Second-line and Beyond Therapies for Advanced Upper GI Cancers

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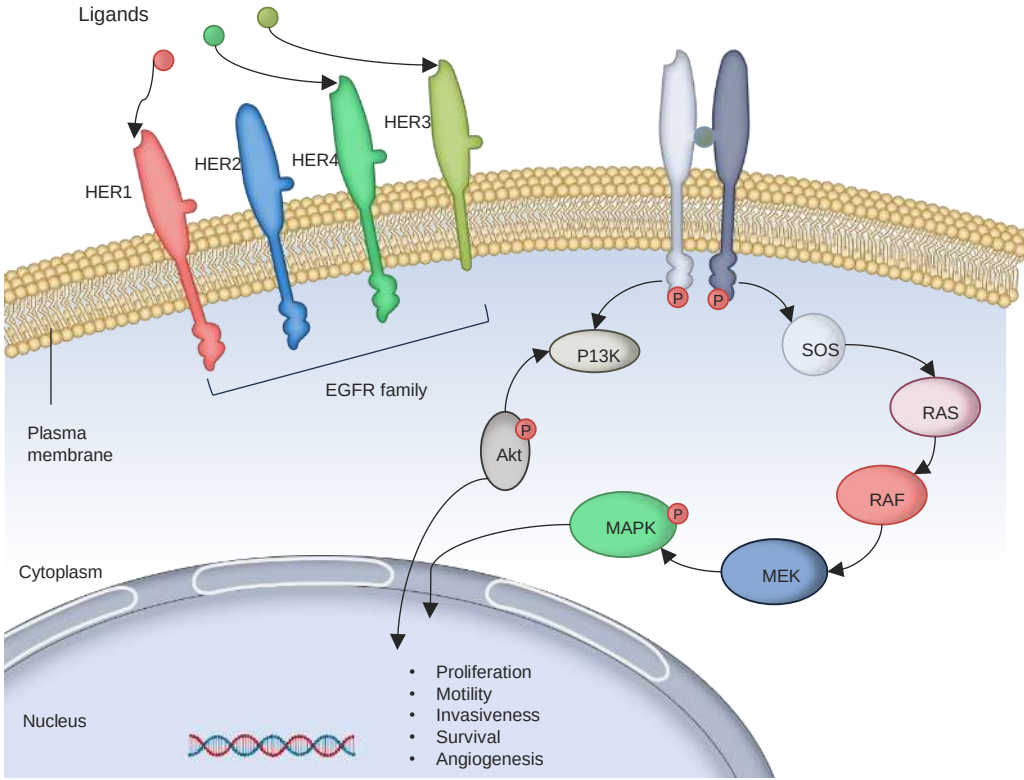
ERBB Family: Targeting HER2 and HER3

- Human epidermal growth factor receptor family includes:
  - EGFR
  - HER2 (ERBB2)
  - HER3 (ERBB3)
  - HER4 (ERBB4)
- Common structural features
- Aberrantly activated in multiple cancers
- Serves as drug targets and biomarkers for precision oncology



Adapted from Ross JS. *Drug News Perspect*. 2009;22(2):93-106. Adapted from Reinholz MM et al. *Lancet Oncol*. 2009;10(3):267-77.

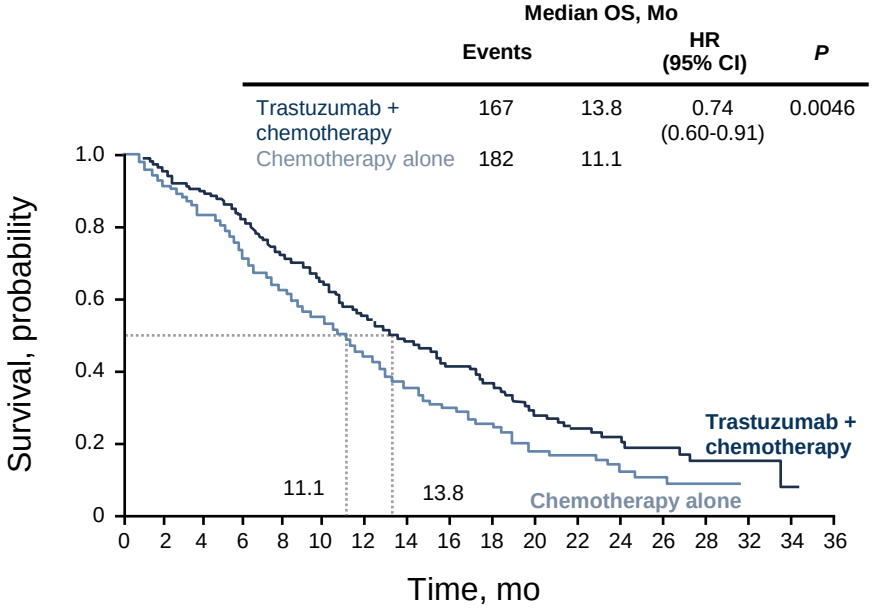
Progress in Validating HER2-Directed Therapy in GI Malignancies

