Antibody-Drug Conjugate
The Next Wave of Gastric Cancer Treatment

2024/07/20

臺中榮總 腫瘤內科
石宇軒

53y/o Male, BW:53kg, BSA:1.55

EG junction cancer, adenocarcinoma, with liver metastasis, stage **IV**

2022/12

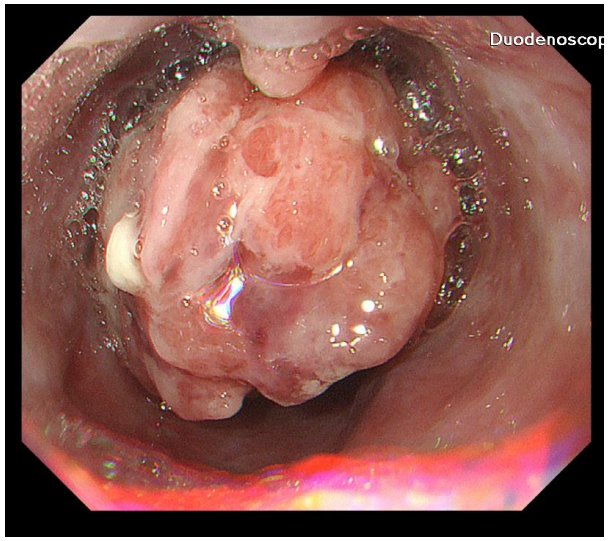
Initial Presentation

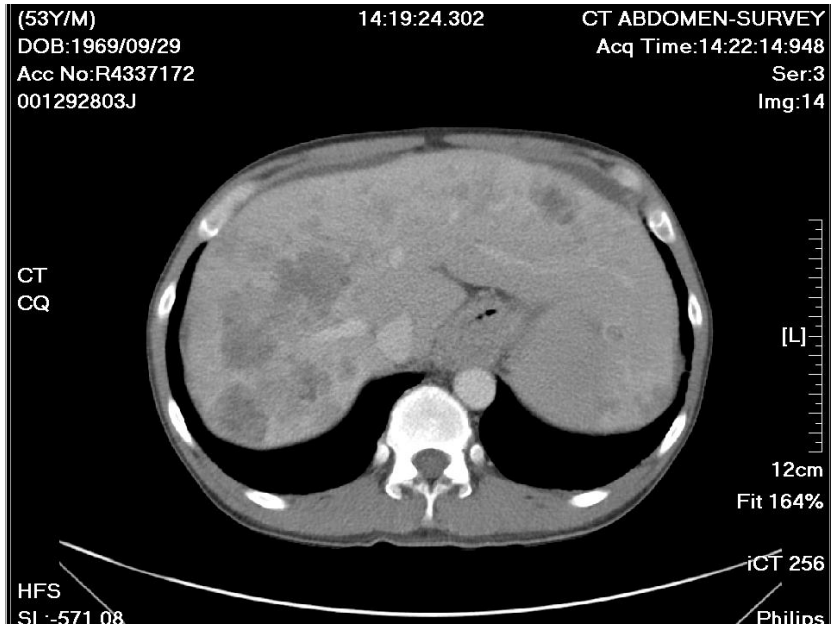
Anemia
Vomiting
UGI scopy: huge E-C junction mass

cT4aN+M1, stage **IV**

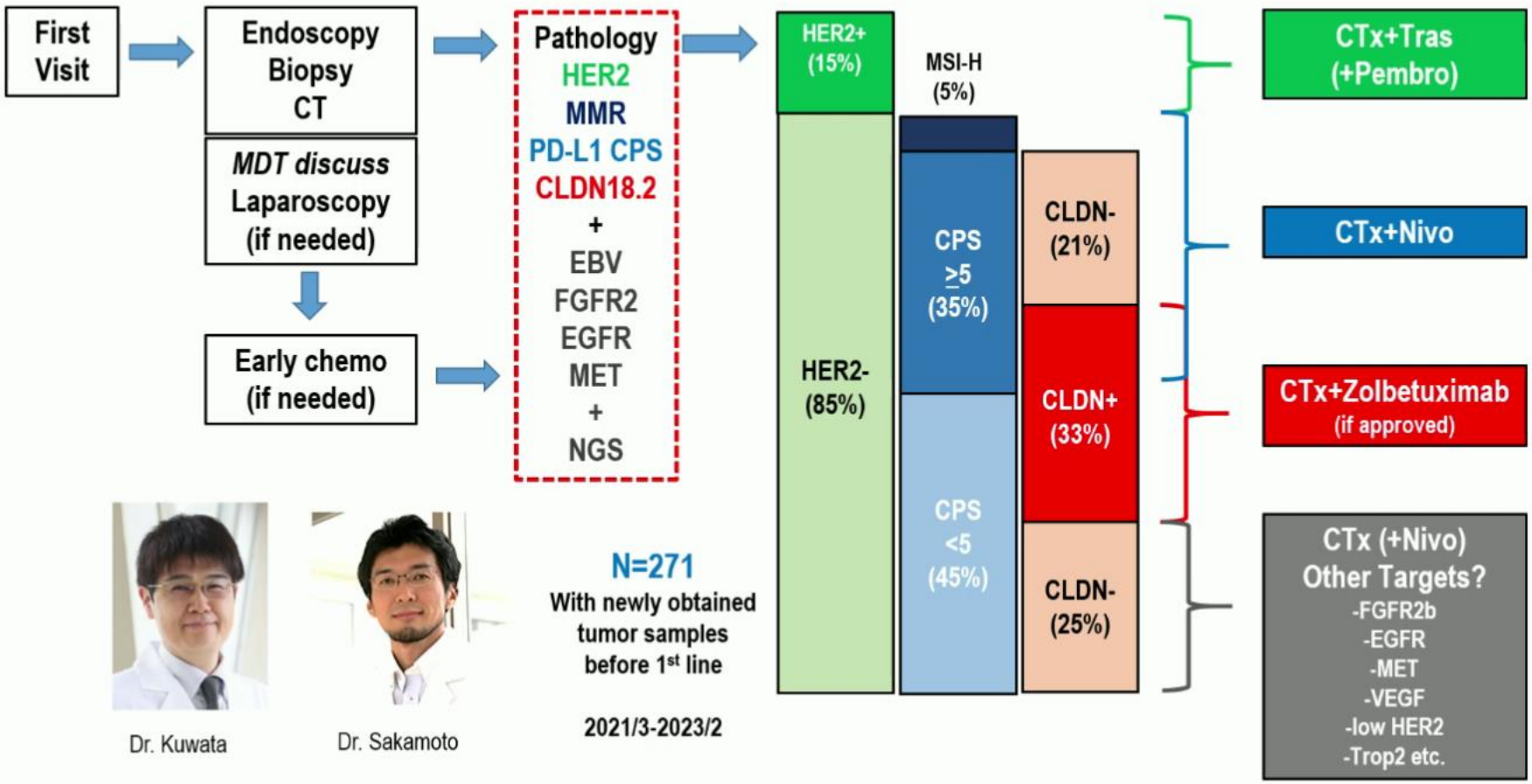
HER2 IHC:2+, ISH: amplification

PDL1 CPS:1 (28-8)





Possible stratification by biomarkers (experience in NCCHE)



Dr. Kuwata

Dr. Sakamoto

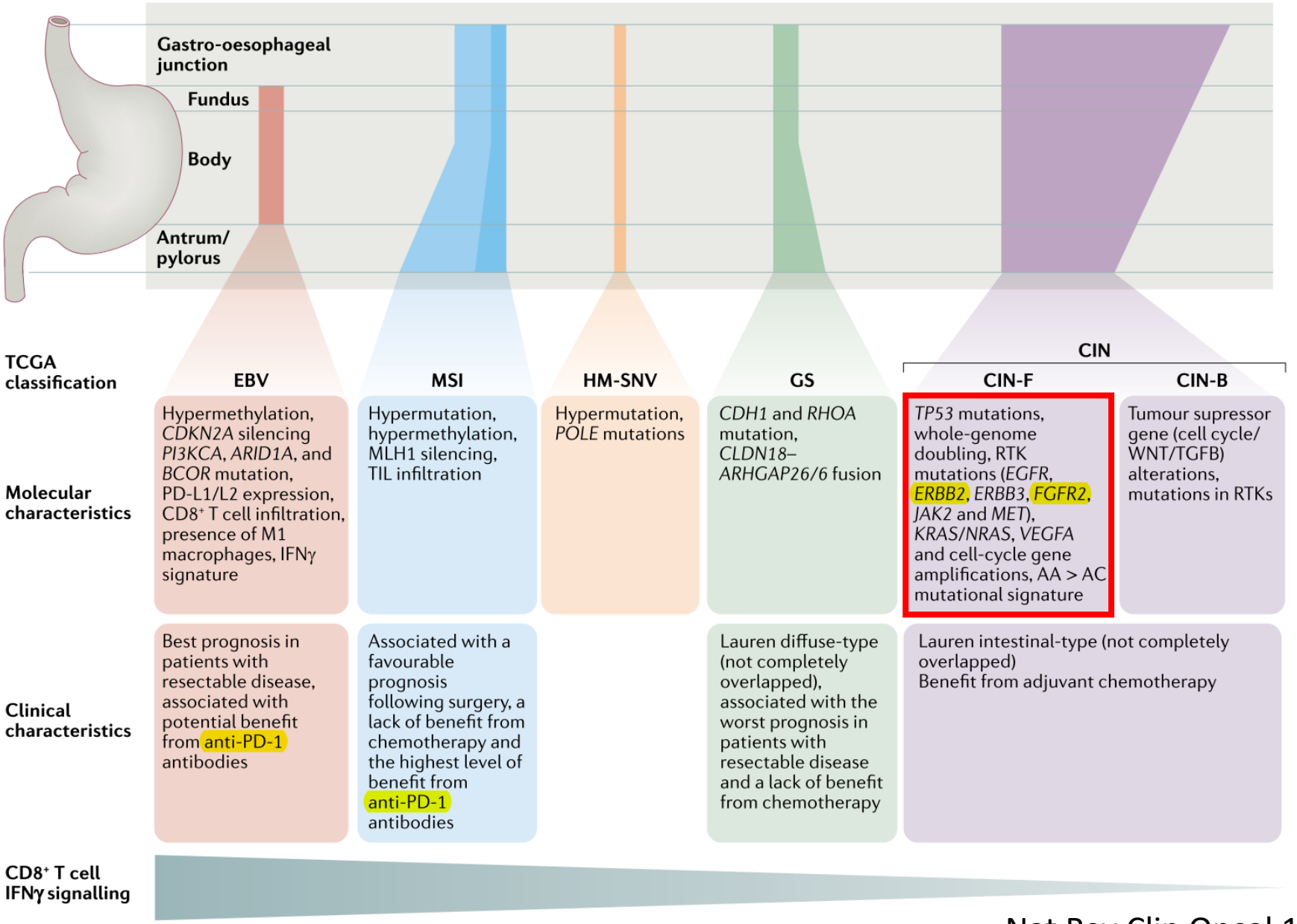
N=271
With newly obtained tumor samples before 1st line

2021/3-2023/2

Kohei Shitara

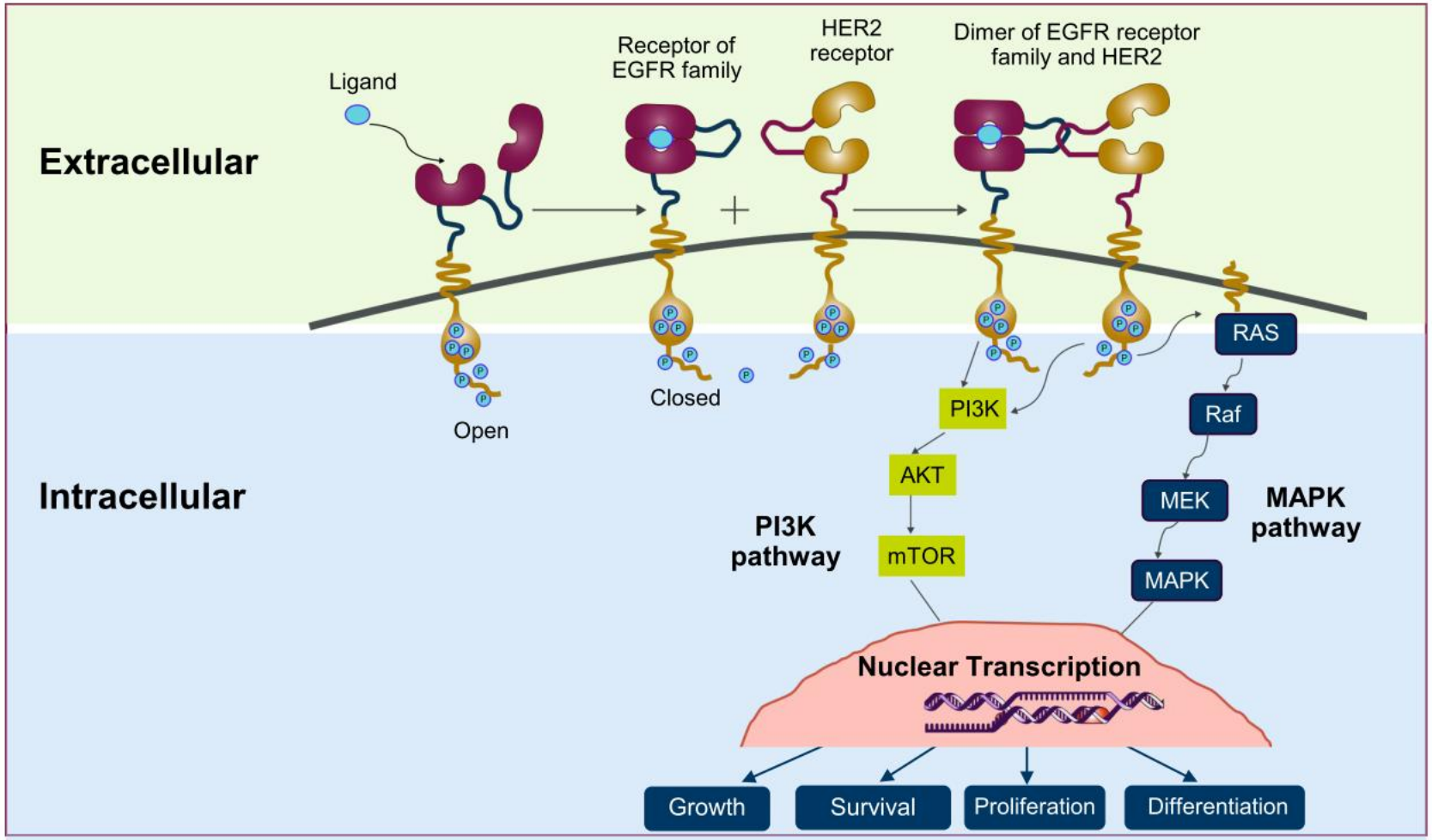
HER2 and beyond: What's next?

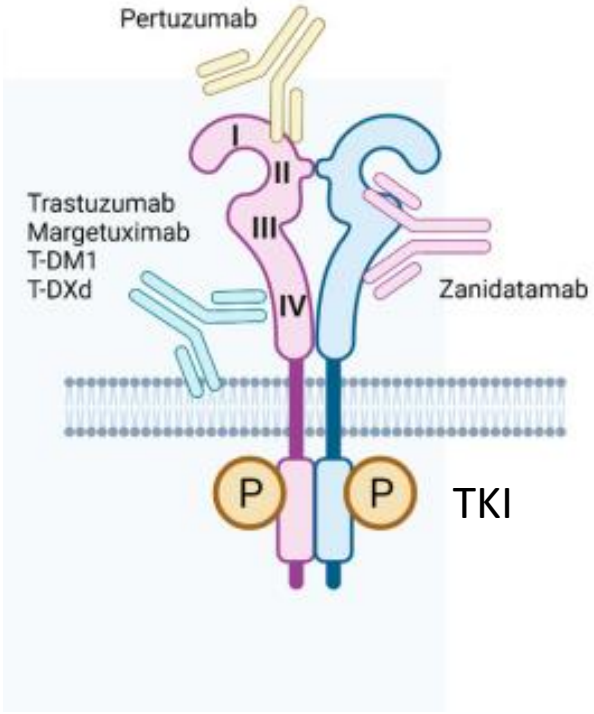
Molecular Classification



Nat Rev Clin Oncol 18, 473–487 (2021).

HER2 Pathway





Int. J. Mol. Sci. 2016; 17:2095
Int. J. Mol. Sci. 2023, 24, 11403

Prevalence of HER2+ GC in Taiwan

CGMH
All surgical specimens

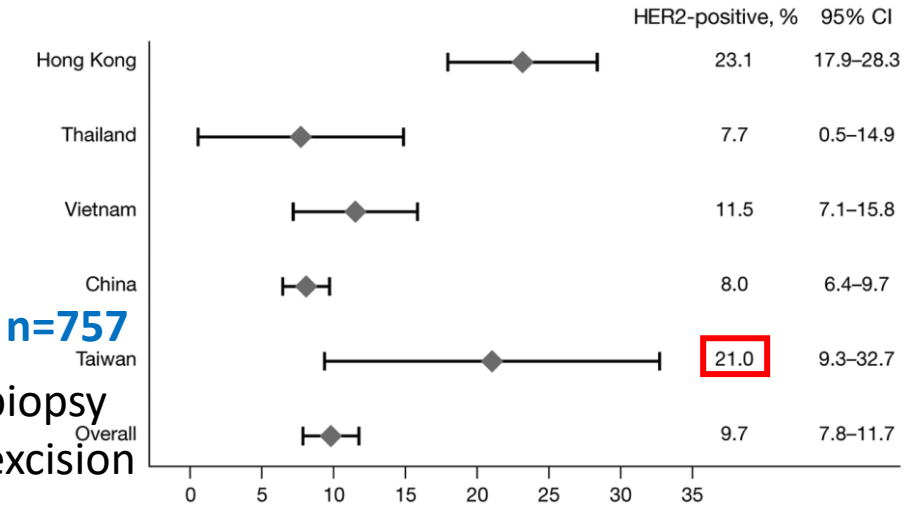
Table 4. Literature review of HER-2 overexpression and *HER-2* amplification in gastric cancer

Study	Country	*n*	% HER-2$^+$ (definition)	Association	Prognostic factor
Tanner et al. (2005) [8]	Finland	131	12.2 (FISH +)	Intestinal type	Yes
Park et al. (2006) [16]	Korea	182	15.9 (IHC 2+ or 3+)	Intestinal type	Yes
Kim et al. (2007) [12]	Korea	248	22.6 (IHC 2+ or 3+)	Differentiation Intestinal type	Yes
Hoffman et al. (2008) [14]	Germany, China, Mexico	168	13.6 (IHC 3+ or IHC 2+ and FISH +)	Intestinal type	Not done
Barros-Silva et al. (2009) [10]	Portugal	463	9.3 (IHC 2+ or 3+)	Intestinal type Expansive type	Yes
Begnami et al. (2011) [15]	Brazil	221	12 (IHC 2+ or 3+)	Differentiation Intestinal type	Yes
Hsu et al. (2011), current series	Taiwan	1,036	6.1 (IHC 3+ or IHC 2+ and FISH +)	Differentiation	No

Abbreviations: FISH, fluorescence in situ hybridization; HER-2, human epidermal growth factor receptor 2; IHC, immunohistochemistry.

