOTE-811 phase 3 study

Pembrolizumab/trastuzumab/chemotherapy FDA approved May 2021 in HER2+ disease



PEMBRO + trastuzumab	n = 124[a]
Any decrease	97%
Decrease of ≥ 80%	32%

Adapted from Janjigian 2021.



Placebo + trastuzumab	n = 122[a]
Any decrease	90%
Decrease of ≥ 80%	15%

Adapted from Janjigian 2021.

ORR and DCR, % (95% CI)	PEMBRO + trastuzumab (n = 133)	Placebo + trastuzumab (n = 131)
ORR	74.4%	51.9%
ORR Difference[b]	22.7% (11.2-33.7) *P* = 0.00006	

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

Duration of Response	PEMBRO + trastuzumab (n = 133)	Placebo + trastuzumab (n = 131)
Median[c]	10.6 mo	9.5 mo
Range	1.1+ to 16.5+	1.4+ to 15.4+
≥ 6-mo duration[c]	70.3%	61.4%
≥ 9-mo duration[c]	58.4%	51.1%

- Grade 3-5 AE rates did not differ between treatment arms (57%)

[a]Participants with RECIST-measurable disease at baseline and ≥1 evaluable post-baseline measurement. [b]Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. [c]Kaplan-Meier estimation. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Janjigian YY et al. Presented at ASCO 2021. Abstract 4013.

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Ipilimumab or FOLFOX in combination with Nivolumab and Trastuzumab in previously untreated HER2 positive Esophago Gastric Adenocarcinoma – the randomized AIO INTEGA trial.

Alexander Stein

Hematology-Oncology Practice Hamburg-Eppendorf

University Cancer Center Hamburg

AIO-Intega notable facts

- Relatively large phase II (n=82) with translation research
- Chemotherapy free arm nivo1/ipi3/trastuzumab
- Patients enrolled irrespective PDL1 status; PDL1 is not predictive
- Trast/Nivo/FOLFOX ORR 56% (74% in Phase III w/ pembro/traz/chemo))
- ctDNA decline after 1st cycle predictive of outcome mOS 8.5 vs. 31.2 months
- Grade ≥ 3 TRAE higher with chemo by 20% , QOL favored the chemotherapy arm likely due to better efficacy

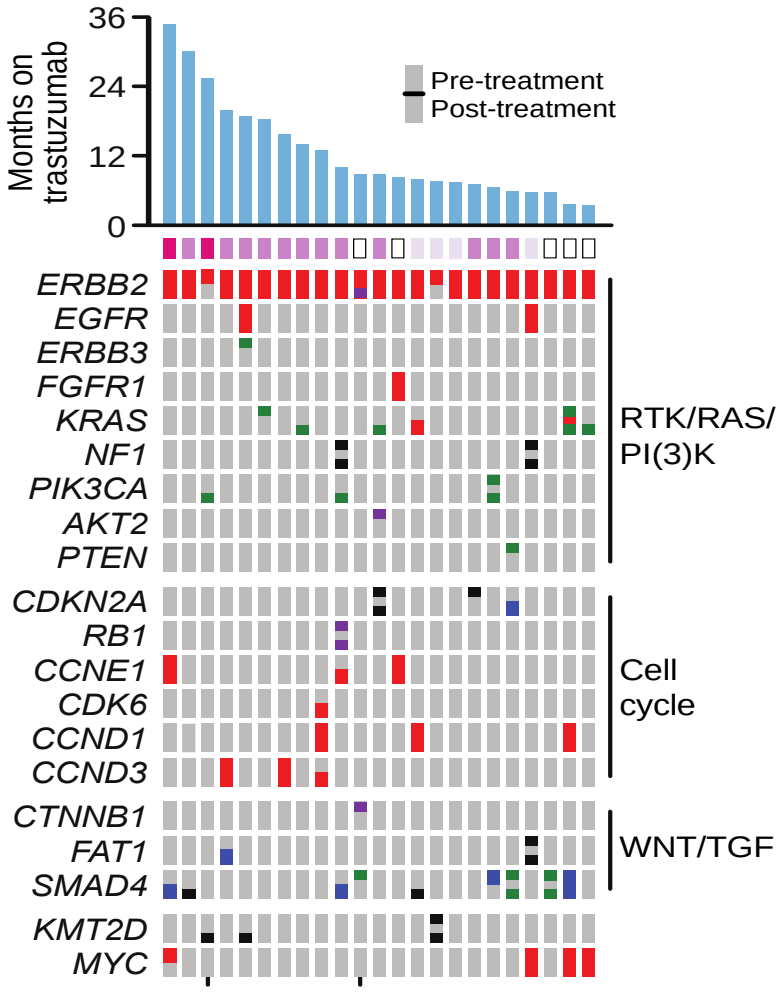
	PEMBRO + trastuzumab + capecitabine + oxaliplatin
ORR, n (%; 95% CI)[a]	32 (91; 78-97)
Best response, n (%)[a] CR PR SD PD	 6 (17) 26 (74) 3 (8) 0
Disease control rate, %	100
Median PFS, months 6-month rate, %	13.0 75
Median OS, months 12-month rate, %	27.3 80