Agent	Regulatory Status	Indicated for Patients With:
Trastuzumab	**Approved in the US and EU**	HER2-overexpressing metastatic gastric/GEJ cancers
Trastuzumab + pembrolizumab	**Approved in the US and EU**	PD-L1 positive HER2-expressing gastric/GEJ cancers
Trastuzumab deruxtecan (T-DXd)	**Approved in the US, EU, and Japan**	Locally advanced or metastatic HER2+ gastric/GEJ adenocarcinoma who have received a prior trastuzumab-based regimen

GI = gastrointestinal.

ToGA: Chemotherapy ± Trastuzumab as First-Line Therapy in HER2+ mGC

- Randomized phase 3 study of patients with HER2+ gastric or GEJ cancer
- 594 patients randomly assigned to chemotherapy (fluoropyrimidine + platinum) with or without trastuzumab
- Significant improvement in OS in HER2+ mGC with addition of trastuzumab to chemotherapy led to approval in many countries

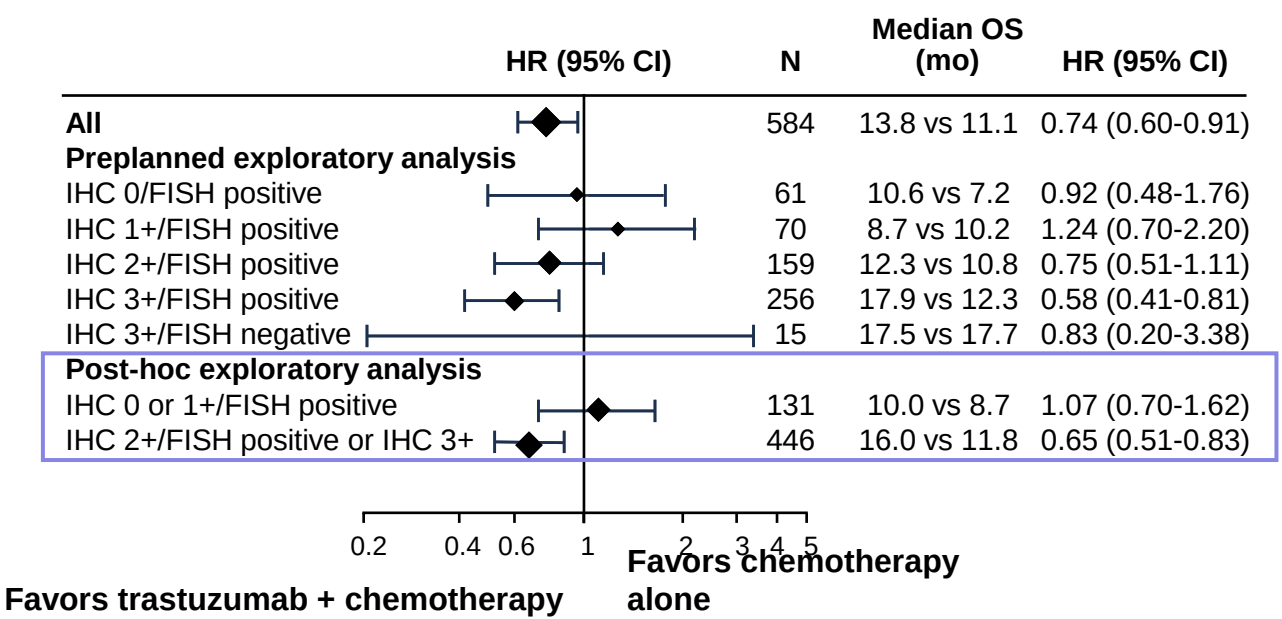


mGC = metastatic gastric cancer

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

ToGA: HER2 Subgroup Analysis

- Overall survival benefit of trastuzumab appeared to vary by HER2 subgroup (best for HER2 3+ and *ERBB2* amplification)



Trastuzumab Regulatory Approvals

- US: IHC 3+ and/or FISH+ tumors (2010)
- Europe: IHC 2+/FISH+ or IHC 3+ (2022)

FISH = fluorescence in situ hybridization

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

Negative Phase 3 Studies in Advanced Gastric/GEJ Cancers

First-Line Studies

- **JACOB**: capecitabine/cisplatin/trastuzumab ± pertuzumab (N=780)
  - OS: 17.5 vs 14.2 mo (HR: 0.84; *P*=0.057)
- **HELOISE**: capecitabine/cisplatin + 2 dose levels of trastuzumab (N=400)
- **LOGiC**: capecitabine/oxaliplatin ± lapatinib (N=545)
  - No difference in OS (12.2 vs 10.5 mo; HR: 0.91)