CMUH+ n=757

44.5% biopsy
55.5% excision



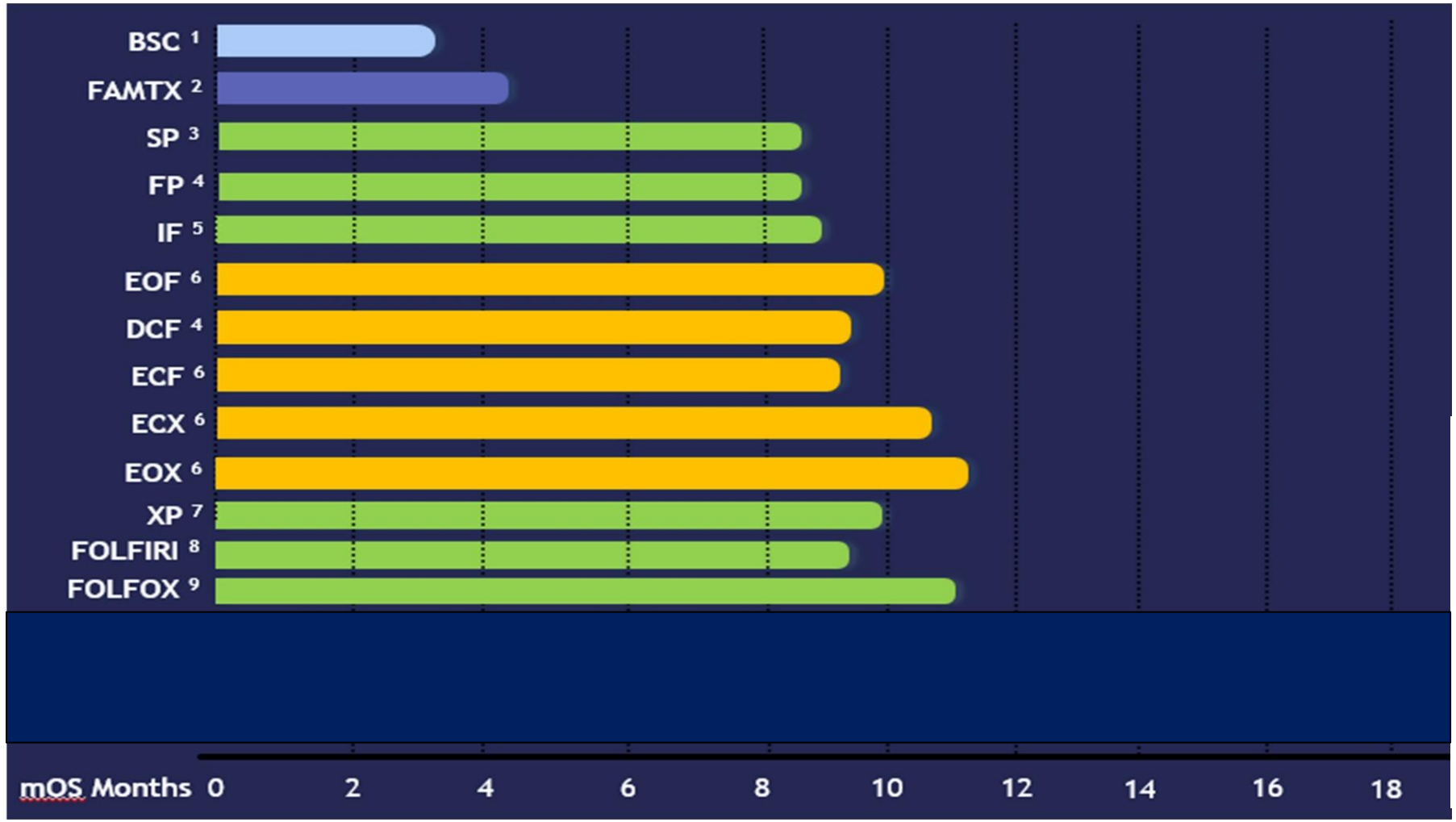
TCVGH mGC

HER2 overexpression, n/total n (%)		
0, 1+, 2+	225/262	(85.9)
3+	37/262	(14.1)

Asia Pac J Clin Oncol. 2017 Jun;13(3):249-260.
Oncologist. 2011;16(12):1706-13
Clin Med Insights Oncol. 2022 Sep 18:16:11795549221123617

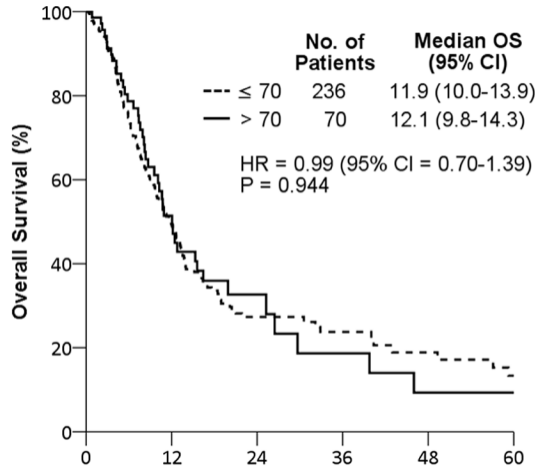
First Line Therapy

First Line Management of Advanced GEA



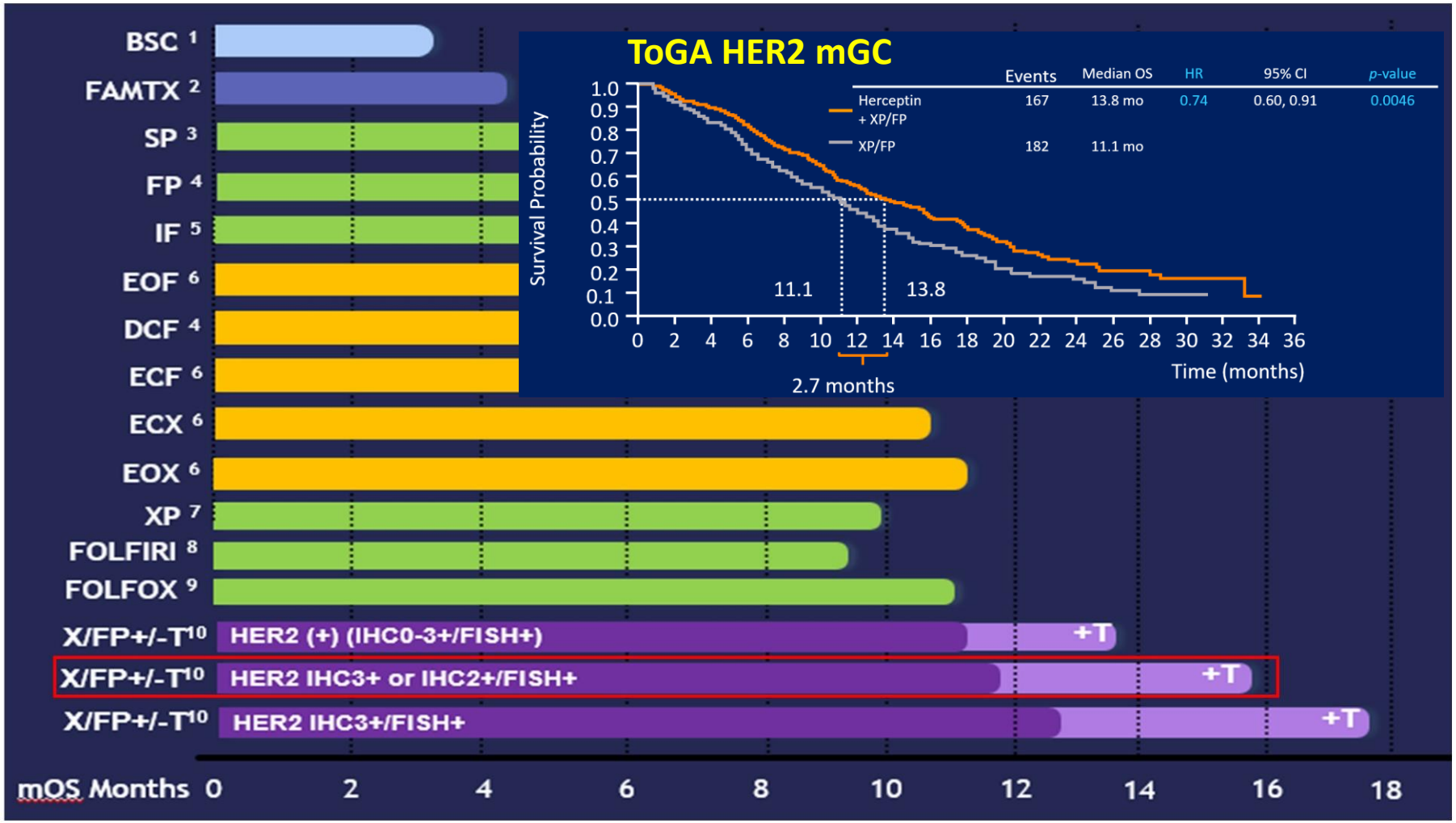
HER2-
mOS = ~10-11m
1yr OS = ~40%
2yr OS = ~15-20%
5yr OS < ~2%

TCVGH mGC



1. Murad AM et al. *Cancer*. 1993;72(1):37-41; 2. Vanhoefer U et al. *J Clin Oncol*. 2000;18(14):2648-2657; 3. Ajani JA et al. *J Clin Oncol*. 2010;28(9):1547-1553; 4. Van Cutsem E et al. *J Clin Oncol*. 2006;24(31):4991-4997; 5. Dank M et al. *Ann Oncol*. 2008;19(8):1450-1457; 6. Cunningham D et al. *N Engl J Med*. 2008;358(1):36-46; 7. Kang YK et al. *Ann Oncol*. 2009;20(4):666-673; 8. Guimbaud R et al. *J Clin Oncol*. 2014;32(31):3520-3526; 9. Shah MA et al. *JAMA Oncol*. 2017;3(5):620-627; 10. Bang YJ et al. *Lancet*. 2010;376(9742):687-697.

First Line Management of Advanced GEA



HER2-
mOS = ~10-11m
1yr OS = ~40%
2yr OS = ~15-20%
5yr OS < ~2%

HER2+
mOS = ~14-16m
1yr OS = ~55-65%
2yr OS = ~25-30%
5yr OS < ~10-15%

1. Murad AM et al. *Cancer.* 1993;72(1):37-41; 2. Vanhoefer U et al. *J Clin Oncol.* 2000;18(14):2648-2657; 3. Ajani JA et al. *J Clin Oncol.* 2010;28(9):1547-1553; 4. Van Cutsem E et al. *J Clin Oncol.* 2006;24(31):4991-4997; 5. Dank M et al. *Ann Oncol.* 2008;19(8):1450-1457; 6. Cunningham D et al. *N Engl J Med.* 2008;358(1):36-46; 7. Kang YK et al. *Ann Oncol.* 2009;20(4):666-673; 8. Guimbaud R et al. *J Clin Oncol.* 2014;32(31):3520-3526; 9. Shah MA et al. *JAMA Oncol.* 2017;3(5):620-627; 10. Bang YJ et al. *Lancet.* 2010;376(9742):687-697.

Subsequent Negative Phase II/III Studies in Advanced GC

First-line Studies

- JACOB: capecitabine/cisplatin/trastuzumab ± pertuzumab (N = 780)
  - OS: 17.5 vs 14.2 mo (HR: 0.84; *P* = .057)
- HELOISE: capecitabine/cisplatin + higher dose trastuzumab (N = 248)
- LOGiC: capecitabine/oxaliplatin ± lapatinib (N = 545)
  - No difference in OS (12.2 vs 10.5 mo; HR: 0.91)

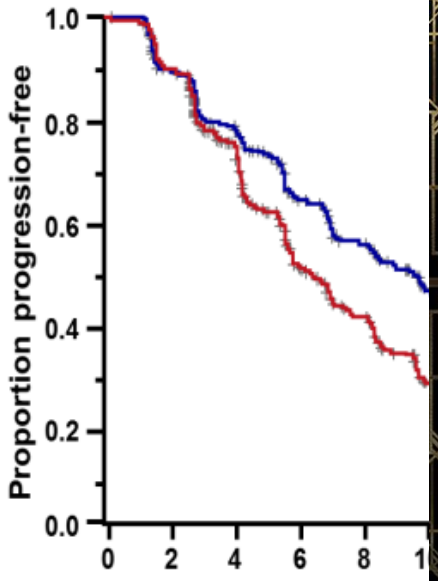
Second-line Studies

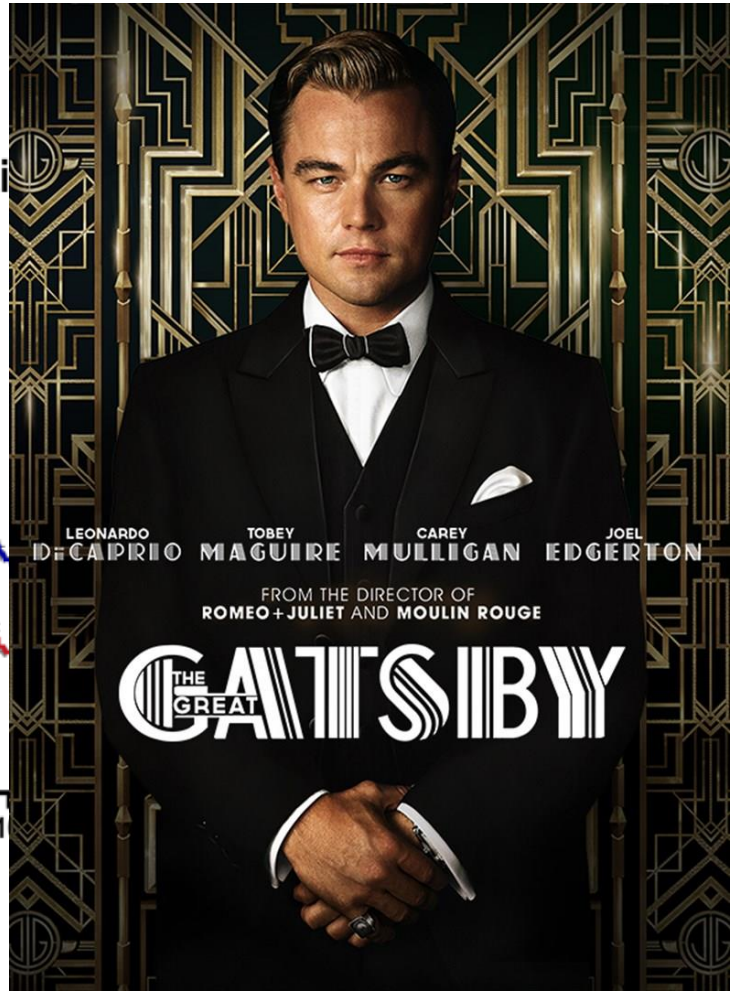
- TyTAN: paclitaxel ± lapatinib (N = 261)
- GATSBY: paclitaxel or docetaxel vs T-DM1 (N = 415)
- T-ACT: paclitaxel ± trastuzumab (N = 91)

Tabernero. Lancet Oncol. 2018;19:1372. Shah. JCO. 2017;35:2558. Randolph Hecht. JCO. 2016;34:443.
Satoh. JCO. 2014;32:2039. Thuss-Patience. Lancet Oncol. 2017;18:640. Makiyama. JCO. 2020;38:1919.

Different Story of **HER2+** BC vs. GC

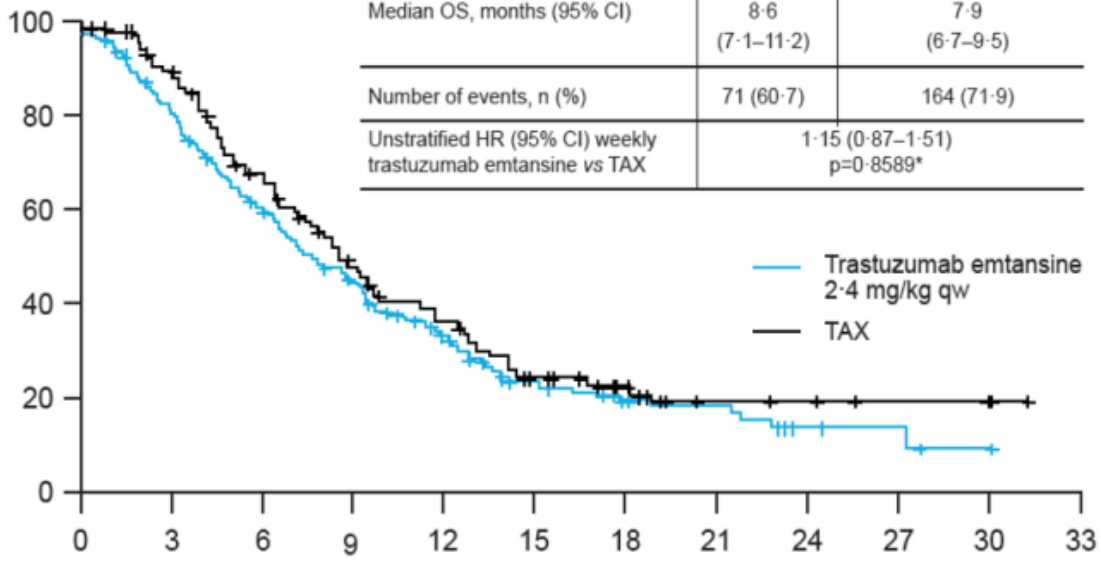
HER2+ Breast cancer
Phase III:EMILIA
T-DM1 vs. Cape+lapati





HER2+ Gastric cancer
Phase II/III: GATSBY
T-DM1 vs taxanes

	TAX (n=117)	Trastuzumab emtansine 2·4 mg/kg qw (n=228)
Median OS, months (95% CI)	8·6 (7·1–11·2)	7·9 (6·7–9·5)
Number of events, n (%)	71 (60·7)	164 (71·9)
Unstratified HR (95% CI) weekly trastuzumab emtansine *vs* TAX	1·15 (0·87–1·51) p=0·8589*	

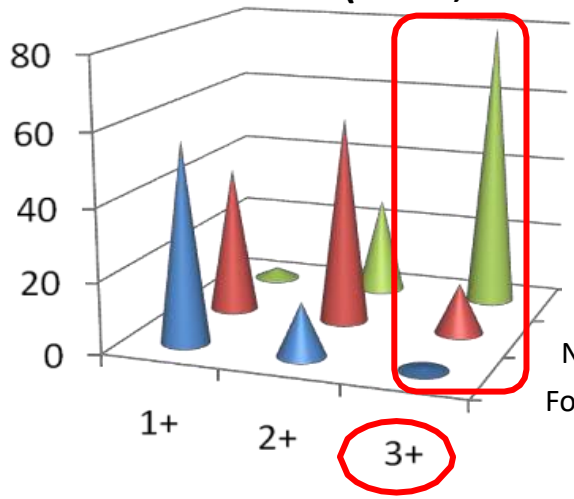


Thuss-Patience OC, et al.Lancet Oncol. 2017

- T-DM1 did not improve OS compared with 2nd-line taxanes
- ORR 20% in GC vs. 44% in BC

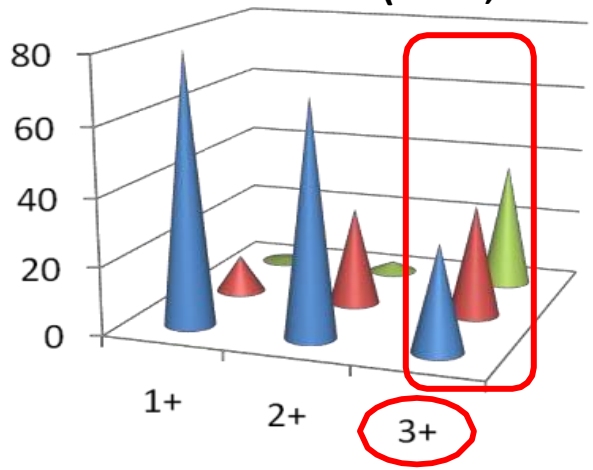
Intratumoral Heterogeneity and Incomplete Membrane Staining of HER2

Breast Cancer (HERA; N = 1969)



Homogeneous (>80%)
Nonhomogeneous
Focal (<30%)

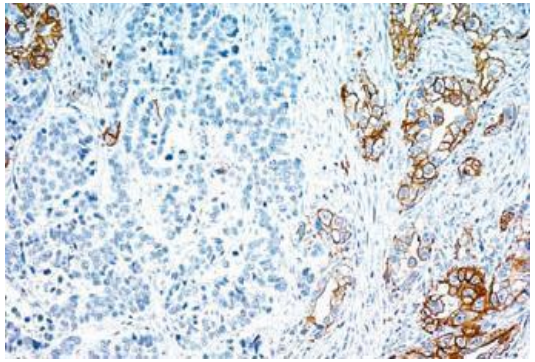
Gastric Cancer (ToGA; N = 1453)