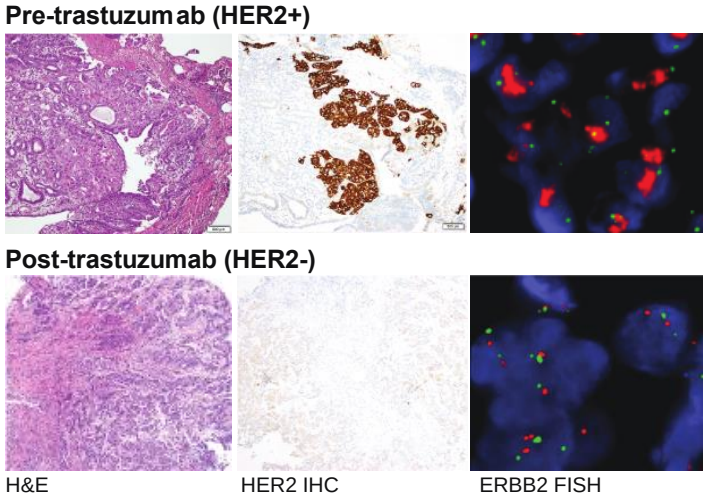
	All (n=88) ITT AIO-Intega	
	Trast/Nivo/ Ipi	Trast/Nivo/FOLFOX
ORR	32%	56%
mPFS	3.2 mo	10.7 mo
PFSR@12	15%	37%
mDOR	5.8 mo	9.2 mo
mOS	16.4 mo	21.8 mo
OSR@12	57%	70%

[a]Among patients with evaluable disease (n = 35).
Janjigian YY et al. *Lancet Oncol*. 2020;21:821-831.

ACQUIRED TRASTUZUMAB RESISTANCE

Loss of *ERBB2* and KRAS and PIK3CA ALTERATIONS IN 20% OF CASES





Janjigian et al *Cancer Discovery* 2017

2021 ESMO congress

Primary Analysis of a Phase 2, Open-Label, Single Arm Trial of Trastuzumab Deruxtecan in Western Patients With HER2-Positive Unresectable or Metastatic Gastric or Gastroesophageal Junction Cancer on or After a Trastuzumab-containing Regimen

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On behalf of the DESTINY-Gastric02 investigators