Second-Line Studies

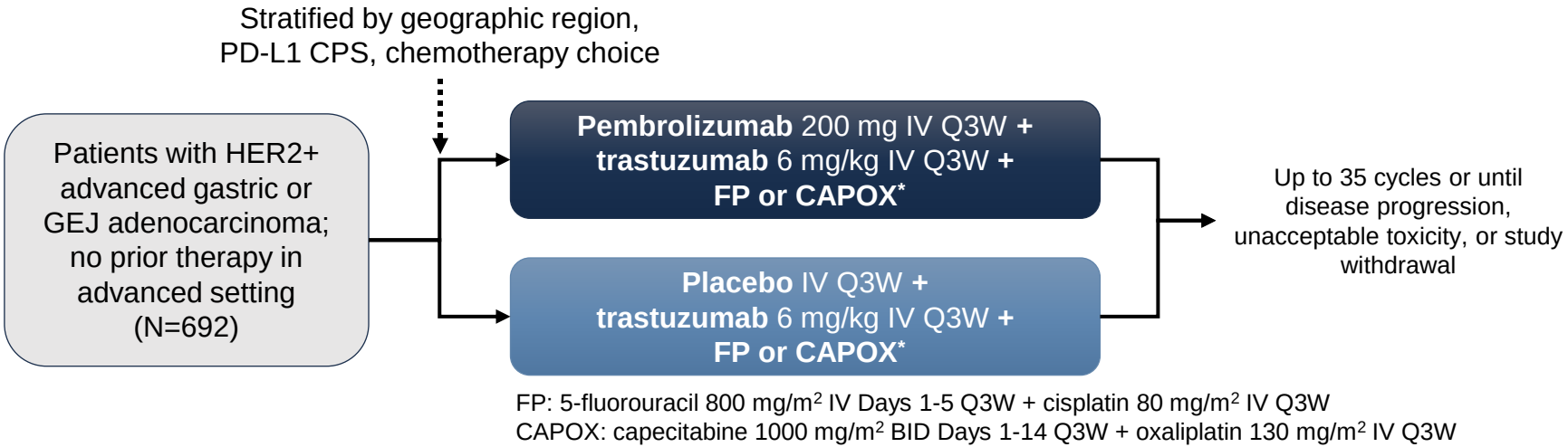
- **TyTAN**: paclitaxel ± lapatinib (N=261)
- **GATSBY**: paclitaxel or docetaxel vs T-DM1 (N=415)
- **T-ACT**: paclitaxel ± trastuzumab (N=91)

T-DM1 = ado-trastuzumab emtansine

Tabernero J et al. *Lancet Oncol.* 2018;19(10):1372-84. Shah MA et al. *J Clin Oncol.* 2017;35(22):2558-67. Hecht JR et al. *J Clin Oncol*. 2016;34(5):443-551. Satoh T et al. *J Clin Oncol*. 2014;32(19):2039-49. Thuss-Patience PC et al. *Lancet Oncol*. 2017;18(5):640-53. Makiyama A et al. *J Clin Oncol*. 2020;38(17):1919-27.

KEYNOTE-811: Pembrolizumab + Trastuzumab + Chemotherapy for First-Line Treatment of HER2+ mGC

- **Randomized, double-blind, placebo-controlled phase 3 study**



FP: 5-fluorouracil 800 mg/m^2 IV Days 1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W
CAPOX: capecitabine 1000 mg/m^2 BID Days 1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W

- **Primary endpoints**: OS, PFS per RECIST v1.1 by BICR
- **Secondary endpoints**: ORR and DOR per RECIST v1.1 by BICR, safety

*Trastuzumab 8 mg/kg loading dose.

BID = twice a day; DOR = duration of response; IV = intravenous; Q3W = every 3 weeks; RECIST = response evaluation criteria in solid tumors.

Janjigian Y et al. *Nature*. 2021;600(7890):727-30.