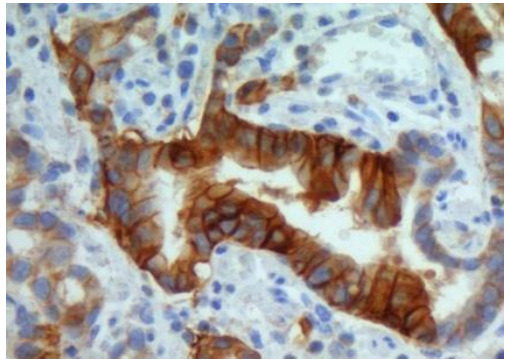


3+: moderate to strong complete or basolateral 3+ / positive membrane staining in >10% of tumor cells

Tumor heterogeneity is more common in GC vs BC

Incomplete membrane staining with IHC is more common in GC vs BC



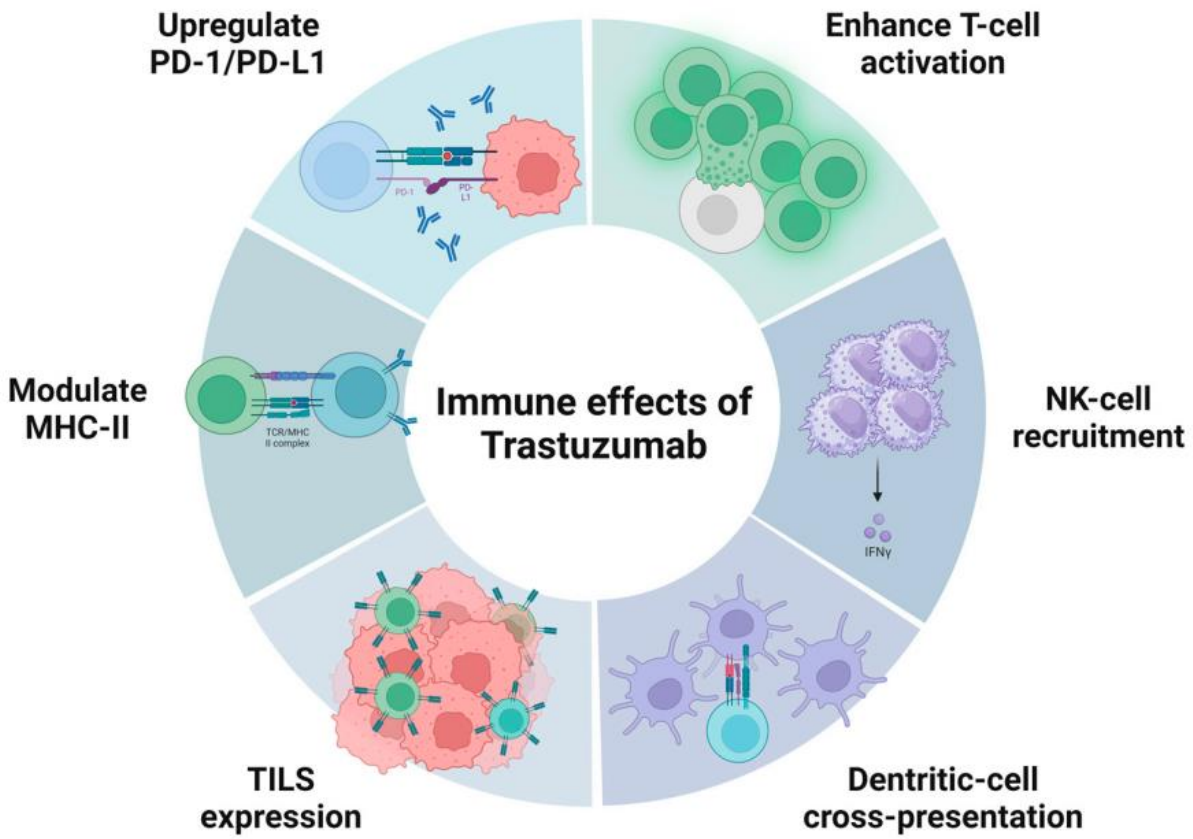


Overexpression of HER2, EGFR, MET, FGFR by IHC in 9%-25%
Coexpression in 19%

Hofmann. Histopathology. 2008;52:797. Modified slide courtesy of K. Shitara.

Slide credit: clinicaloptions.com

Immune effects of Trastuzumab observed in preclinical studies



Int. J. Mol. Sci. 2023, 24, 11403

KEYNOTE-811 Study Design (NCT03615326)

Phase 3 Randomized, Placebo-Controlled

HER2標靶+PD1免疫

Key Eligibility Criteria

- Advanced, unresectable G/GEJ adenocarcinoma
- No prior systemic therapy in advanced setting
- HER2+ by central review (IHC 3+ or IHC 2+ ISH+)
- ECOG PS 0 or 1

R 1:1
N=698

Pembrolizumab 200 mg IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Placebo IV Q3W + Trastuzumab and FP or CAPOX[a]
for up to 35 cycles

Stratification Factors

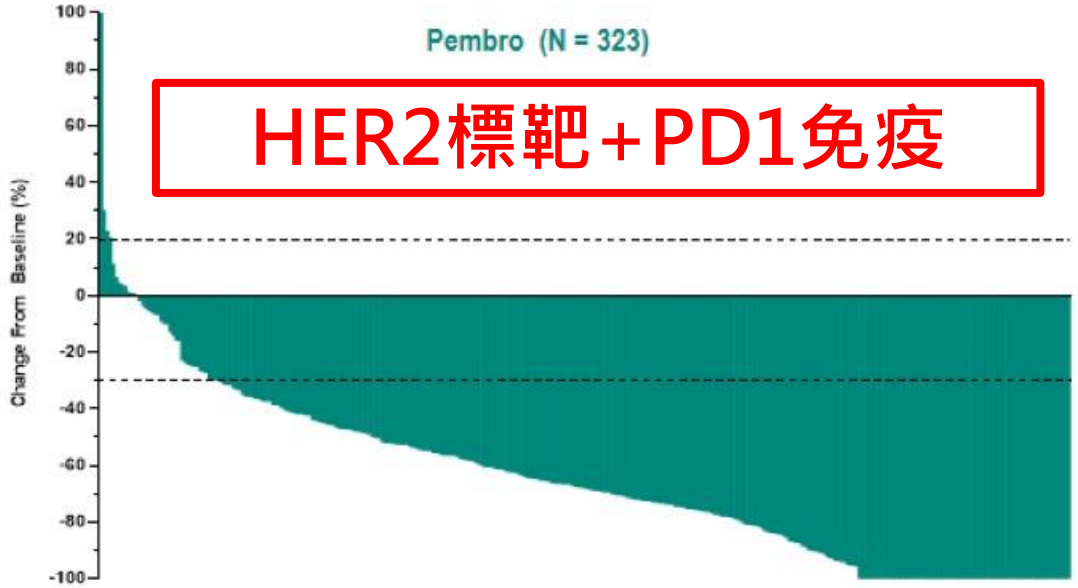
- Geographic region
- PD-L1 CPS <1 vs CPS ≥1
- Chemotherapy choice

Endpoints

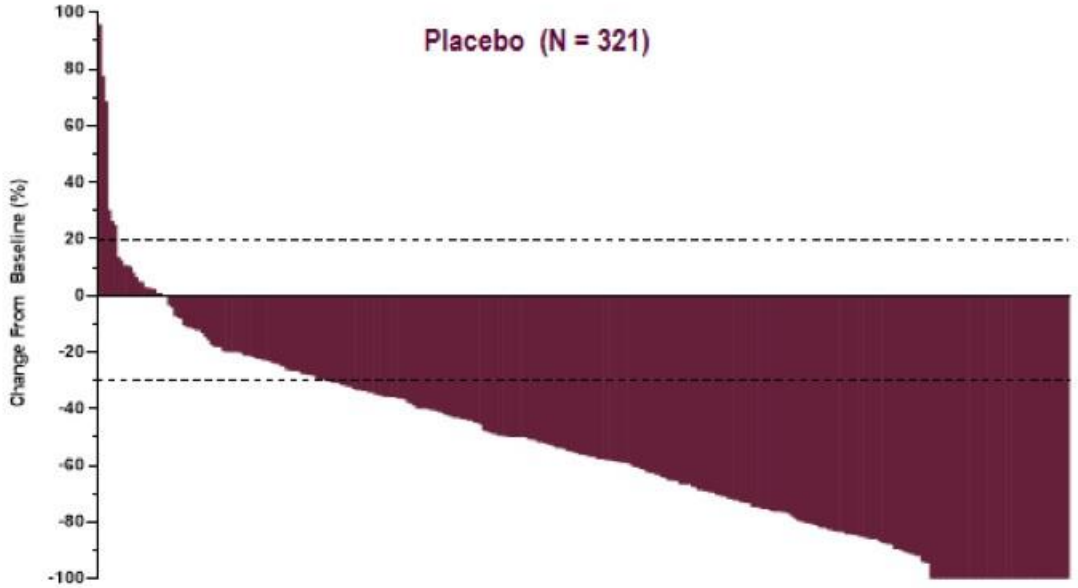
- Dual primary: OS, PFS
- Secondary: ORR, DOR , safety

[a]Trastuzumab: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W. PFS, ORR, DOR per RECIST by BICR.

Antitumor Response at IA3



HER2標靶+PD1免疫



Response and Duration	Pembro N = 350	Placebo N = 348
ORR, % (95% CI)	**73 (68-77)**	**60 (55-65)**
Best response, n (%)		
CR	58 (17)	39 (11)
PR	196 (56)	170 (49)
SD	67 (19)	95 (27)
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+)

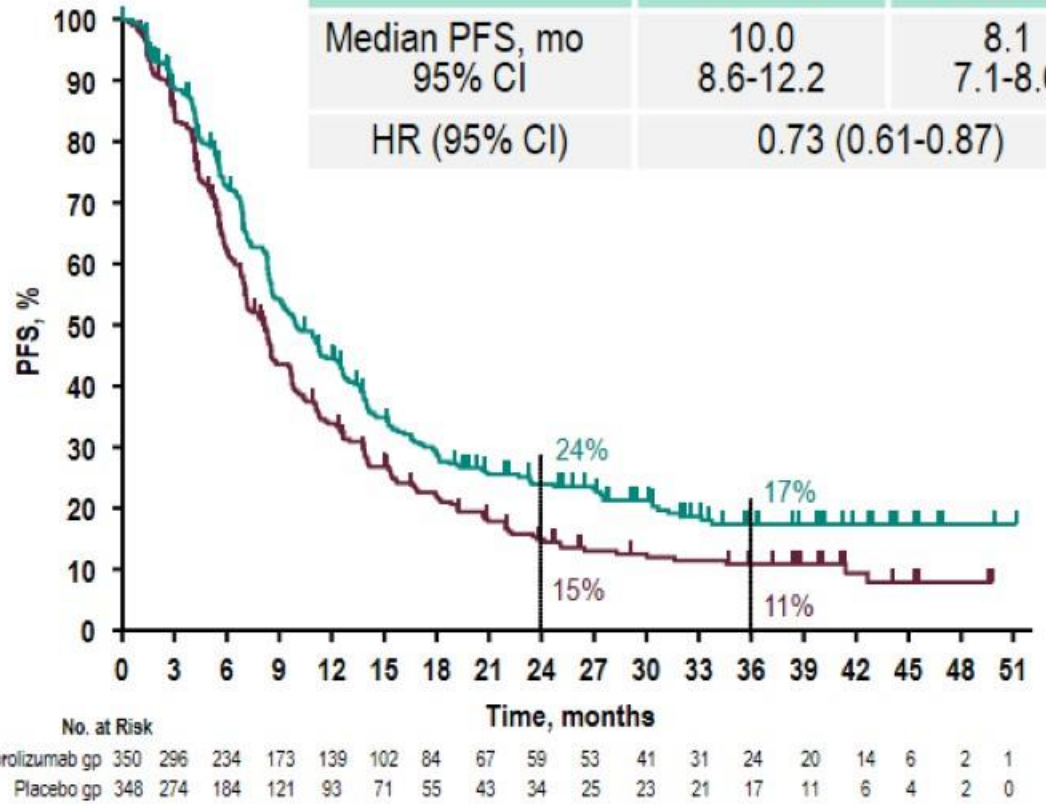
Data cut-off: March 29, 2023. ORR at IA1 was 74% (11% CR) in the pembro gp vs 52% (3% CR) in the pbo gp (ORR difference: 22% [95% CI, 11-34]; P=0.00006). ORR at IA3 in CPS ≥1 was 73% in the pembro gp vs 58% in the pbo gp.
NE, post-baseline assessment not evaluable. NA, no post-baseline assessment available for response evaluation. + indicates no progressive disease at time of last disease assessment.

Progression-Free Survival at IA3: 38.5 months of follow-up[a]

RECIST V1.1, BICR

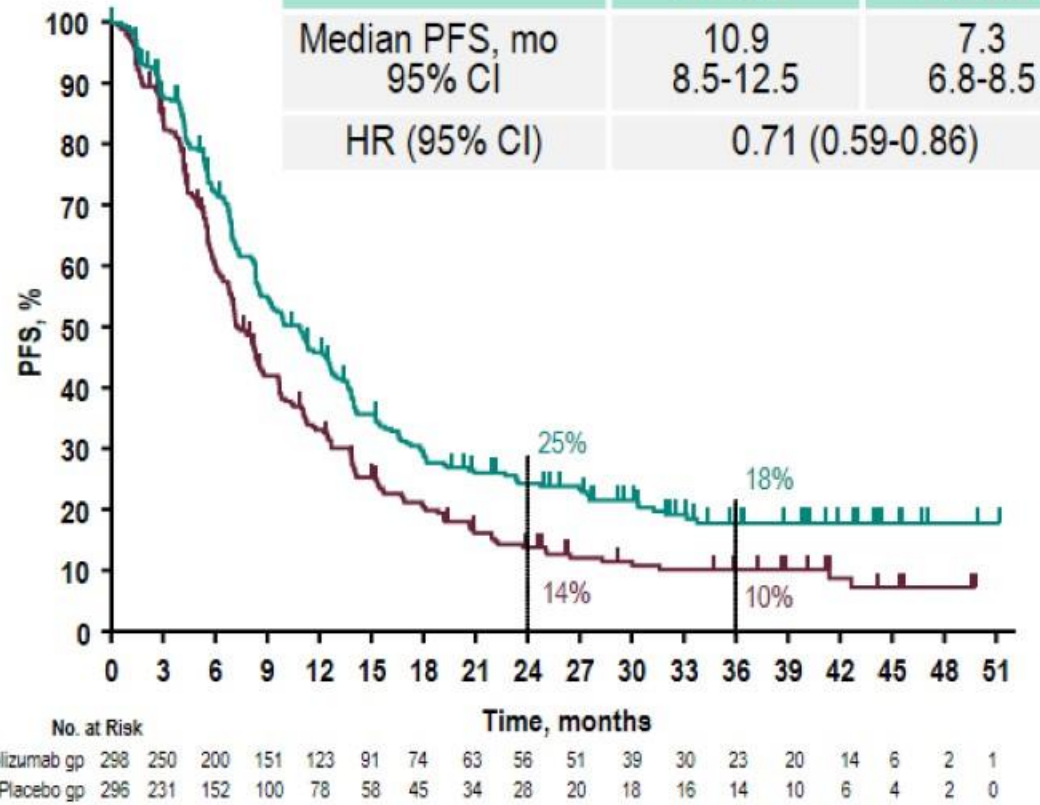
All patients

	Pembro	Placebo
Median PFS, mo 95% CI	10.0 8.6-12.2	8.1 7.1-8.6
HR (95% CI)	0.73 (0.61-0.87)	



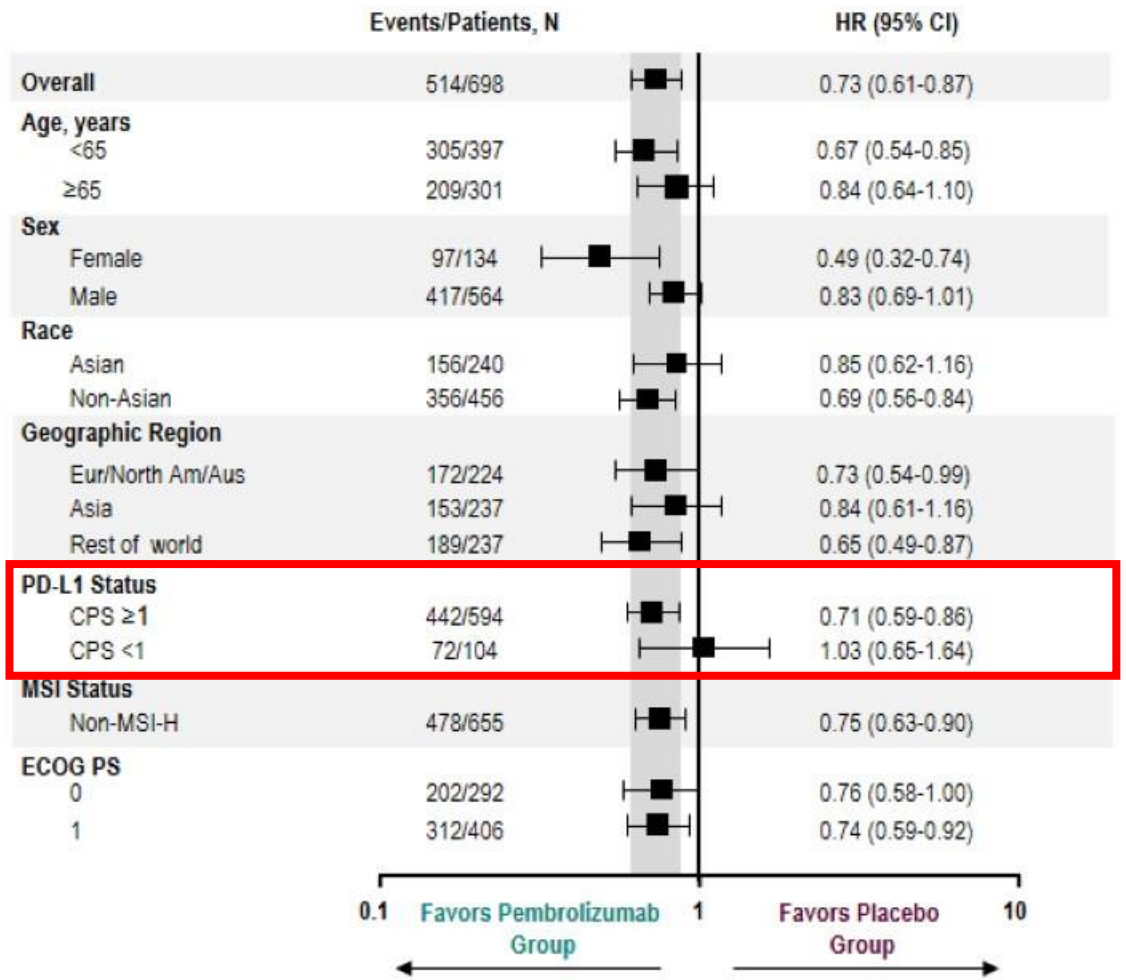
PD-L1 CPS ≥1[b]

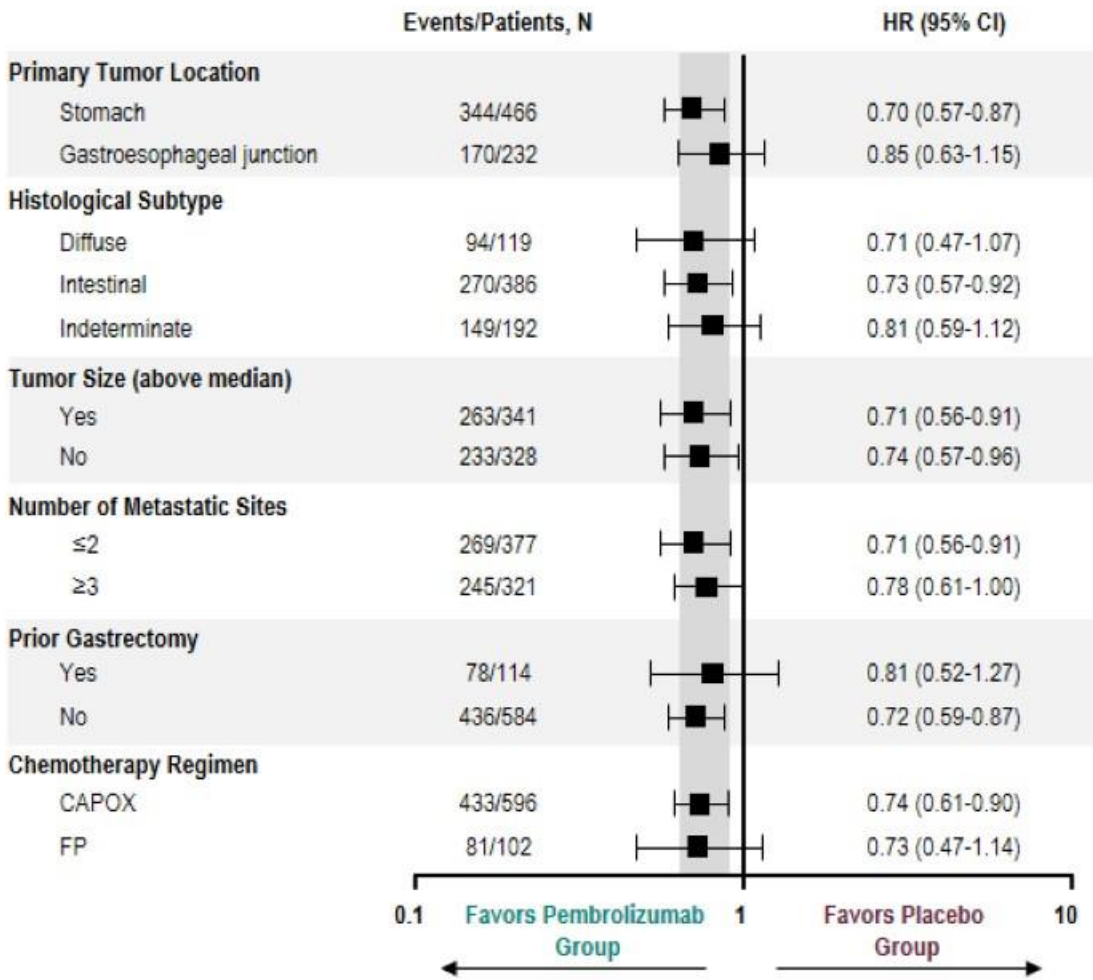
	Pembro	Placebo
Median PFS, mo 95% CI	10.9 8.5-12.5	7.3 6.8-8.5
HR (95% CI)	0.71 (0.59-0.86)	



Data cut-off: March 29, 2023. [a]Median follow-up. [b]Not a prespecified endpoint.