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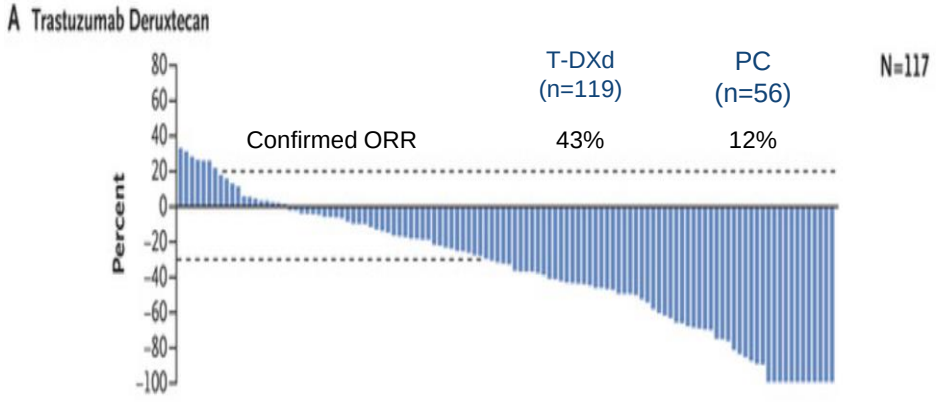
Destiny West Gastric02 notable facts

- 66% GEJ primary (in East Gastric01 86% gastric)
- Re-biopsy for HER2 mandated and centrally reviewed on all (only 30% in Gastric 01)
- Primary endpoint confirmed ORR 38%; median PFS 5.5 months (27% ORR, PFS 4.2 Ramuciurmab/paclitaxel)
- No new safety signals; 7.6% ILD; no Grade 3-4 ILD events, one Grade 5
- 27% Grade $\geq$ 3 TRAE (also favorably compared in Ramucirumab/paclitaxel)

T-Dxd after trastuzumab progression

DESTINY-Gastric01 ≥3rd line in East



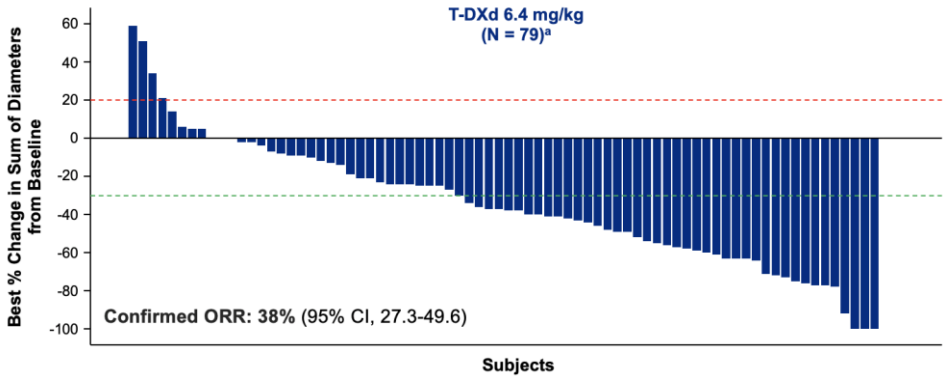
	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) mo
Trastuzumab Deruxtecan	62/125	12.5 (9.6–14.3)
Physician's Choice of Chemotherapy	39/62	8.4 (6.9–10.7)

Hazard ratio for death, 0.59 (95% CI, 0.39–0.88)
P=0.01

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI) mo
Trastuzumab Deruxtecan	73/125	5.6 (4.3–6.9)
Physician's Choice of Chemotherapy	36/62	3.5 (2.0–4.3)

Hazard ratio for disease progression or death, 0.47 (95% CI, 0.31–0.71)

DESTINY-Gastric02 – 2nd line in West



PFS 5.5 DOR 8.1

Shitara K et al. NEJM, 2020.

Conclusions: HER2 in EG adenocarcinoma

- First-line trastuzumab/anti-PD1/chemotherapy important option
  - CTLA4 blockade w/ dual HER2/PD-1 inhibition not enough
- Second-line HER2 remains a viable therapeutic target
  - T-Dxd has similar ORR in 2nd Western patients (despite mandatory biopsies) and $\geq$3rd line Eastern patients
  - Co-occurring activation in GEJ/E CIN tumors likely driving the resistance

Thank you for your attention

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