KEYNOTE-811: Pembrolizumab + Trastuzumab + Chemotherapy for First-Line Treatment of HER2+ mGC

	Efficacy Population*	
Outcome	**Pembrolizumab (n=133)**	**Placebo (n=131)**
ORR, % (95% CI)	**74.4 (66.2-81.6)**	**51.9 (43.0-60.7)**
ORR difference	**22.7 (11.2-33.7); *P*=0.00006**	
DCR, % (95% CI)	96.2 (91.4-98.8)	89.3 (82.7-94.0)
Best response, n (%)		
• 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)
DOR	(n=99)	(n=68)
• Median, mo (range)	10.6 (1.1+ to 16.5+)	9.5 (1.4+ to 15.4+)
• ≥6-mo duration, %	70.3	61.4
• ≥9-mo duration, %	58.4	51.1

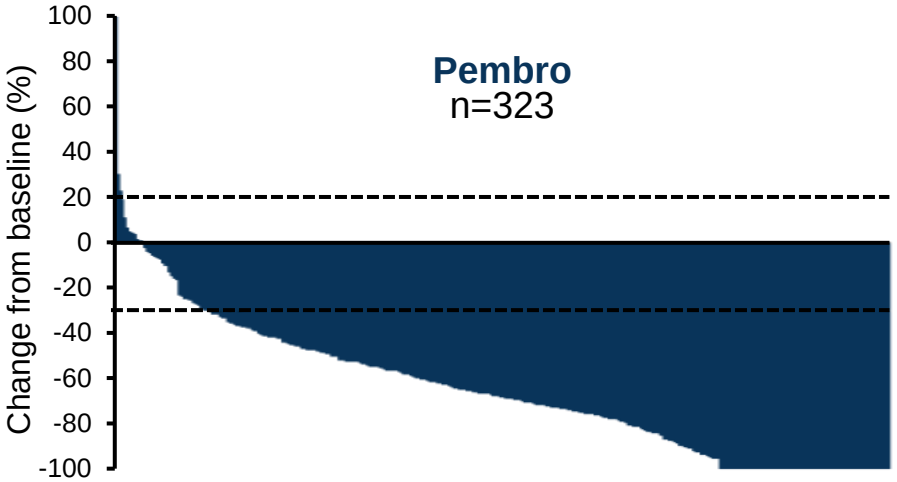
FDA approved: May 2021

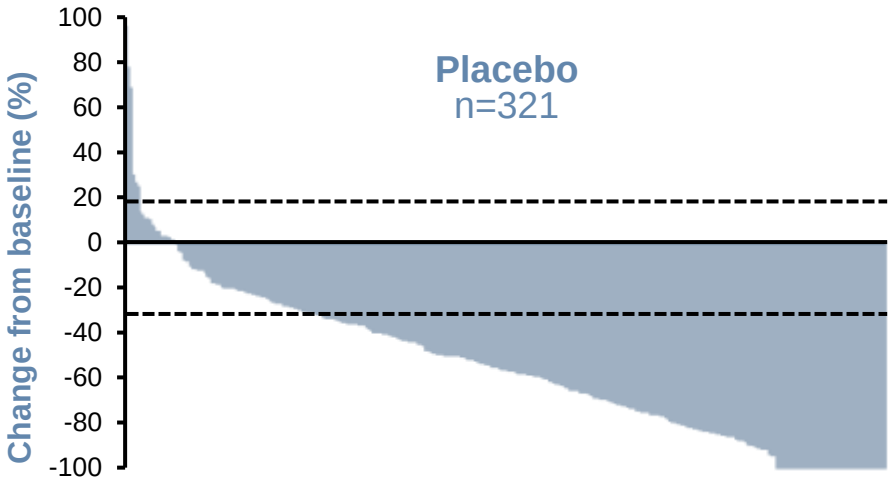
*Efficacy analysis: first 264 patients enrolled; safety analysis: 433 patients who received ≥1 dose of study medication.
CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease
Janjigian Y et al. *Nature*. 2021;600(7890):727-30.

KEYNOTE-811: Antitumor Response on Pembrolizumab/Trastuzumab/Chemotherapy

Best Response, n (%)	Pembro N=350	Placebo N=348
CR	**58 (17)**	**39 (11)**
PR	**196 (56)**	**170 (49)**
SD	67 (19)	95 (27)
PD	19 (5)	23 (7)
NE or NA	10 (3)	21 (6)

Response and Duration	Pembro N=350	Placebo N=348
ORR, % (95% CI)	73 (68-77)	60 (55-65)
DCR, % (95% CI)	92 (88-94)	87 (83-91)
DOR, median (range), mo	11.3 (1.1+ to 49.7+)	9.5 (1.4+ to 48.7+)