Progression-Free Survival in Key Subgroups at IA3



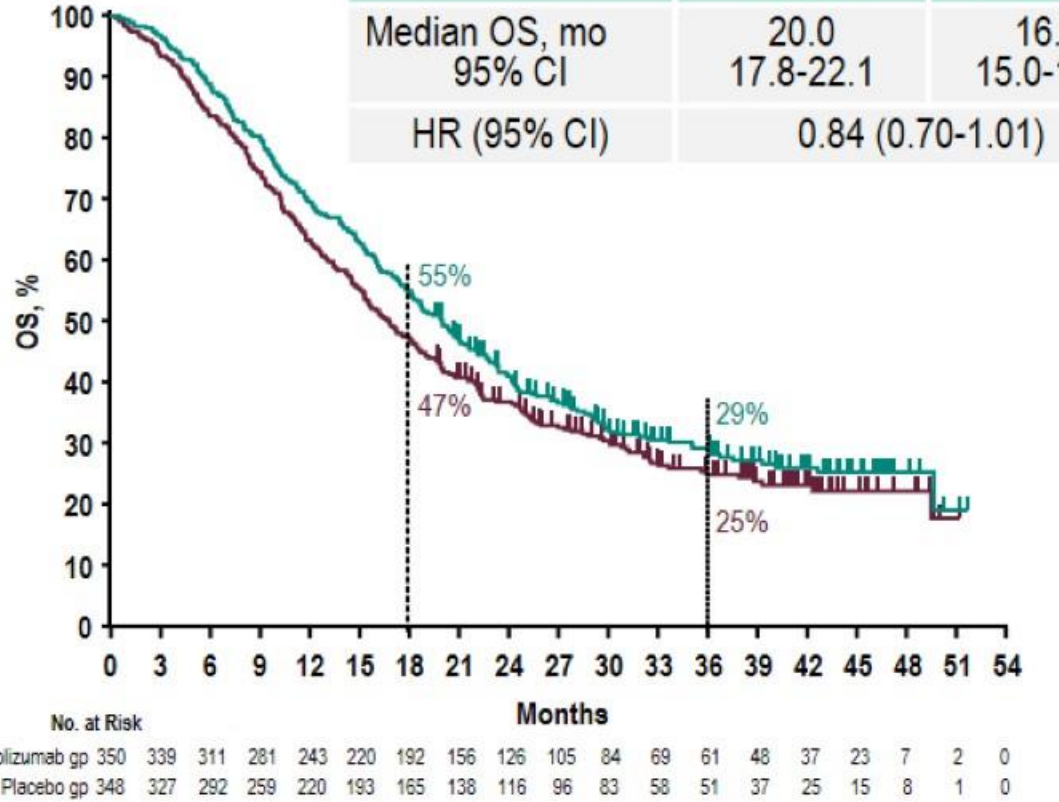


Data cut-off: March 29, 2023.

Overall Survival at IA3

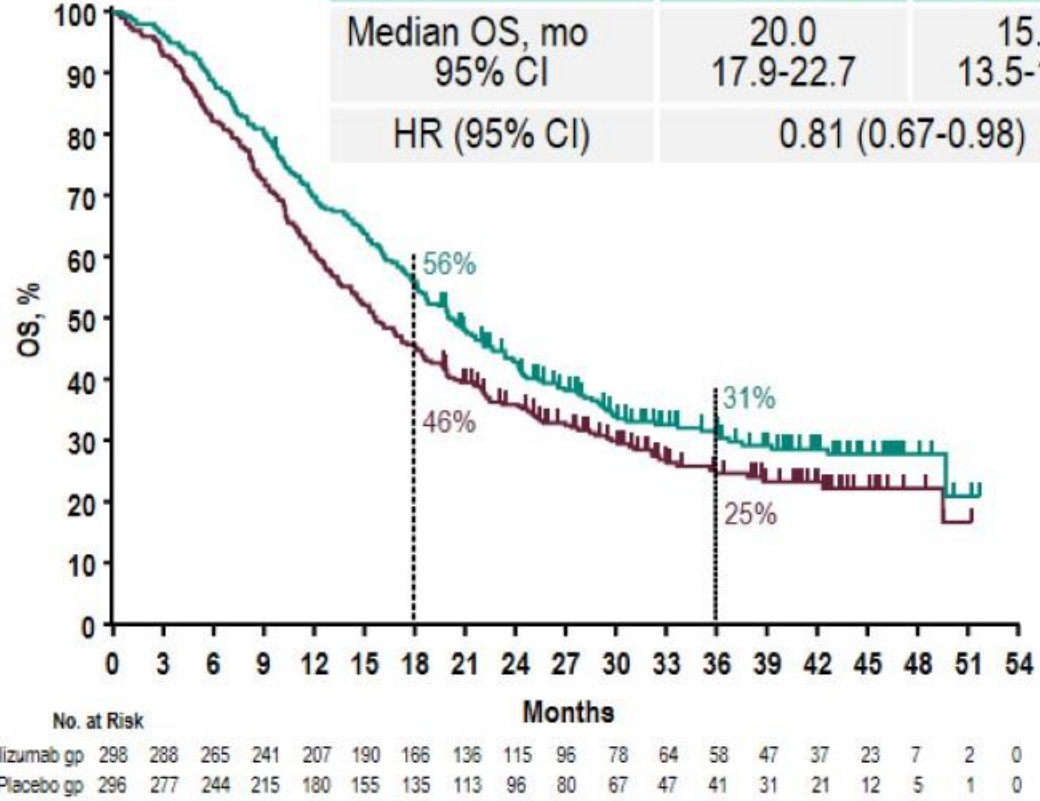
All patients

	Pembro	Placebo
Median OS, mo 95% CI	20.0 17.8-22.1	16.8 15.0-18.7
HR (95% CI)	0.84 (0.70-1.01)	



✓ PD-L1 CPS ≥1[a]

	Pembro	Placebo
Median OS, mo 95% CI	20.0 17.9-22.7	15.7 13.5-18.5
HR (95% CI)	0.81 (0.67-0.98)	



Data cut-off: March 29, 2023. OS did not meet the prespecified criteria for significance at IA3 and will be retested at final analysis. [a]Not a prespecified endpoint.

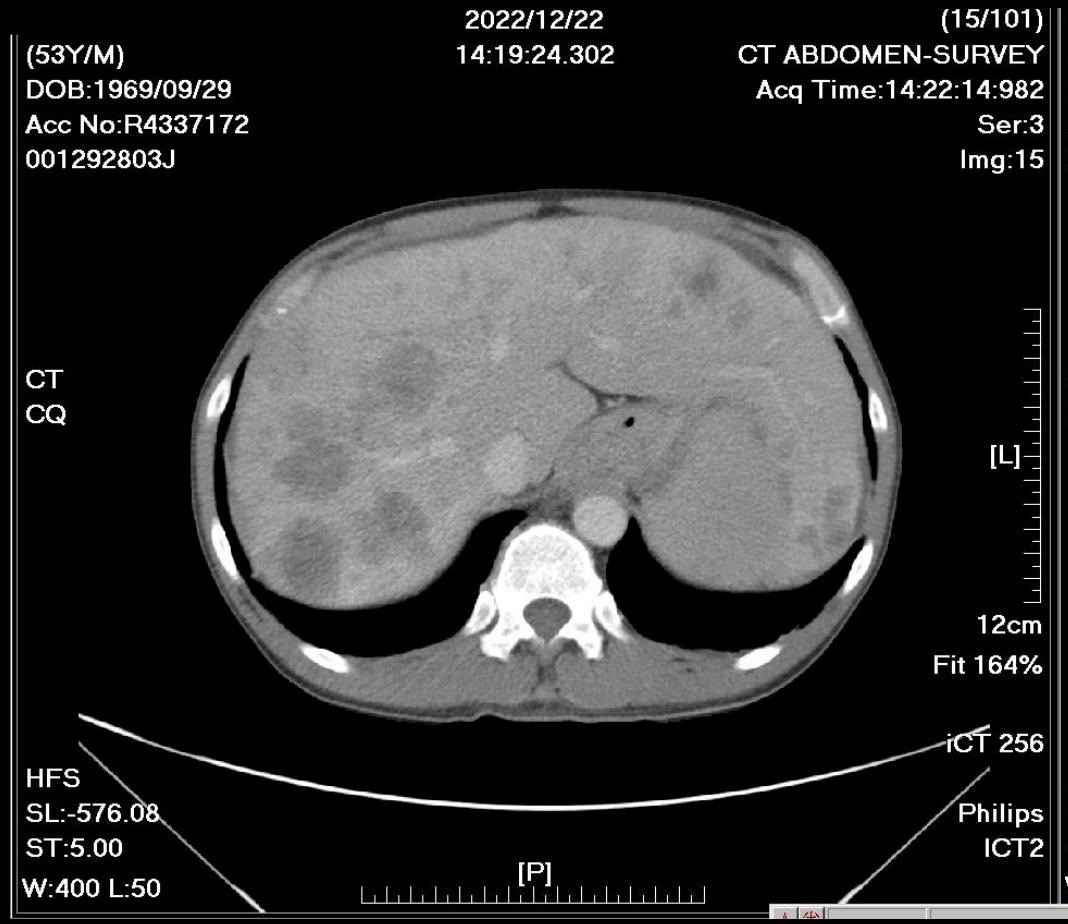
FDA amends pembrolizumab's gastric cancer indication

On November 7, 2023, the Food and Drug Administration revised the existing indication of pembrolizumab (Keytruda, Merck) with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. **This updated indication, which remains approved under accelerated approval regulations, restricts its use to patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.**

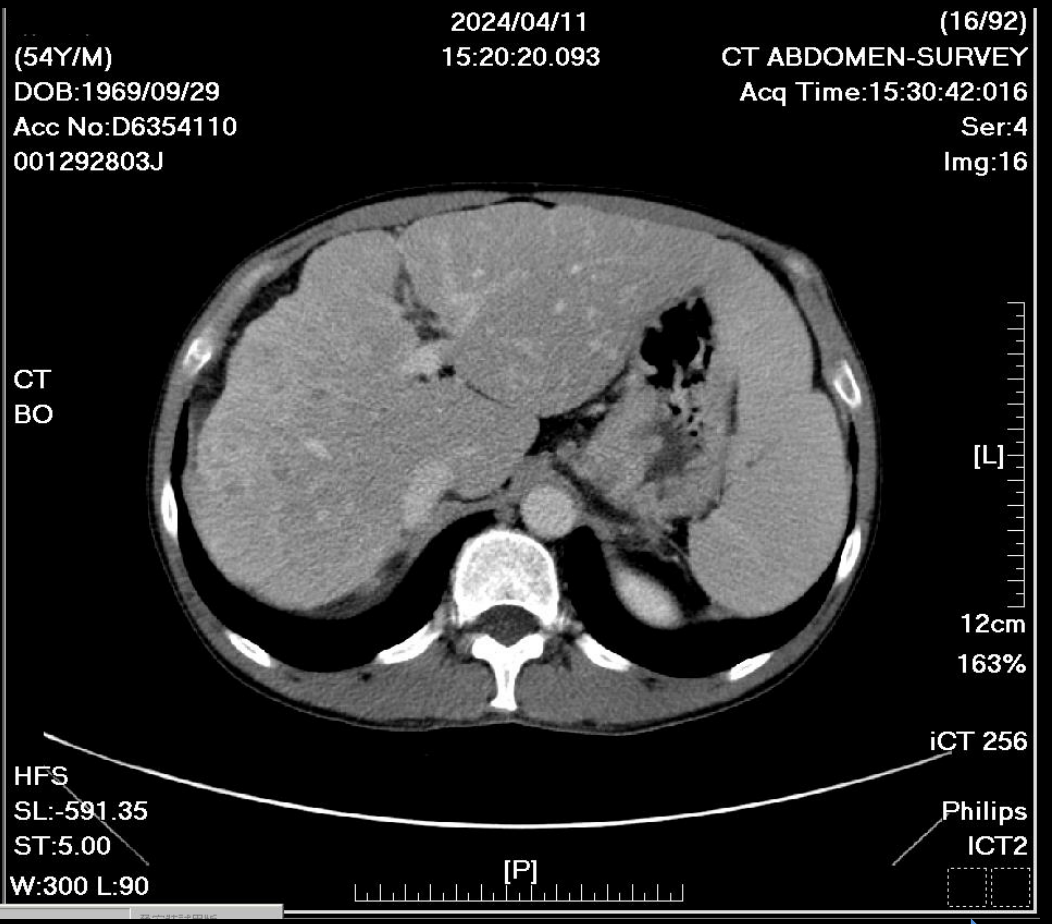
The FDA also approved the Agilent PD-L1 IHC 22C3 pharmDx as a companion diagnostic device to select patients with gastric or GEJ adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1).

53y/o Male EG junction cancer, adenocarcinoma, liver metastasis
T4bN+M1, stage IV. HER2 IHC:2+, ISH:amplification, PDL1 CPS:1

2022/12/22



2024/4/11



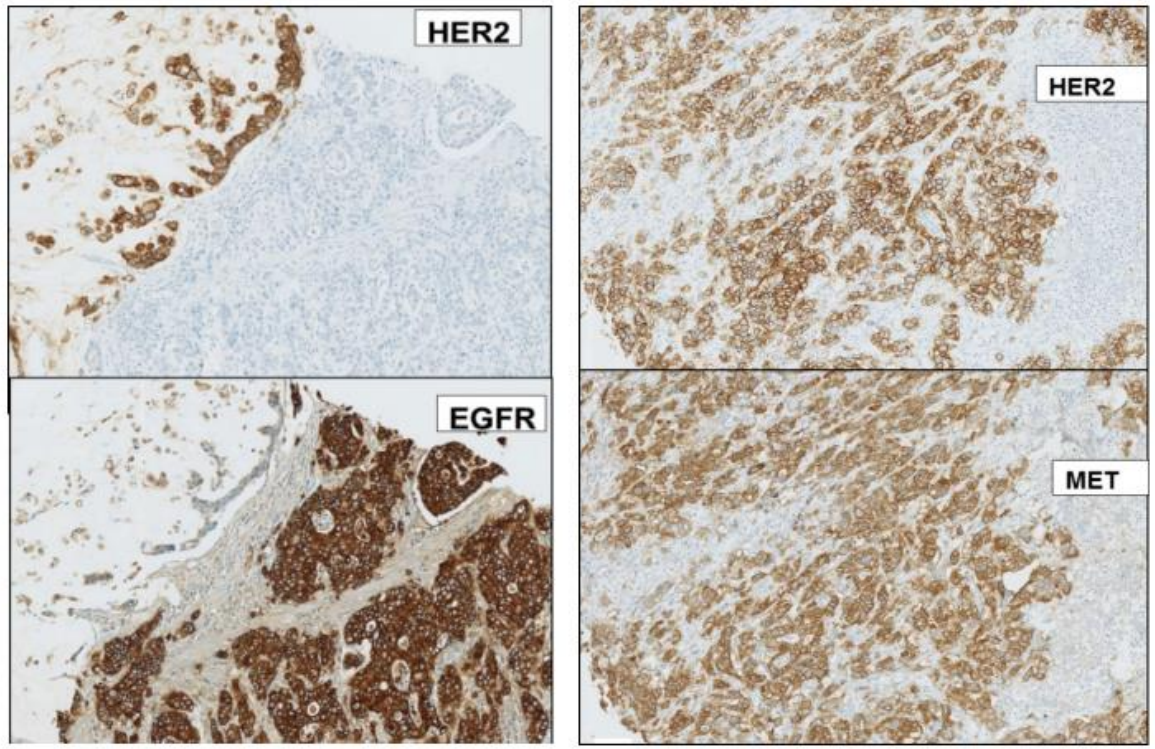
Pembrolizumab + Trastuzumab + Cisplatin + 5-FU

Trastuzumab Resistance

Resistance to Trastuzumab in gastric cancer

Reported Anti-HER2 resistance

1. **Intratumoral heterogeneity of HER2 expression**
   (Loss of HER2 after Trastuzumab)
2. **Activation of downstream pathway**
   (*RAS-MAPK, PI3K/AKT*)
3. **Activation of totally unrelated pathway** survival
   (other RTK, etc MET, or cell signal)
4. Activation of the other HER pathway by other family members
   (incomplete blockade of the HER family)
5. Activating mutations in HER2
6. Loss of the target (p95 HER2)
7. Mechanical blockade of target (mucins etc.)