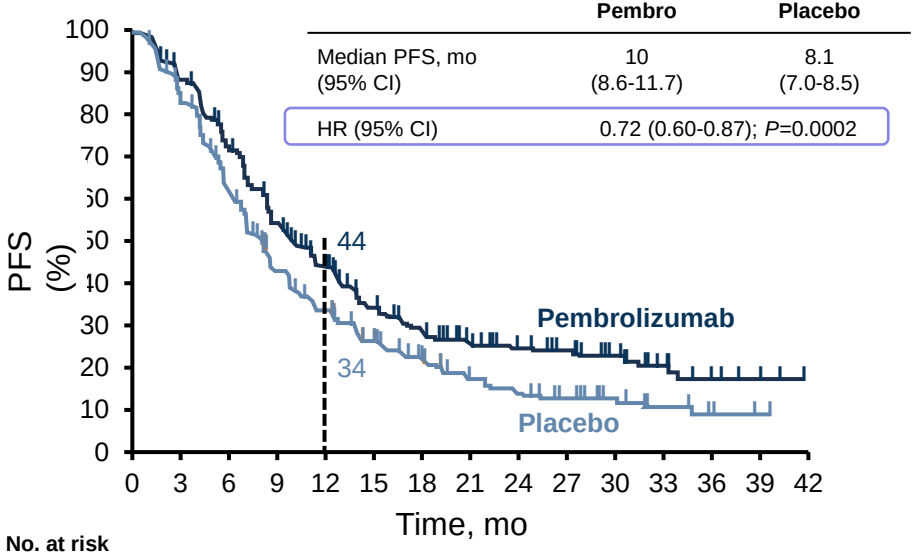




Janjigian Y et al. *Lancet*. 2023;402(10418):2197-208.

Key Efficacy Data From KEYNOTE-811[1]

All Patients

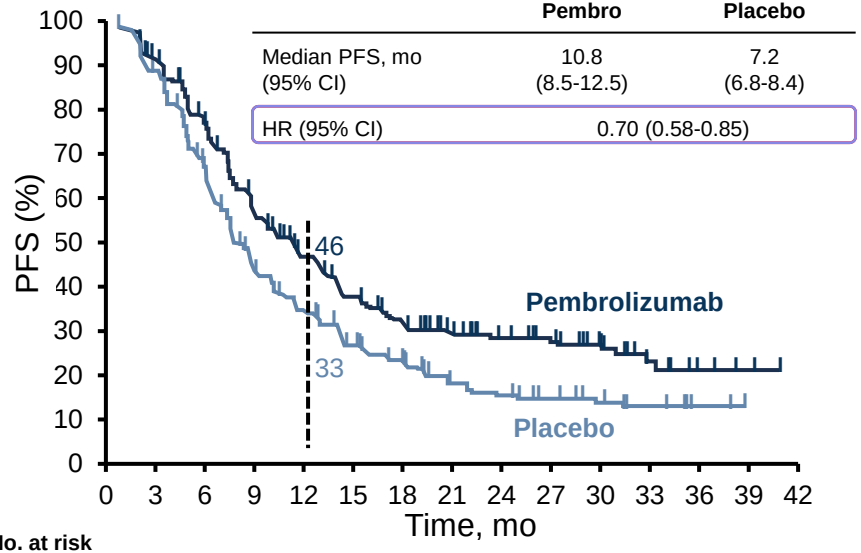


	Pembro	Placebo
Median PFS, mo (95% CI)	10 (8.6-11.7)	8.1 (7.0-8.5)
HR (95% CI)	0.72 (0.60-0.87); *P*=0.0002	

No. at risk

Pembro	350	296	234	171	129	90	65	50	42	34	26	14	5	2	0
Placebo	348	273	183	120	90	66	47	32	26	19	13	7	3	1	0

PD-L1 CPS ≥1



	Pembro	Placebo
Median PFS, mo (95% CI)	10.8 (8.5-12.5)	7.2 (6.8-8.4)
HR (95% CI)	0.70 (0.58-0.85)	

No. at risk

Pembro	298	250	200	150	116	84	61	48	40	33	26	14	5	2	0
Placebo	296	231	150	98	76	54	38	24	20	15	12	6	3	1	0

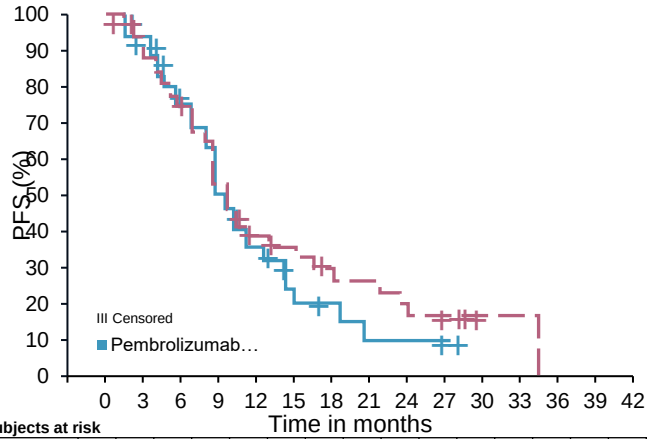
Janjigian Y et al. *Lancet*. 2023;402(10418):2197-208. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-amends-pembrolizumabs-gastric-cancer-indication. Accessed May 9, 2024.

KEYNOTE-811: Efficacy Results in Patients With CPS <1

PFS

Treatment	n	Median, mo (95% CI)
Pembro + chemo	52	9.5 (8.3-11.3)
Placebo + chemo	52	9.6 (7.9-13.0)

HR 1.17 (95% CI, 0.73-1.89), *P*=0.7432



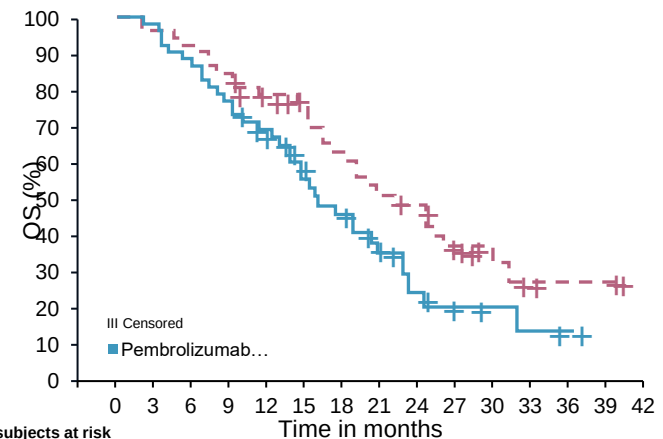
No. of subjects at risk

Pembrolizumab + SOC	52	46	34	21	13	6	4	2	2	1	0	0	0	0	0
SOC	52	42	33	22	14	12	9	8	6	4	1	1	0	0	0

OS

Treatment	n	Median, mo (95% CI)
Pembro + chemo	52	16.1 (13.9-20.8)
Placebo + chemo	52	22.3 (16.6-30.1)

HR 1.61 (95% CI, 0.98-2.64), *P*=0.9722



No. of subjects at risk

Pembrolizumab + SOC	52	51	46	40	33	23	18	12	7	4	3	2	1	0	0
SOC	52	50	48	43	38	34	27	20	18	11	8	3	3	2	0

FDA approval amended for only tumors with PD-L1 CPS ≥1

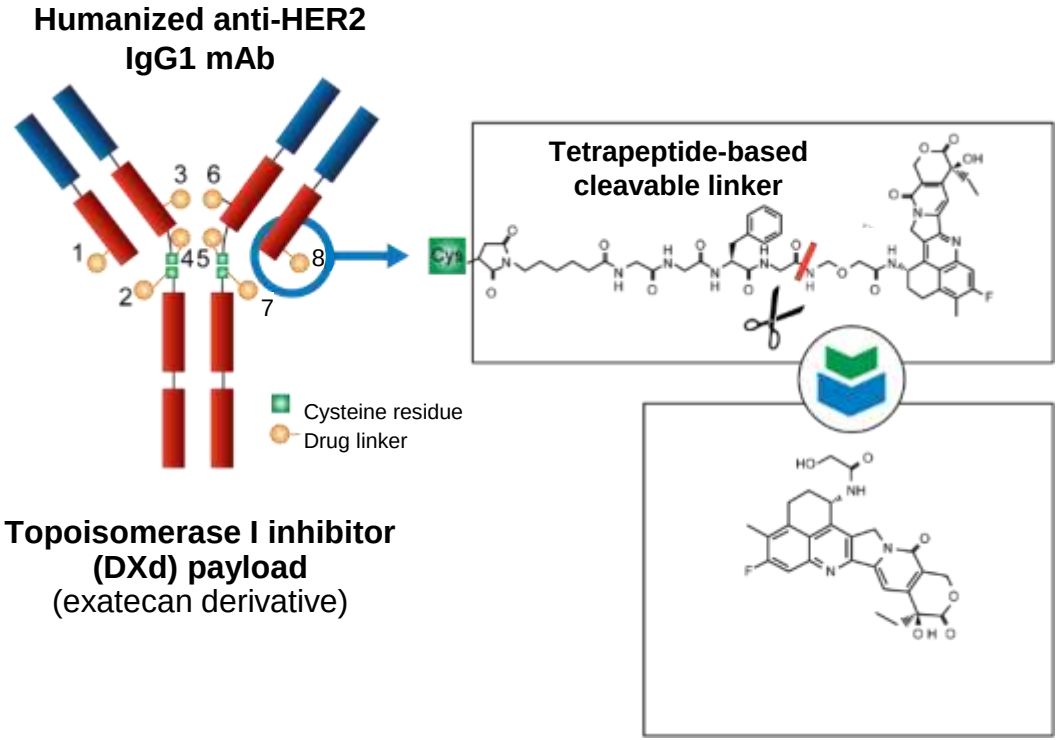
In a subgroup analysis for PD-L1 CPS <1 (N=104), the HR for OS and PFS were 1.41 (95% CI 0.90-2.20) and 1.03 (95% CI 0.65-1.64), respectively

SOC = standard of care

EMA EPAR Assessment report. https://www.ema.europa.eu/en/documents/variation-report/keytruda-h-c-003820-ii-0133-epar-assessment-report-variation_en.pdf. Accessed April 22, 2024.