NCCHE

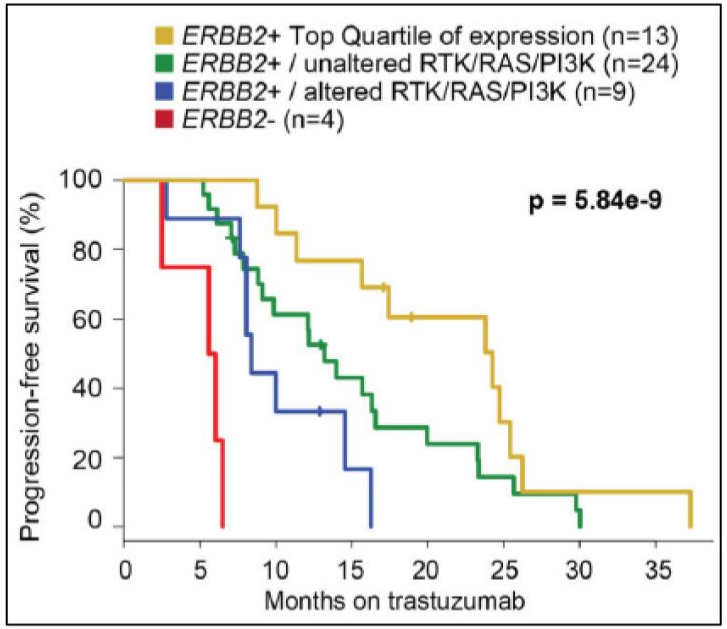
- Intratumoral heterogeneity of HER2 expression is common
- Co expression with other RTKs are also common

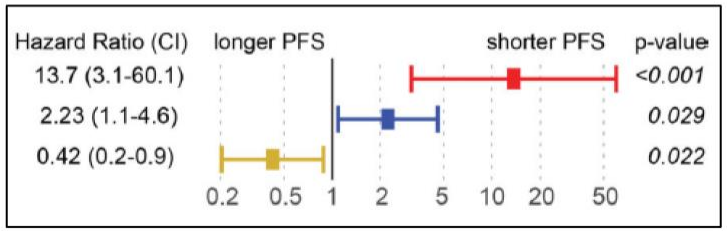
Wulfkuhle, et al. Clin Cancer Res 2017; Wang et al, Gut 2018
Janjigian YY,et al. Cancer Discov 2018; Pietrantonio, et al.Clin Cancer Res 2017

Drug Resistance After Receiving Anti-HER2 Therapy

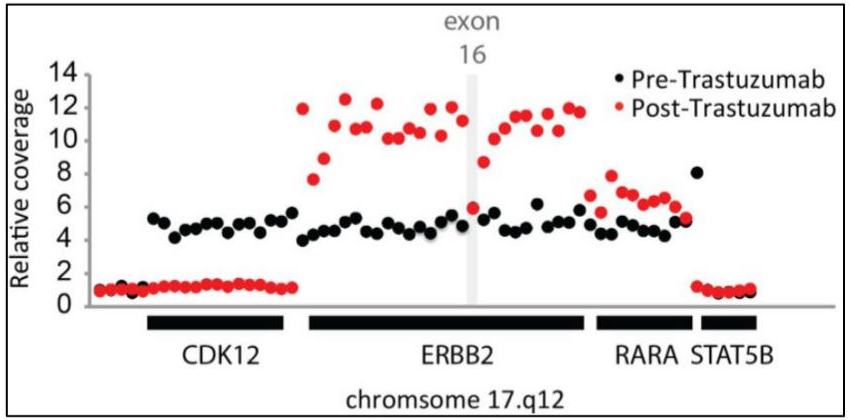
Intrinsic and acquired trastuzumab resistance

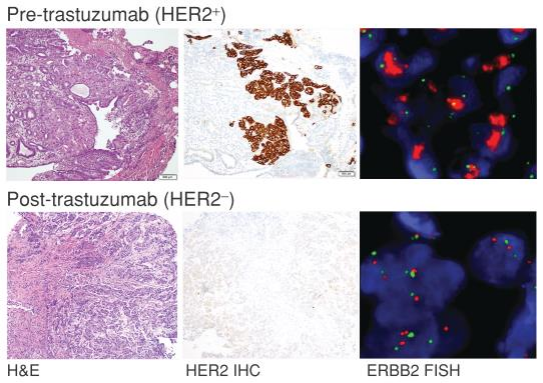
Intrinsic resistance



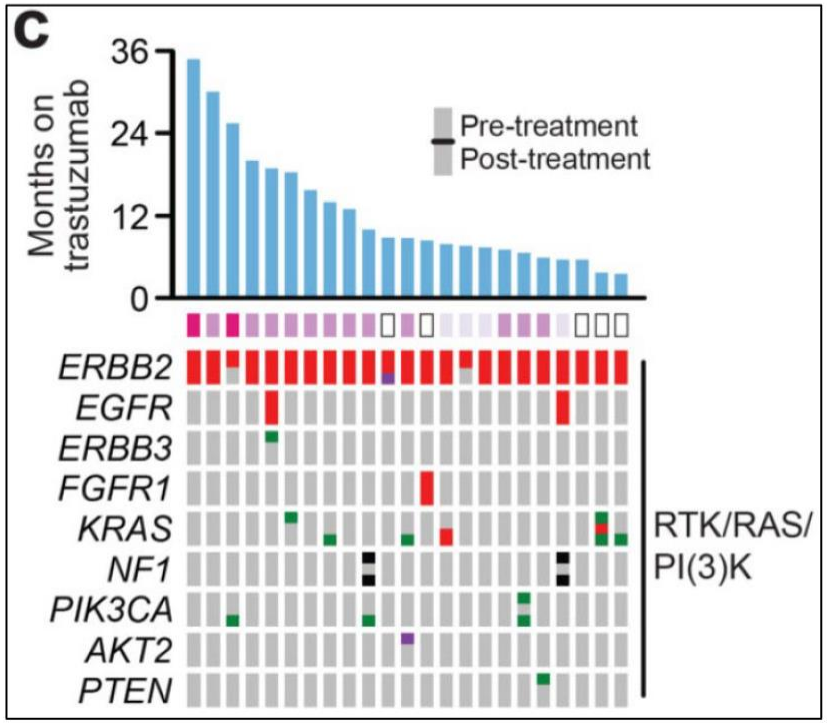


ERBB2 exon 16 deletion after trastuzumab treatment





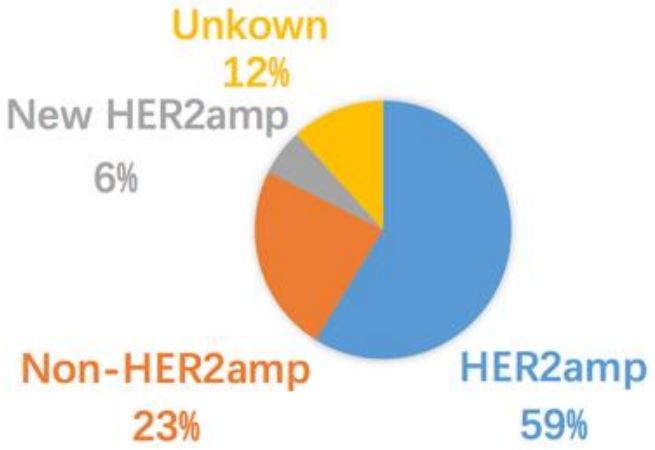
Co-mutations in RTK/RAS/PI3K pathway that bypassing the need of HER2 activation



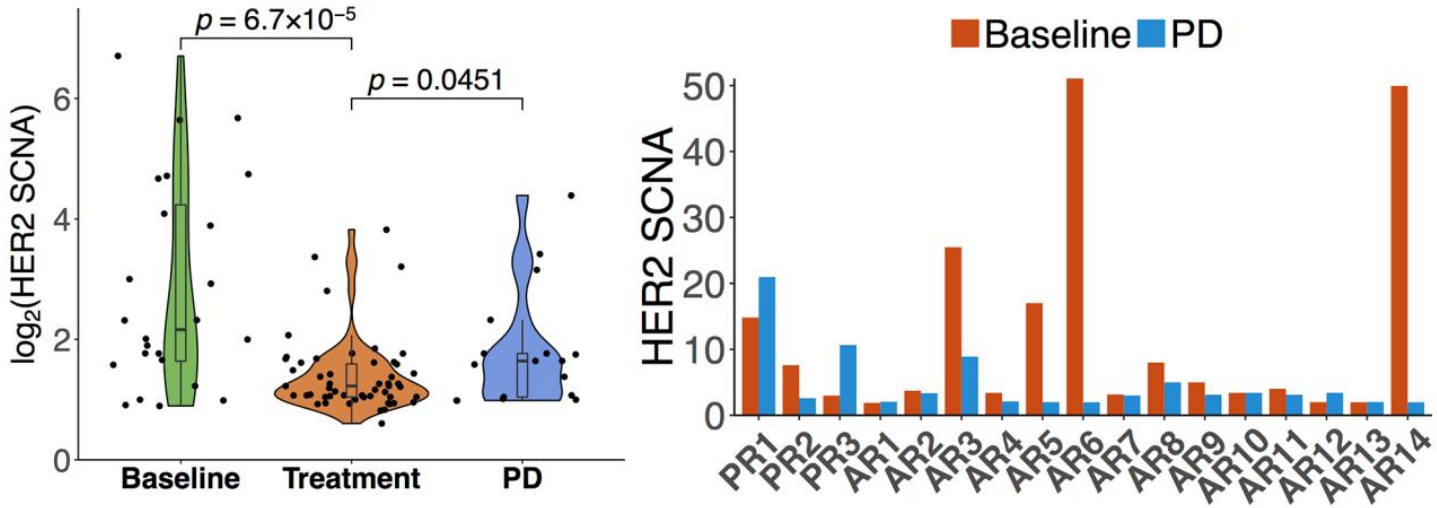
Janjigian YY et al., Genetic Predictors of Response to Systemic Therapy in Esophagogastric Cancer. Cancer Discov. 2018;8(1):49-58.

The role of ctDNA

- Concordance between ctDNA and tissue-based HER2 amplification
  - 61% (Maron Clin. Cancer Res. 2019;25:7098–7112.)
  - 91.2% (Wang. Eur. J. Cancer. 2018;88:92–100.)



Trastuzumab Resistance Clones at PD



HER2 Copy Number at Baseline and PD

Wang. Gut. 2019;68:1152.

Trastuzumab Beyond Progression

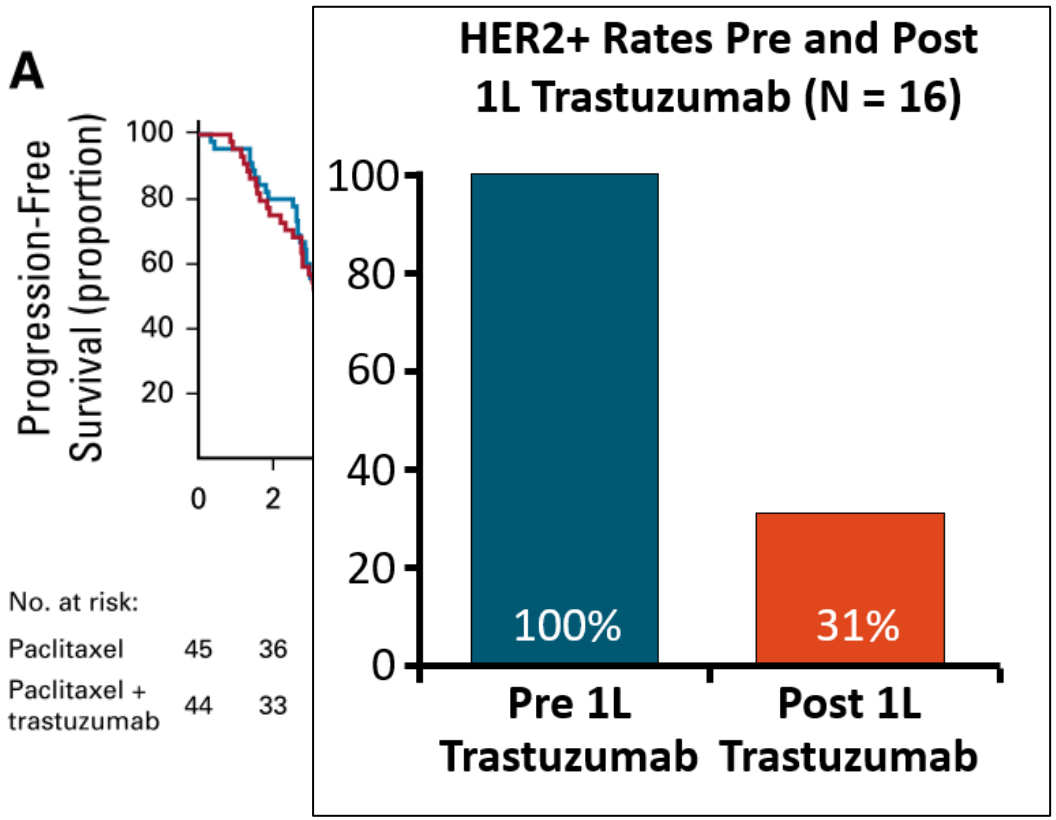
original reports

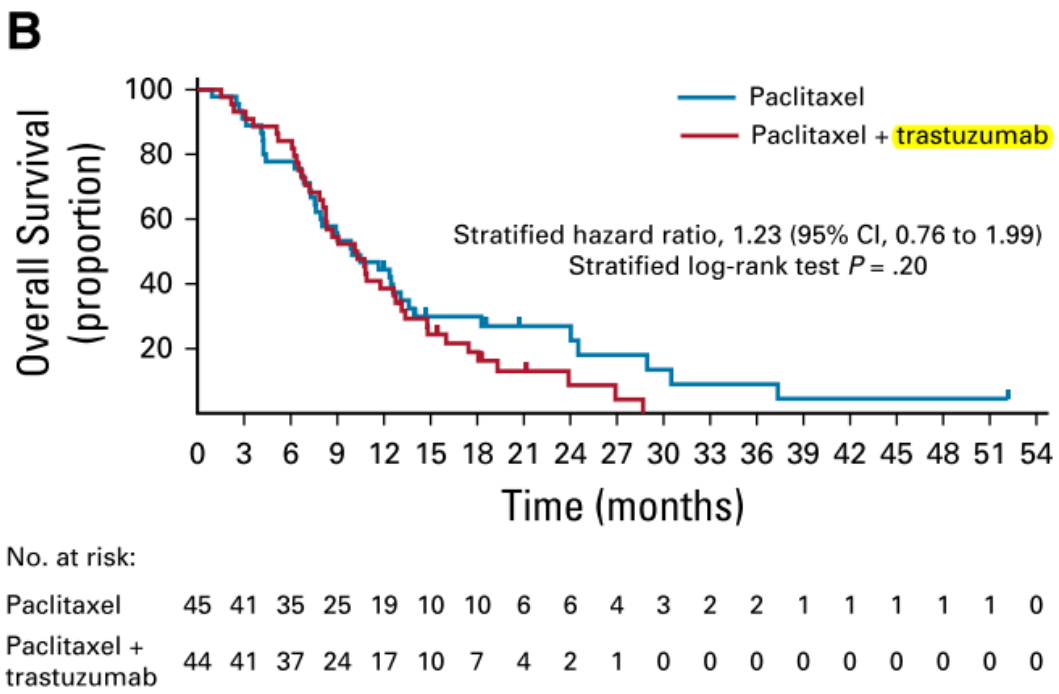
Randomized, Phase II Study of Trastuzumab Beyond Progression in Patients With HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer: WJOG7112G (T-ACT Study)

Akitaka Makiyama, MD, PhD[1]; Yasutaka Sukawa, MD, PhD[2]; Tomomi Kashiwada, MD, PhD[3]; Junji Kawada, MD[4]; Ayumu Hosokawa, MD, PhD[5]; Yoshiki Horie, MD, PhD[6]; Akihito Tsuji, MD, PhD[7]; Toshikazu Moriwaki, PhD, MD[8]; Hiroaki Tanioka, MD, PhD[9]; Katsunori Shinozaki, MD, PhD[10]; Keita Uchino, MD, PhD[11]; Hirofumi Yasui, MD[12]; Hiroshi Tsukuda, MD[13]; Kazuhiro Nishikawa, MD, PhD[14]; Hiroyasu Ishida, MD, PhD[15]; Takeharu Yamanaka, PhD[16]; Kentaro Yamazaki, MD[17]; Shuichi Hironaka, MD, PhD[18]; Taito Esaki, MD, PhD[19]; Narikazu Boku, MD, PhD[20]; Ichinosuke Hyodo, MD, PhD[8]; and Kei Muro, MD[21]

Trastuzumab Beyond Progression?

	PTX/Tmab	PTX	HR (p-value)
OS	10.2 mo	10.0 mo	1.23 (0.20)
PFS	3.7 mo	3.2 mo	0.91 (0.33)





JCO 2020:38:1919-27.

Trastuzumab **Beyond Progression?**

Trastuzumab Combined With Ramucirumab and Paclitaxel in Patients With Previously Treated Human Epidermal Growth Factor Receptor 2–Positive Advanced Gastric or Gastroesophageal Junction Cancer

2021 ASCO 2022 ASCO GI

Chang Gon Kim, MD, PhD[1]; Minkyu Jung, MD, PhD[1]; Hyo Song Kim, MD, PhD[1]; Choong-kun Lee, MD, PhD[1]; Hei-Cheul Jeung, MD, PhD[2]; Dong-Hoe Koo, MD, PhD[3]; Woo Kyun Bae, MD, PhD[4]; Dae Young Zang, MD, PhD[5]; Bum Jun Kim, MD, PhD[5]; Hyunki Kim, MD, PhD[6]; Un-Jung Yun, PhD[1,7]; Jingmin Che, MS[7,8]; Sejung Park, PhD[7]; Tae Soo Kim, PhD[7]; Woo Sun Kwon, PhD[7]; Juin Park, BS[7,9]; Sang Woo Cho, BS[7,10]; Chung Mo Nam, PhD[11]; Hyun Cheol Chung, MD, PhD[1]; and Sun Young Rha, MD, PhD[1,10]

Phase Ib: RP2D

Trastuzumab + Ramucirumab + Paclitaxel for RP2D (N=3~6)

Phase II: Efficacy

Trastuzumab + Ramucirumab + Paclitaxel with RP2D (N=50 including phase Ib)

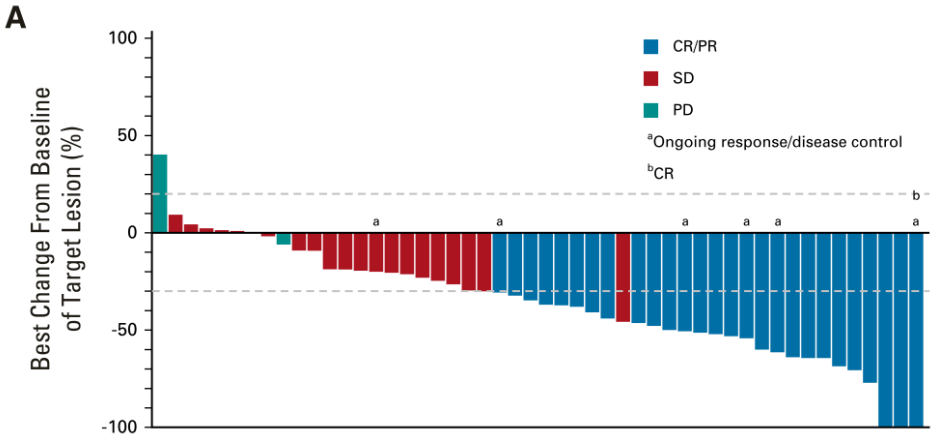
	Paclitaxel	Trastuzumab	Ramucirumab
Dose level (1)	80mg/m² on days 1, 8, and 15	4mg/kg (loading dose) followed by 2mg/kg on days 1, 8, 15, and 22	8mg/kg on days 1 and 15
Dose level (-1)	70mg/m² on days 1, 8, and 15		
Cycled every 28 days			

Category	Frequency (N = 50)
Best response, No. (%)	
CR	1 (2)
PR	26 (52)
SD	21 (42)
PD	2 (4)

ORR: 54%

DCR: 96%

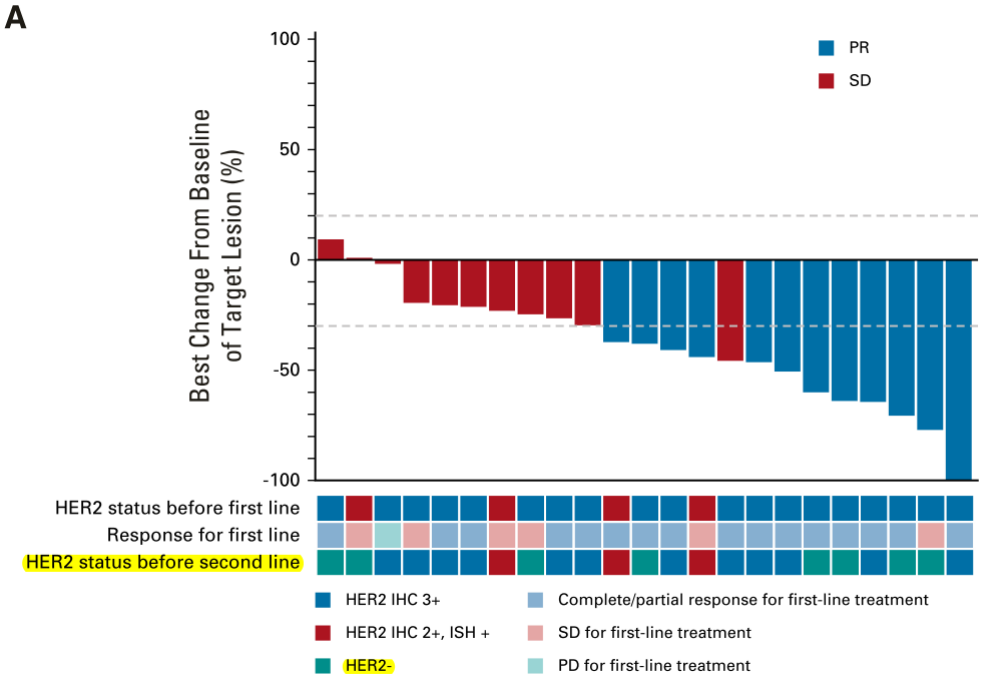
Tumor shrinkage: 82% (41/50)

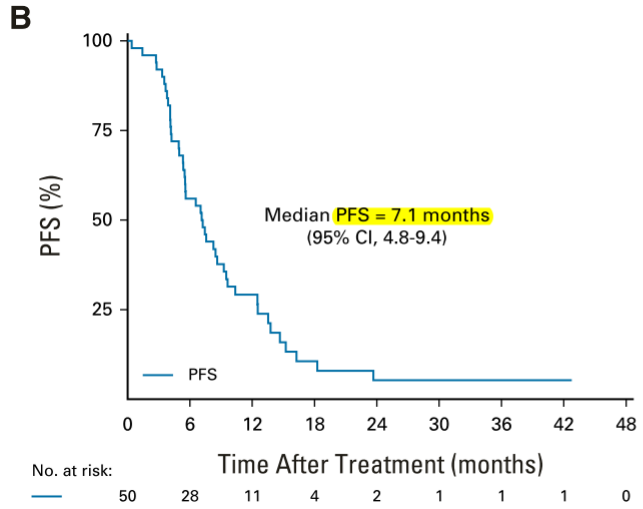


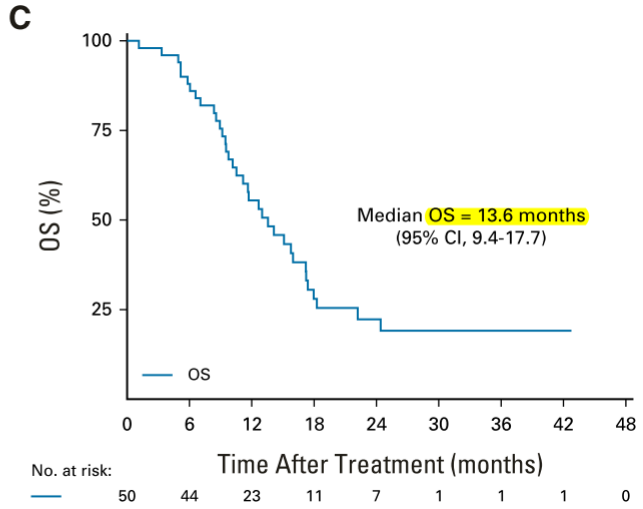
J Clin Oncol. 2023 Sep 20;41(27):4394-4405.