Trastuzumab Deruxtecan

- Antibody-drug conjugate of trastuzumab with a topoisomerase inhibitor
- Potential advantages
  - High potency payload
  - High ratio of trastuzumab: payload molecules
  - “Bystander” effect



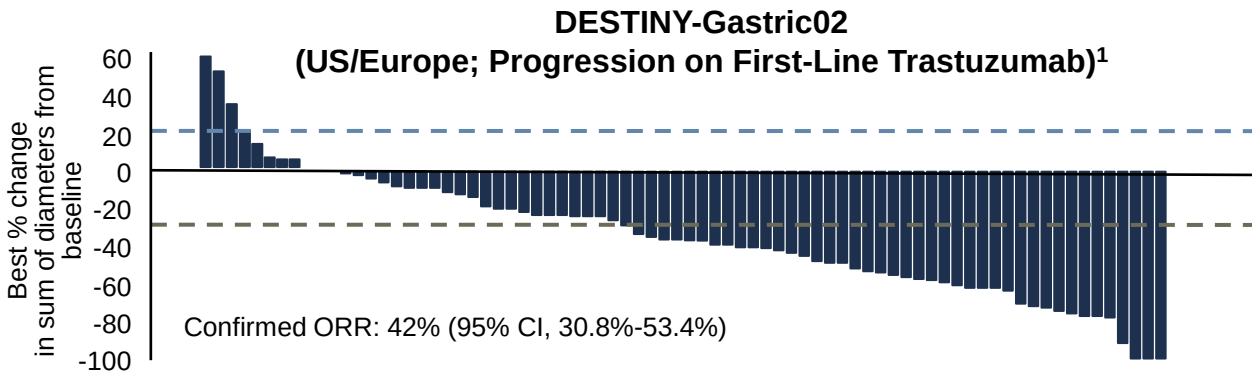
mAb = monoclonal antibody

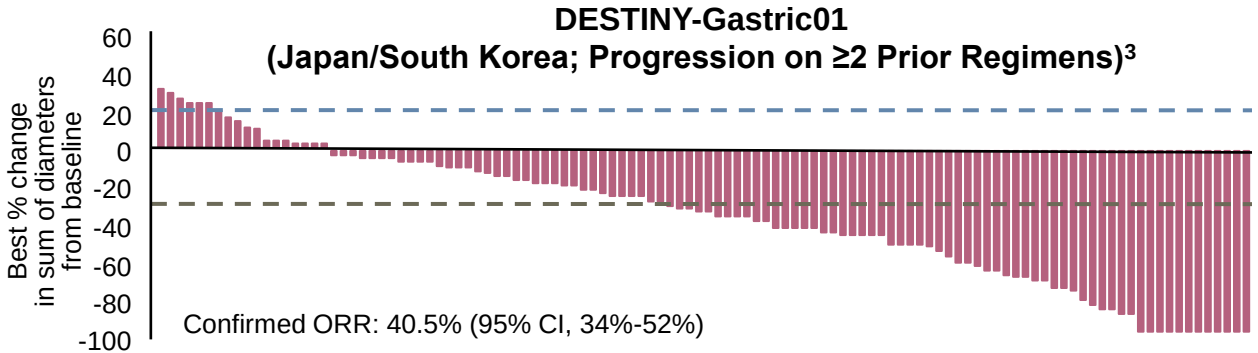
Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-85. Trail P et al. *Pharmacol Ther.* 2018;181:126-42.
Ogitani O et al. *Cancer Sci*. 2016;107(7):1039-46.

Tumor Volume Change: T-DXd in HER2+ Advanced Gastric/GEJ Cancer After Trastuzumab (DESTINY-Gastric01 and 02)

Efficacy[1,2]	T-DXd (N=79)
ORR, % (95% CI)	42 (30.8-53.4)
Median DOR, mo	8.1
Median PFS, mo (95% CI)	5.6 (4.2-8.3)
Median OS, mo (95% CI)	12.1 (9.4-15.4)

Survival, mo (95% CI)[4]	T-DXd (n=125)	Chemo (n=62)
Median OS	12.5 (9.6-14.3)	8.4 (6.9-10.7)
HR for death = 0.59; *P*=0.01		
Median PFS	5.6 (4.3-6.9)	3.5 (2.0-4.3)
HR for PD or death = 0.47		





1. Van Cutsem E et al. *Lancet.* 2023;24(7):744-56. 2. Ku G et al. *Ann Oncol*. 2022;33(suppl 7):1100. 3. Shitara K et al. *N Engl J Med*. 2020;382(25):2419-30. 4. Yamaguchi et al. *J Clin Oncol*. 2022;40(suppl 4):242.