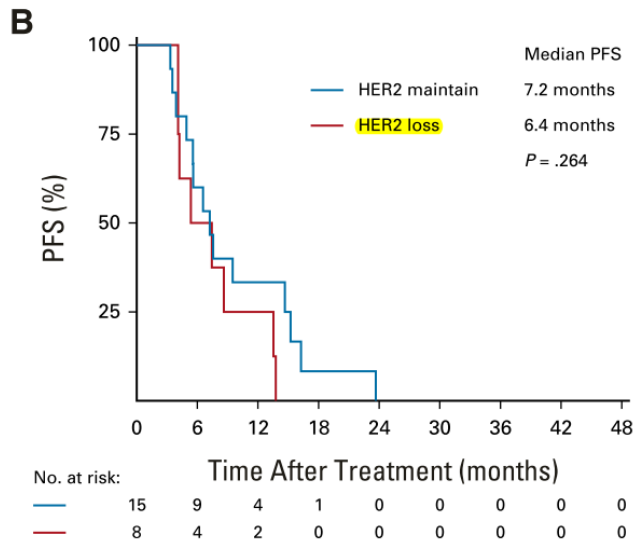
Trastuzumab **Beyond Progression?**

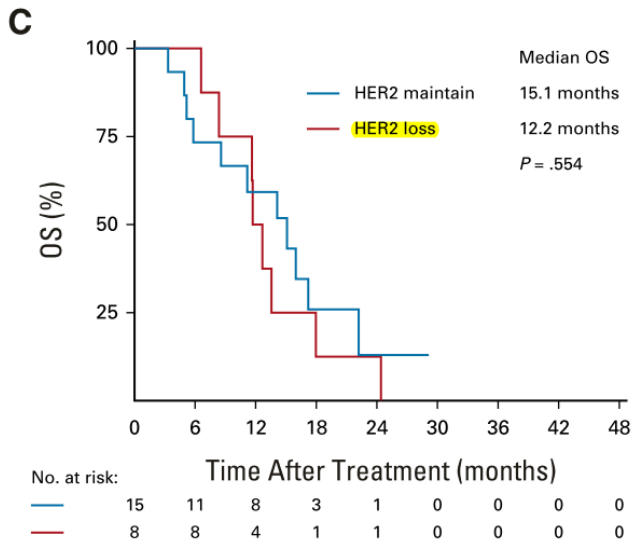
RAINBOW trial OS:9.6m











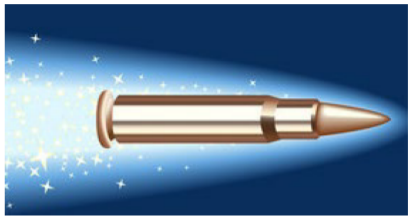
- HER2- loss after 1st line treatment was 8/23(34.7%)
- **Triplet** regimen might cover various tumor clones
- Novel agents? Re-biopsy?

J Clin Oncol. 2023 Sep 20;41(27):4394-4405.

Trastuzumab deruxtecan

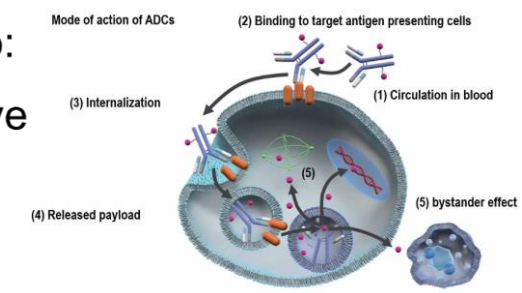
Trastuzumab deruxtecan (T-DXd) Was Designed With 7 Key Attributes

T-DXd is an antibody drug conjugate (ADC) composed of 3 components[1,2]:

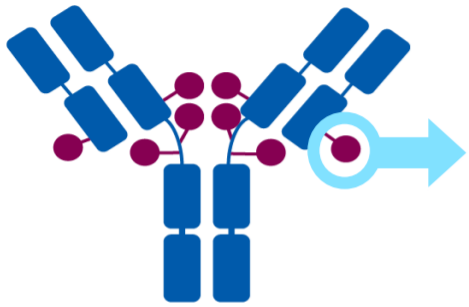


Paul Ehrlich: "Magic Bullet"

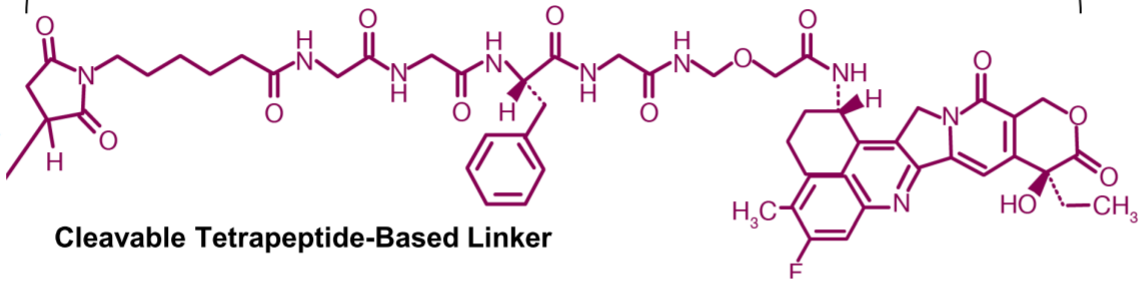
- A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab, covalently linked to:
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker



Humanized anti-HER2 IgG1 mAb[1-3]



Deruxtecan[1,2]



Cleavable Tetrapeptide-Based Linker

Topoisomerase I Inhibitor payload
(DXd=DX-8951f derivative)

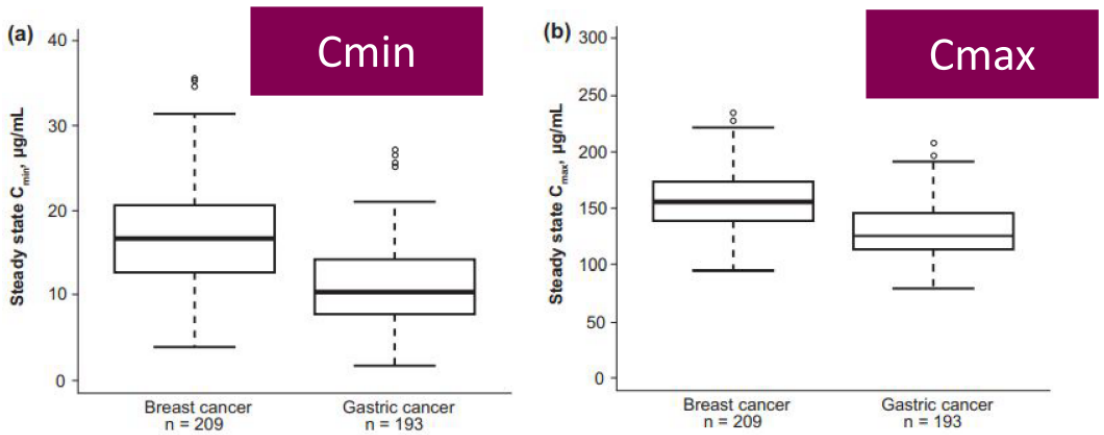
Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
High potency of payload [a,1,2]
High drug to antibody ratio ≈ 8 [a,1,2]
Payload with short systemic half-life [a,1,2]
Stable linker-payload [a,1,2]
Tumor-selective cleavable linker [a,1,2]
Bystander antitumor effect [a,1,4]

[a]The clinical relevance of these features is under investigation.

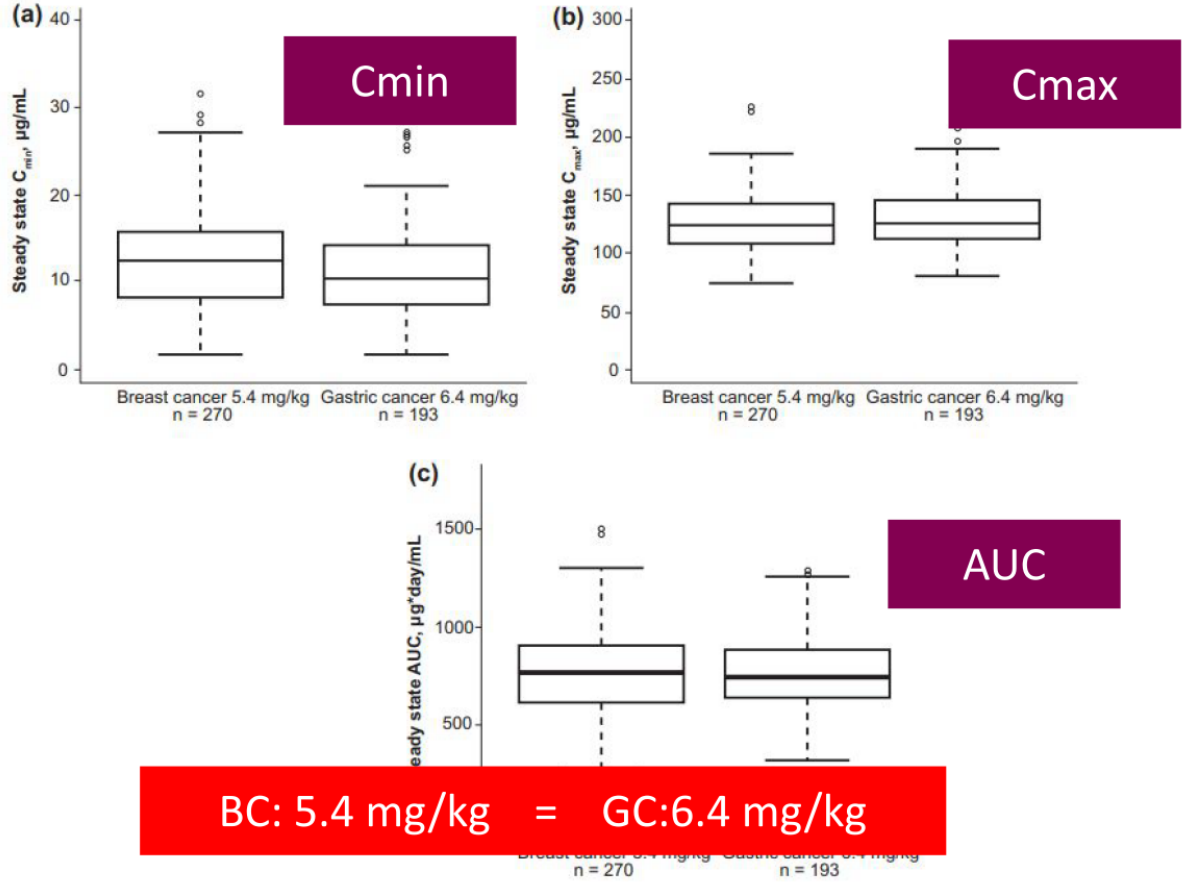
1. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 2. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108. 3. Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142. 4. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046.

T-DXd 6.4 mg/kg as the recommended dose in HER2-positive gastric cancer by Population Pharmacokinetic Modeling

- 808 patients (217 with GC, 512 with BC, and 79 with other cancers)



BC: 6.4 mg/kg > GC:6.4 mg/kg



BC: 5.4 mg/kg = GC:6.4 mg/kg

Yoshihara et al, Pharmacometrics 2023

Population Pharmacokinetic study between breast vs gastric

Table 2. Summary of Model-Predicted Interstitial Lung Disease by Country/Race

	Japanese Asian		Non-Japanese Asian	
End point	Breast cancer 5.4 mg/kg	Gastric cancer 6.4 mg/kg	Breast cancer 5.4 mg/kg	Gastric cancer 6.4 mg/kg
Any-grade ILD over 90 days	3.9 (3.0–4.9)	4.1 (3.2–5.3)	0.5 (0.0–1.1)	0.7 (0.0–1.3)
Any-grade ILD over 180 days	9.7 (8.2–11.8)	10.2 (8.7–12.8)	1.4 (0.0–2.8)	1.7 (0.0–3.4)
Any-grade ILD over 360 days	19.8 (17.4–23.3)	20.5 (18.1–24.6)	3.0 (0.0–6.0)	3.8 (0.0–7.5)
Grade ≥3 ILD over 90 days	0.9 (0.5–1.3)	1.0 (0.6–1.4)	0.9 (0.5–1.3)	0.8 (0.5–1.2)
Grade ≥3 ILD over 180 days	1.8 (1.1–2.7)	2.0 (1.2–3.0)	1.8 (1.1–2.7)	1.6 (0.9–2.5)
Grade ≥3 ILD over 360 days	2.3 (1.6–2.9)	2.5 (1.8–3.2)	2.2 (1.5–2.8)	2.0 (1.4–2.7)

- ILD incidence seems to be comparable between 5.4 in breast and 6.4 in gastric

Yoshihara K, et al. J Clin Pharmacol. 2023

DESTINY-Gastric01: randomized phase 2 study

An open-label, multicenter, randomized phase 2 study

Patients

- **HER2**-expressing advanced gastric or GEJ adenocarcinoma by central assessment (in most recently available tumor samples)
- **≥ 2 Prior** regimens; must include fluoropyrimidine and a platinum agent

劑量決定 Phase 1 study
6.4mg/kg反應率優於5.4mg/kg

REGISTRATION

R 2:1

Primary cohort (HER2 positive [IHC 3+ or IHC 2+/ISH+])
- Progressed on trastuzumab-containing regimen

- **T-DXd** (n = 125)
  6.4 mg/kg, 3-week cycle
- **Physician's choice (PC)**
  (irinotecan or paclitaxel) (n = 62)

Exploratory cohorts (HER2 low)
- Anti-HER2 treatment naive

- **Cohort 1: HER2 (IHC 2+/ISH–)**
  T-DXd (N ≈ 20)
- **Cohort 2: HER2 (IHC 1+)**
  T-DXd (N ≈ 20)

Primary endpoint

- **ORR** by independent central review (ICR)

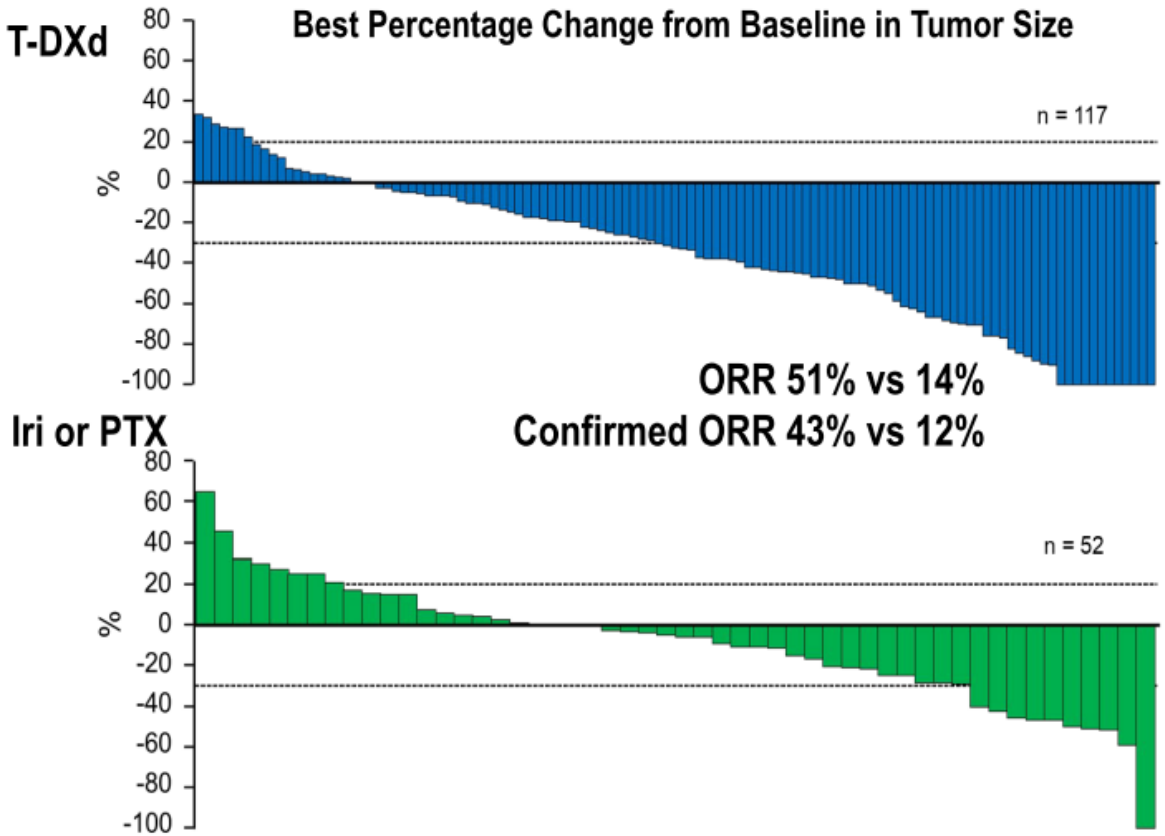
Key secondary endpoint

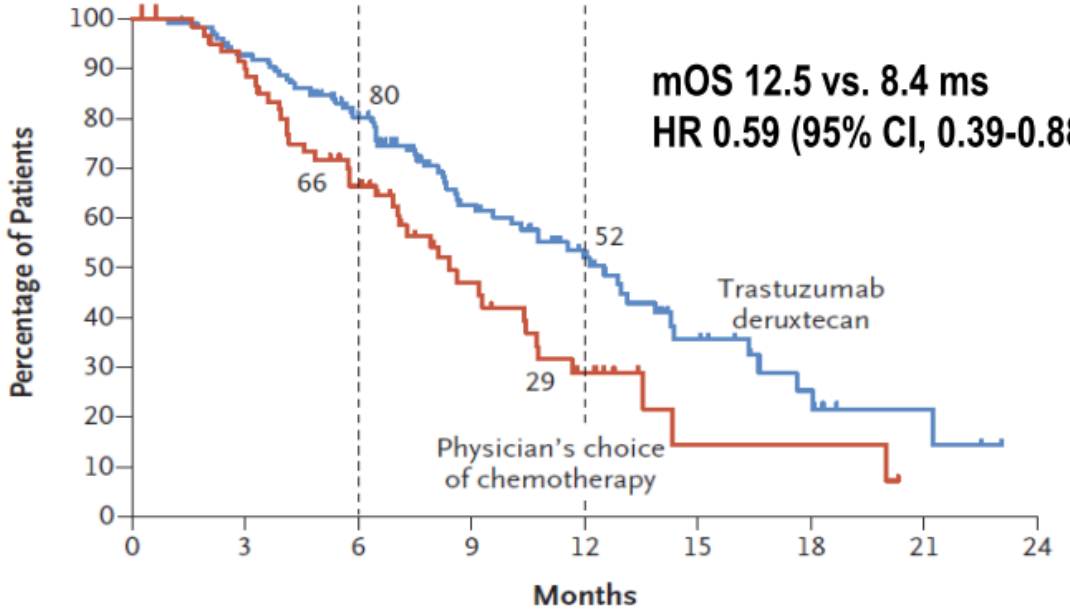
- **OS to be statistically evaluated hierarchically** if the primary endpoint was statistically significant (overall α error was 5%)