AEs: T-DXd in HER2+ Advanced Gastric/GEJ Cancer After Trastuzumab (DESTINY-Gastric01 and 02)

DESTINY-Gastric02
(US/Europe; Progression on 1L Trastuzumab)[1]

TRAEs in ≥15% of Patients, n (%)	T-DXd (N=79)	
	Any Grade	Grade ≥3
Patients with ≥1 TRAE	74 (93.7)	21 (26.6)
Nausea	46 (58.2)	3 (3.8)
Fatigue	29 (36.7)	3 (3.8)
Vomiting	26 (32.9)	1 (1.3)
Diarrhea	22 (27.8)	1 (1.3)
Decreased appetite	18 (22.8)	1 (1.3)
Alopecia	17 (21.5)	0
Anemia	15 (19.0)	6 (7.6)
Decreased platelet count	13 (16.5)	1 (1.3)
Decreased neutrophil count	12 (15.2)	6 (7.6)

DESTINY-Gastric01
(Japan/South Korea; Progression on ≥2 Prior Regimens)[2]

AE in ≥20% of Patients, n (%)	T-DXd (n=125)		Chemo (n=62)	
	Any Gr	Gr 3/4	Any Gr	Gr 3/4
Nausea	79 (63)	6 (5)	29 (47)	1 (2)
↓ neutrophil count	79 (63)	64 (51)	22 (35)	15 (24)
↓ appetite	75 (60)	21 (17)	28 (45)	8 (13)
Anemia	72 (58)	47 (38)	19 (31)	14 (23)
↓ platelet count	49 (39)	14 (12)	4 (6)	2 (4)
↓ white cell count	47 (38)	26 (21)	22 (35)	7 (11)
Malaise	43 (34)	1 (1)	10 (16)	0
Diarrhea	40 (32)	3 (2)	20 (32)	1 (2)
Vomiting	33 (26)	0	5 (8)	0
Constipation	30 (24)	0	14 (23)	0
Pyrexia	30 (24)	0	10 (16)	0
Alopecia	28 (22)	0	9 (15)	0
Fatigue	27 (22)	9 (7)	15 (24)	2 (3)
↓ lymphocyte count	27 (22)	14 (11)	2 (3)	1 (2)

1L = first-line; AE = adverse event; Gr = grade; TRAE = treatment-related adverse event

1. Van Cutsem E. ESMO 2021. Abstract LBA55. 2. Shitara K et al. *N Engl J Med*. 2020;382(25):2419-30.

Management of ILD Associated With Trastuzumab Deruxtecan

Monitor

Suspected ILD

Interrupt drug

Rule out ILD if patient exhibits:

- Radiographic changes suggesting ILD
- Acute onset of new/worsening pulmonary or related symptoms (eg, cough, dyspnea, fever)

Confirm

Assessments should include:

- High-resolution CT
- Pulmonologist consult; if indicated, ILD consult
- Blood culture and CBC; other blood tests as needed
- Bronchoscopy and BAL if indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gases, if indicated
- Collection of 1 blood sample for PK assessment as soon as ILD suspected, if feasible
- Ruling out other causes of ILD (eg, progression, infection, other drugs, radiotherapy)
- Follow-up of all ILD events until resolution and after drug discontinuation

Manage

- Grade 1: Hold until resolved to grade 0, consider corticosteroids (0.5 mg/kg/d prednisolone), then:
  - If resolved ≤28 d from onset: maintain dose
  - If resolved >28 d after onset: reduce dose by 1 level
  - If grade 1 ILD occurs beyond cycle Day 22 and has not resolved within 49 d from last infusion: discontinue drug
- Grades 2-4: Permanently discontinue treatment and promptly initiate systemic corticosteroid treatment (eg, ≥1 mg/kg/d prednisolone or equivalent for at least 14 d followed by taper for at least 4 wk)

BAL = bronchoalveolar lavage; CBC = complete blood count; CT = computed tomography; ILD = interstitial lung disease; PFT = pulmonary function test.

Enhertu (trastuzumab deruxtecan) prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761139s024lbl.pdf.
Modi S et al. *N Engl J Med*. 2020;382(7):610-21.

Conclusions

- Critical to obtain biomarkers to optimally treat advanced Gastric/ GEJ adenocarcinoma
  - PD-L1
  - HER2
  - MMR
  - CLDN18.2
  - FGFR2
- Immunotherapy + chemotherapy for PD-L1 positive gastric/GEJ adeno
- CLDN18.2 positive tumors – zolbetuximab
- HER2 – chemotherapy + pembrolizumab + trastuzumab
- 2nd Line options exist – requires aggressive management and a bit of anticipation!

Thank You!

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