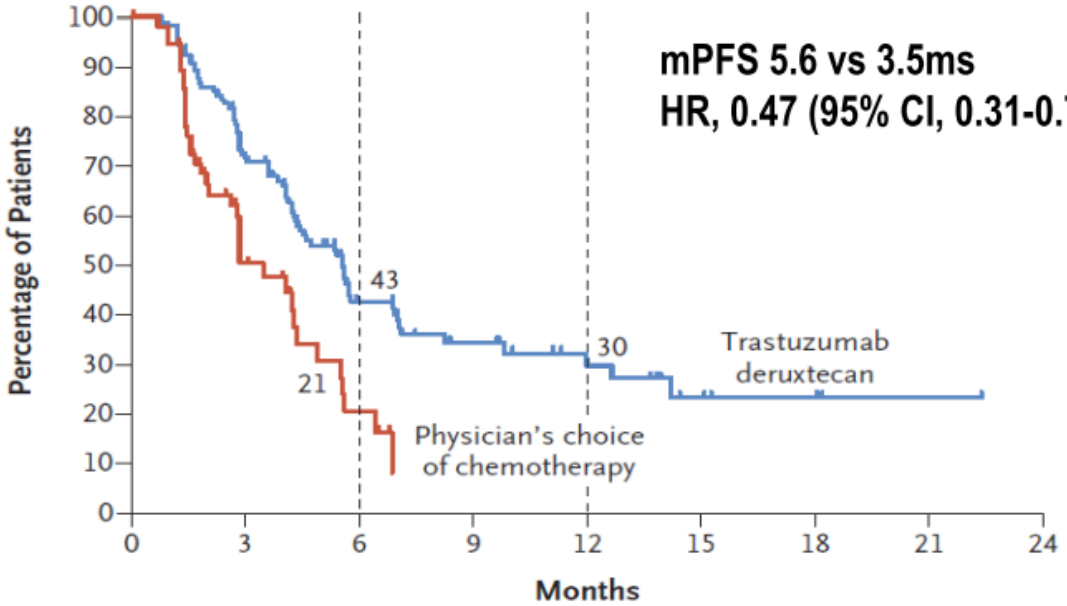
- 187 patients were randomized (T-DXd, n = 125; PC, n = 62)
- 76% of patients had HER2 IHC 3+, **80% from Japan**
- The median number of prior systemic therapies was 2 (range, 2-9)
- **86% had received taxanes, 72% ramucirumab, and 33% anti-PD1**

Shitara K, et al. N Engl J Med. 2020, ASCO 2020

DESTINY-Gastric01: T-DXd vs. chemo in pretreated HER2+ GC



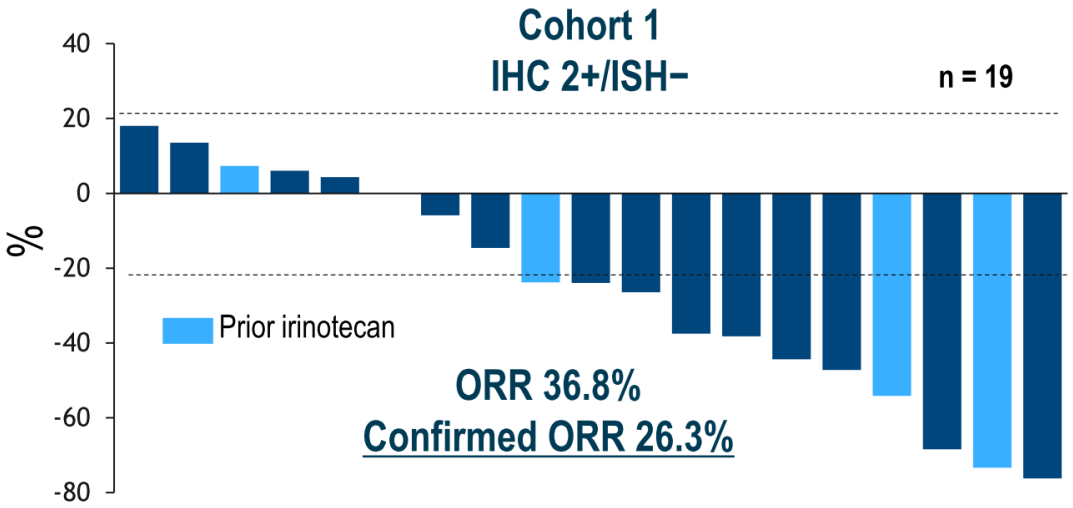


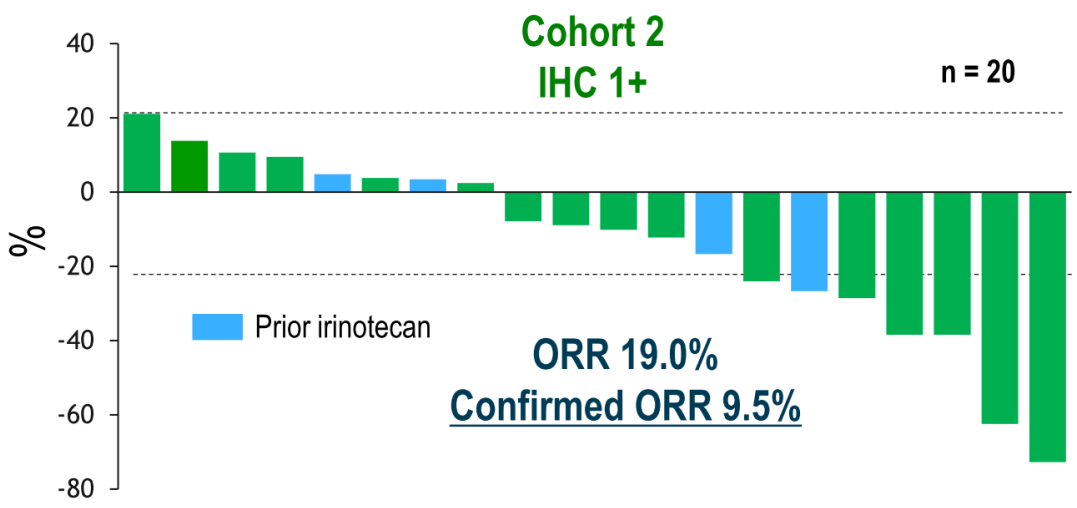


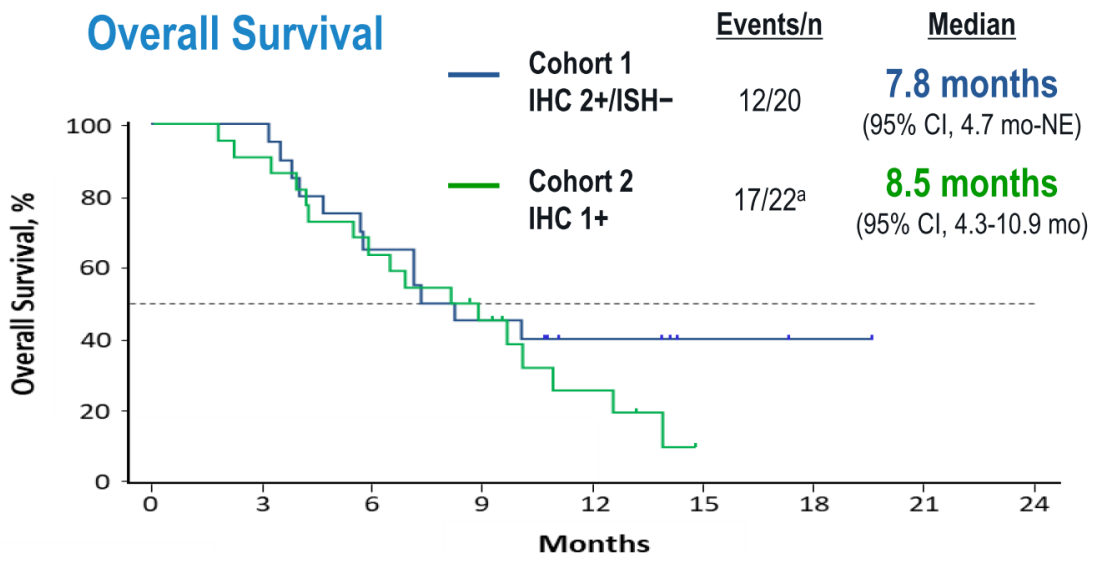
- T-DXd significantly improved ORR and OS
- PFS also apparently favor T-DXd

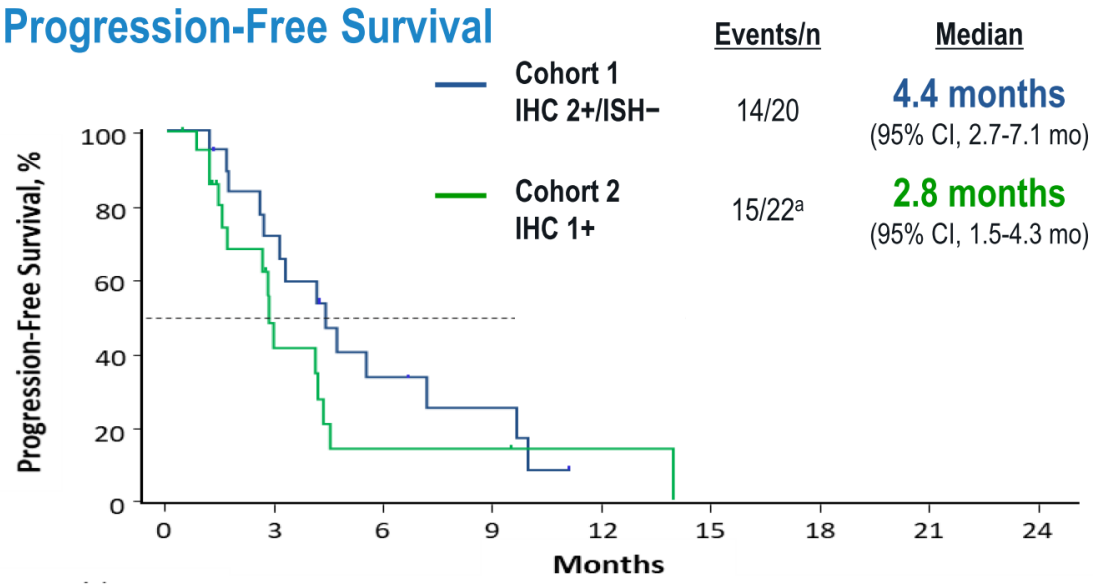
Shitara K, et al. N Engl J Med. 2020

DESTINY-Gastric01: HER2 low cohort









Yamaguchi K, et al. ESMO 2020; JCO 2022

DESTINY-Gastric02: Second-line Trastuzumab Deruxtecan for Advanced HER2+ GC/GEJ Cancers

- Phase II, single-arm study of **Western** patients with HER2+ gastric/GEJ cancers
- Patients progressed while on or after first-line, trastuzumab-based therapy
  - HER2+ by ISH 3+ or ISH 2+/ISH+ **post progression biopsy**
- 1 (96.2%) or 2 (3.8%) prior lines of therapy
- Primary endpoint: Confirmed ORR

Outcome	T-DXd (N = 79)
Median follow-up duration, mo	10.2
Confirmed ORR, n (%)	33 (41.8)
• CR, n (%) • PR, n (%)	4 (5%) 29 (37%)
Median OS, mo (95% CI)	12.1 (9.4-15.4)
12-mo OS rate	50.6%
Median DoR, mo (95% CI)	8.1 (5.9-NE)
Median PFS, mo (95% CI)	5.6 (4.2-8.3)

➢ Confirmed ORR :42% in GC02 and 43% in GC01

➢ Median PFS 5.6ms in GC02 and 5.6ms in GC01

Ku. ESMO 2022. Abstr 1205M0.

Slide credit: clinicaloptions.com

DESTINY-GC01+GC02 **Safety Summary**

BM、GI、ILD

TEAEs associated with:	DESTINY-GC01 (n = 125)	DESTINY-GC02 (n = 79)
T-DXd related any AE	98%	100%
T-DXd related grade≥3	75%	30%
Drug discontinuation	15%	13%
Dose reduction	32%	18%
Specific AEs all grade /≥G3:	**DESTINY-GC01 (n = 125)**	**DESTINY-GC02 (n = 79)**
Neutrophil count decreased	63% / 51%	17% / 8%
Platelet count decreased	39% / 10%	18% / 3%
Nausea	63% / 5%	67% / 8%
Decreased appetite	60% / 17%	33% / 5%
Malaise or Fatigue	34% / 1%	42% / 4%
Diarrhea	32 % / 2%	36% / 1%
ILD / Pneumonitis	10% / 2%	10% / 1%

➢Bone marrow suppressions and mild GI toxicities were common (but lower in GC02 than GC01)

Adequate antiemetics

ILD/Pneumonitis in GC-01

- **12 patients (9.6%)** had T-DXd-related ILD/pneumonitis
- **16 patients (+4 patients)** with ILD at the updated analysis
  - Median time to first onset , **102.5 days** (range, 36-638 days)
  - Most were grade 1-2 (G1-2, n=13; G 3, n=2; G 4, n=1)

ILD/Pneumonitis in GC-02

- **8 patients (10%)** with ILD at the updated analysis
  - Median time to first onset , **80.5 days**
  - Most were grade 1-2 (G1-2, n=6; G5, n=2)
  - Two TRD (ILD or pneumonitis)

Shitara K, et al. N Engl J Med. 2020;Yamaguchi K, et al. ASCO 2021; Van Cutsem E, et al. Lancet Oncol 2023

ILD Mechanisms

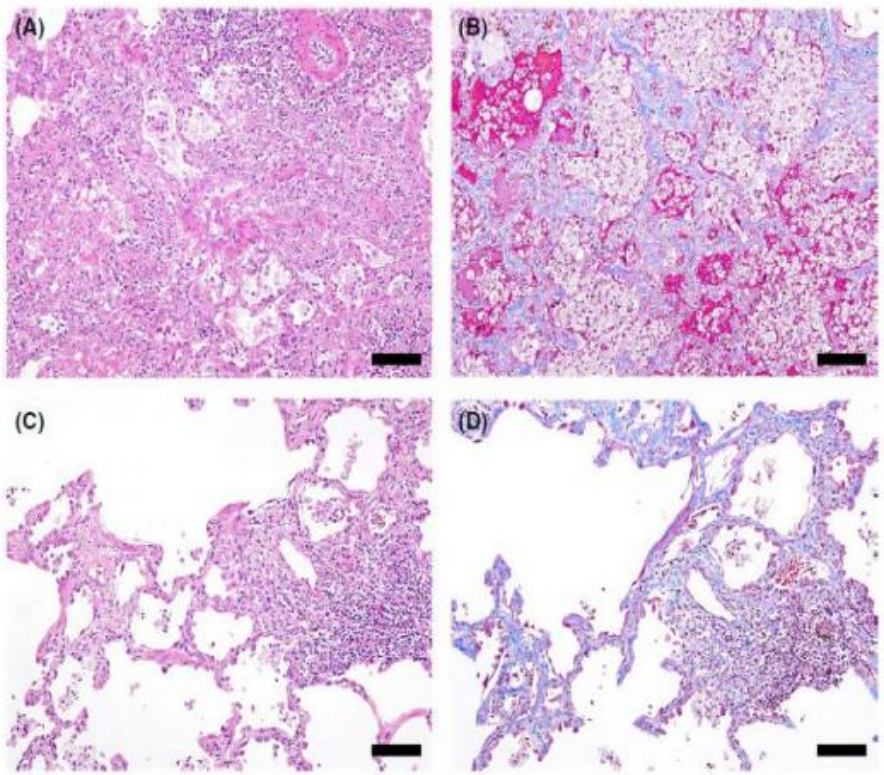


FIGURE 1 Lung interstitial inflammation associated with trastuzumab deruxtecan (T-DXd) treatment in cynomolgus monkeys. A, B, Inflammatory cell infiltrates such as neutrophils and lymphocytes in the alveolar wall, intraalveolar fibrosis, alveolar edema, and aggregates of foamy alveolar macrophages were observed at 78.8 mg/kg T-DXd in the 6-week toxicity study (A, H&E; B, Masson-trichrome). C, D, Thickening of the alveolar wall with lymphocytic inflammation and fibrosis was observed at 30 mg/kg T-DXd in the 3-month toxicity study (C, H&E; D, Masson trichrome). Bar, 100 µm

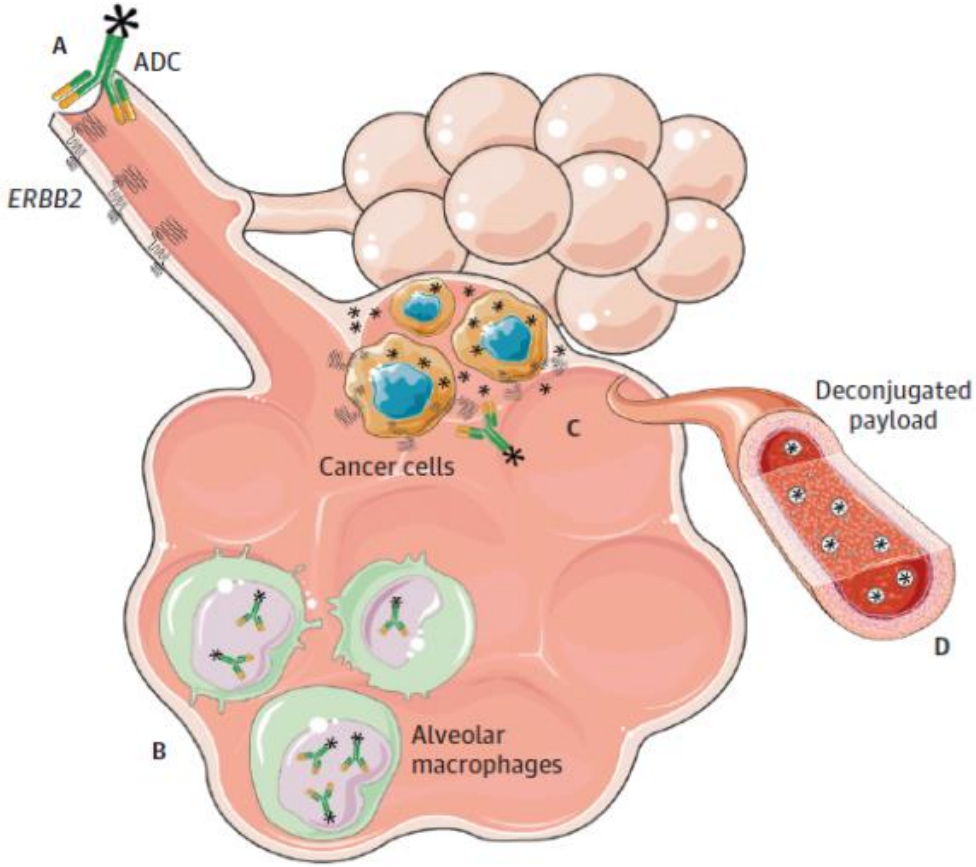
In monkeys model:

-Diffuse lymphocytic infiltrates and slight fibrosis

-DXD did not induce ILD but T-DXD did

-HER2 was not expressed at alveolar level

-Possibly target-independent uptake of T-DXd via Fc into alveolar macrophages by mouse model



A, ERBB2-dependent uptake of the ADC (asterisk). B, ERBB2-independent uptake of the ADC in intra-alveolar immune cells. C, Bystander killing by free payload released from targeted cancer cells. D, Deconjugated payload circulating in the bloodstream. This image was created using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License.[32]

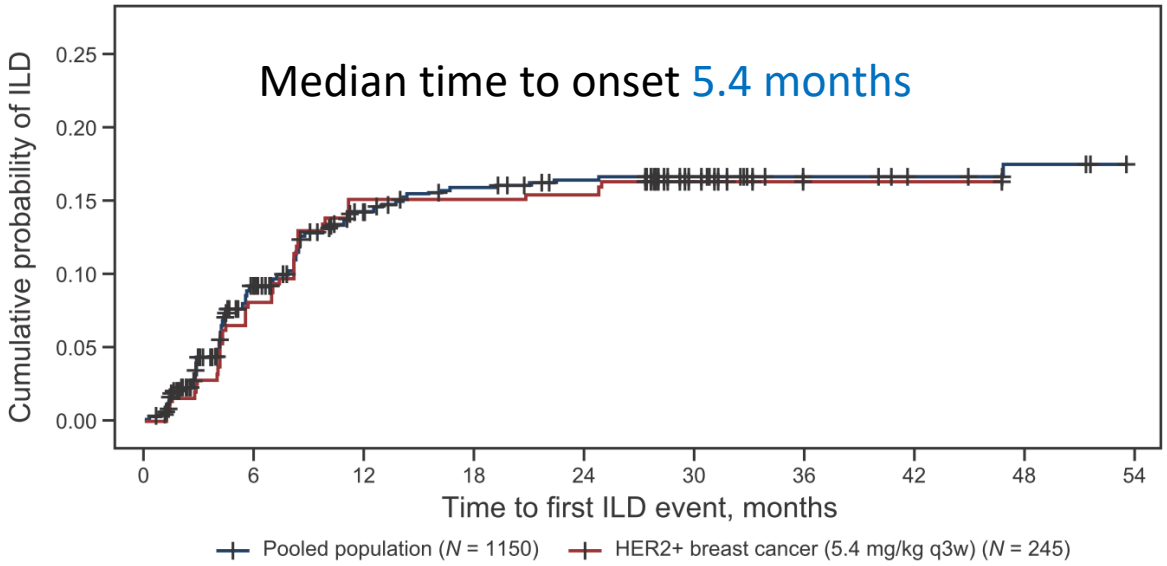
Kumagai K, et al. Cancer Science 2020; Tarantino P, et al. JAMA Oncol 2021

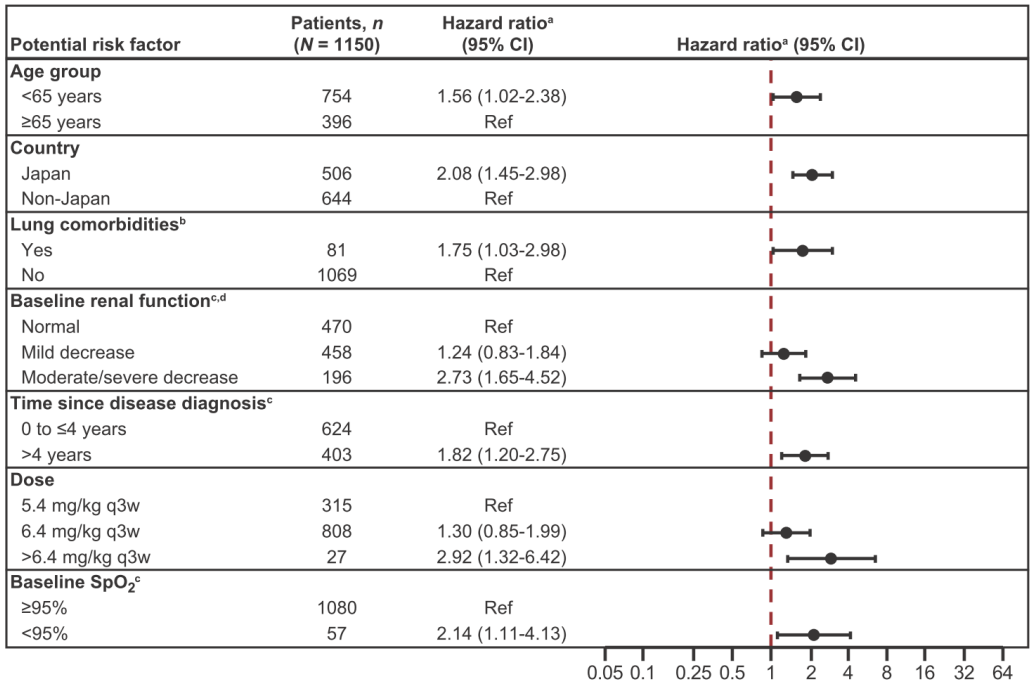
Pooled Analysis of ILD from 8 single arm studies with T-DXd

Table 3. Adjudicated drug-related ILD/pneumonitis by tumor type and grade[a]

25 patients

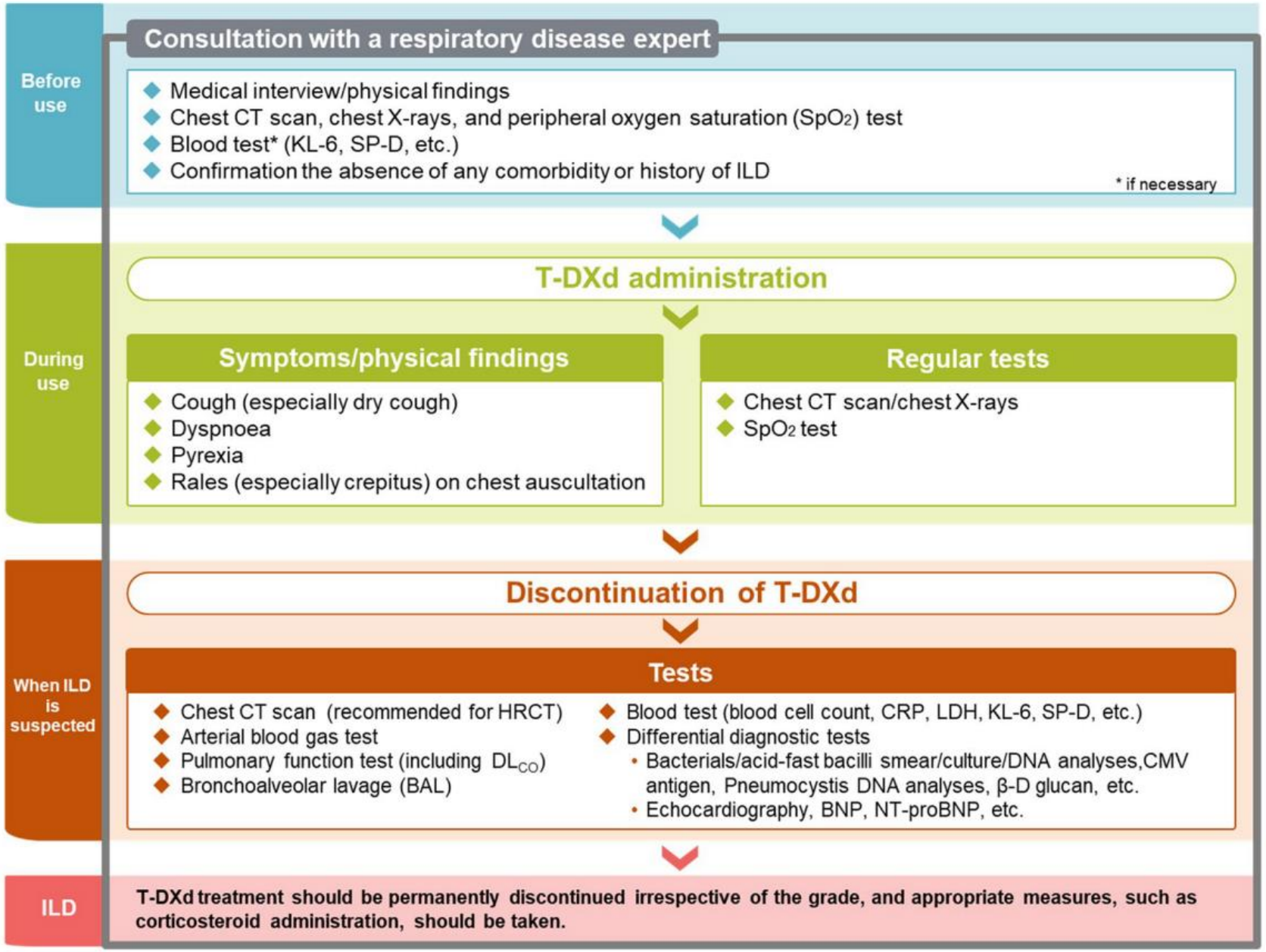
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
All patients ($N = 1150$)	48 (4.2)	89 (7.7)	14 (1.2)	1 (0.1)	25 (2.2)	177 (15.4)
Breast cancer ($n = 510$)	32 (6.3)	51 (10.0)	7 (1.4)	0	15 (2.9)	105 (20.6)
HER2-positive breast cancer treated with T-DXd 5.4 mg/kg q3w ($n = 245$)[b]	9 (3.7)	22 (9.0)	2 (0.8)	0	7 (2.9)	40 (16.3)
Gastric cancer ($n = 294$)	5 (1.7)	15 (5.1)	3 (1.0)	1 (0.3)	1 (0.3)	25 (8.5)
Lung cancer ($n = 203$)[c]	7 (3.4)	16 (7.9)	2 (1.0)	0	6 (3.0)	31 (15.3)
Colorectal cancer ($n = 107$)	0	5 (4.7)	1 (0.9)	0	3 (2.8)	9 (8.4)
Other cancer ($n = 34$)	4 (11.8)	2 (5.9)	1 (2.9)	0	0	7 (20.6)





Powel CA, et al. AACR 2021; ESMO open 2022

Management of T-DXd ILD/pneumonitis



Shitara K, et al. Gastric Cancer. 2021 Jul;24(4):780-789.

Updated guidelines (2019) for ILD monitoring and management in clinical trials

STEP 1: Monitor

Suspected ILD

Interrupt drug

Rule out ILD if a patient develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever.

STEP 2: Confirm

Evaluations should include:

- High-resolution CT
- Pulmonologist consultation (infectious disease consultation as clinically indicated)
- Blood culture and CBC. Other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- PFTs and pulse oximetry
- Arterial blood gasses, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD is suspected, if feasible

All events of ILD, regardless of severity or seriousness, should be followed until resolution including after drug discontinuation.

STEP 3: Manage

Drug must be interrupted for any ILD events regardless of grade

- **Grade 1: Interrupt until fully resolved**, then:
  - if resolved in 28 days or less from date of onset, maintain dose
  - if resolved in greater than 28 days from date of onset, reduce dose one level
  - however, if the event Grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued
- **Grades 2-4: Permanently discontinue treatment.** Refer to toxicity management guidelines for trastuzumab deruxtecan

Strong recommendation of pulmonologist/radiologist consultation (MDT approach)

Powel CA, et al. AACR 2021; ESMO open 2022

Updated guidelines (2019) for ILD monitoring and management in clinical trials

Guidelines were updated to be more specific regarding steroid dose and duration.

	Grade 1	Grade 2	Grade 3/4

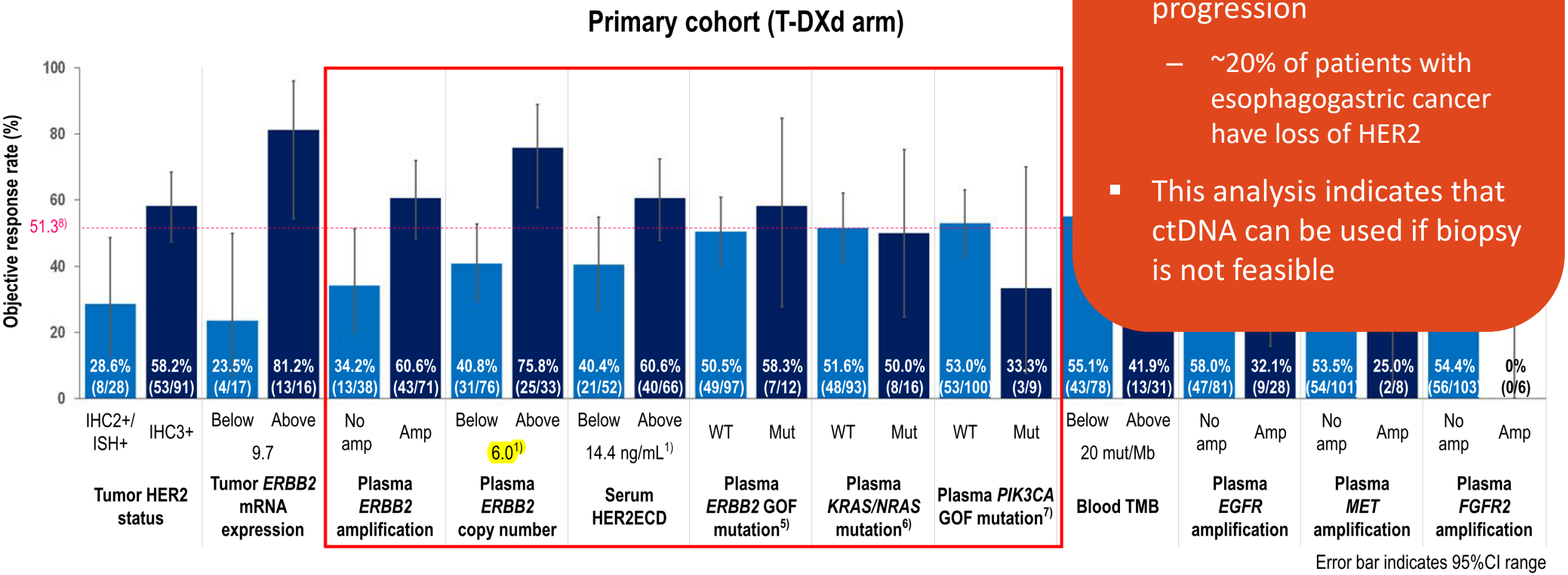
Toxicity management	• Monitor and closely follow-up in 2 to 7 days for onset of clinical symptoms and pulse oximetry
	• Consider follow-up imaging in 1-2 weeks (or as clinically indicated)
	• **Consider starting systemic steroids** (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by **gradual taper over at least 4 weeks**
	• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines
	  • **If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given**
		• Promptly start and **treat with systemic steroids** (e.g., at least 1mg/kg/day prednisone or equivalent) for at **least 14 days** or until complete resolution of clinical symptoms and chest CT findings, then followed by a **gradual taper over at least 4 weeks**
		• Monitor symptoms closely
		• Re-image as clinically indicated
		• If worsening or no improvement in clinical or diagnostic observations in 5 days,
		  • **Consider increasing dose of steroids** (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone)
		  • Re-consider additional work-up for alternative etiologies as described above
		  • Escalate care as clinically indicated
			• Hospitalization required
			• Promptly **initiate empiric high-dose methylprednisolone IV treatment** (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) **for at least 14 days** followed by a gradual taper over at least 4 weeks
			• Re-image as clinically indicated
			• If still no improvement within 3 to 5 days,
			  • Re-consider additional work-up for alternative etiologies as described above
			  • Consider other immuno-suppressants and/or treat per local practice

Strong recommendation of pulmonologist/radiologist consultation (MDT approach)

Powel CA, et al. AACR 2021; ESMO open 2022

Biomarkers in DESTINY-GC01

- FDA urges biopsy of all patients after trastuzumab progression
  - ~20% of patients with esophagogastric cancer have loss of HER2
- This analysis indicates that ctDNA can be used if biopsy is not feasible

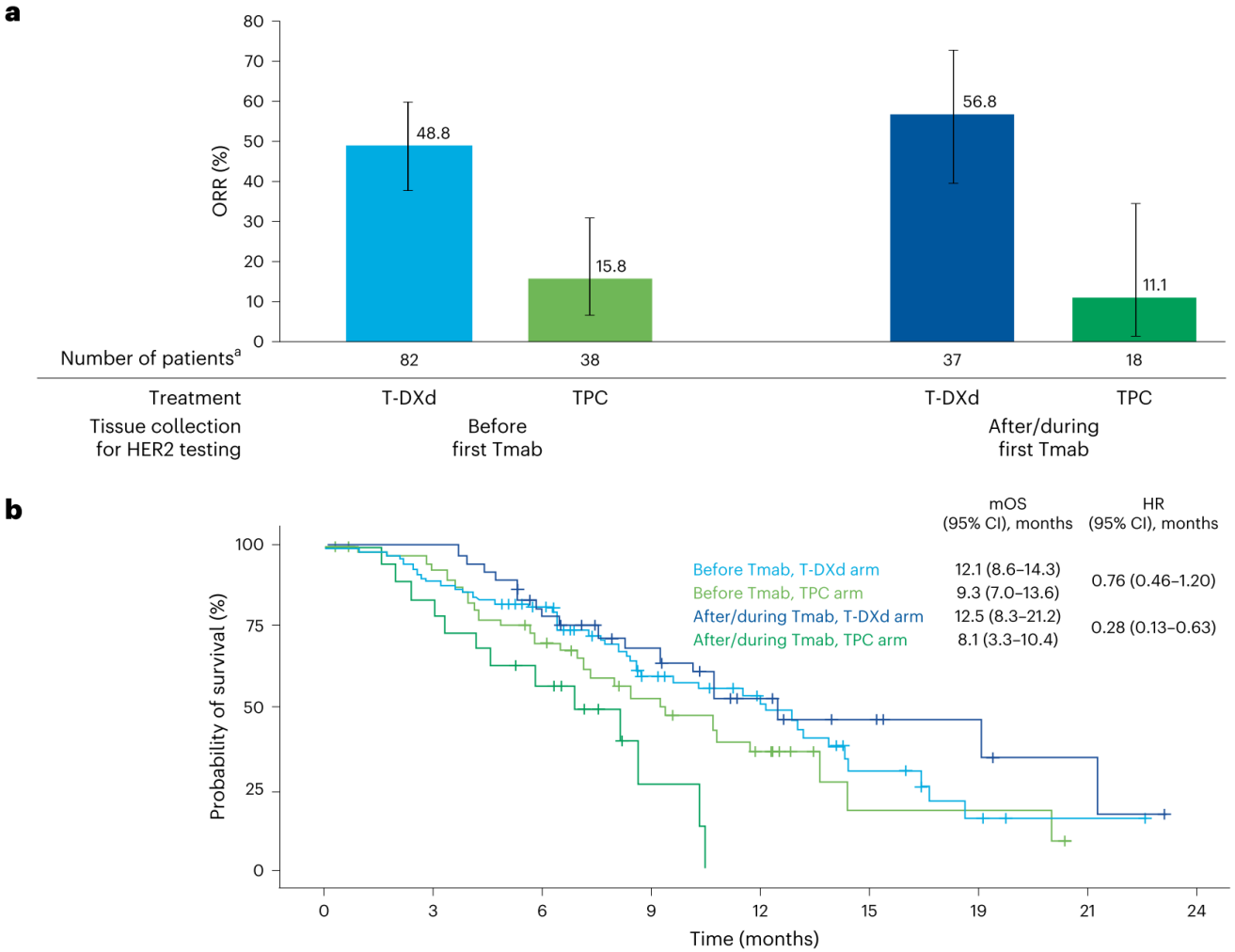


Error bar indicates 95%CI range

ORR appears to be correlated with baseline HER2 level in both tissue (IHC/ISH and mRNA gene expression) and liquid (plasma *ERBB2* copy number)

Shitara K, et al. Manuscript submitted. ESMO-GI 2021

Tissue collection **Timing** ?

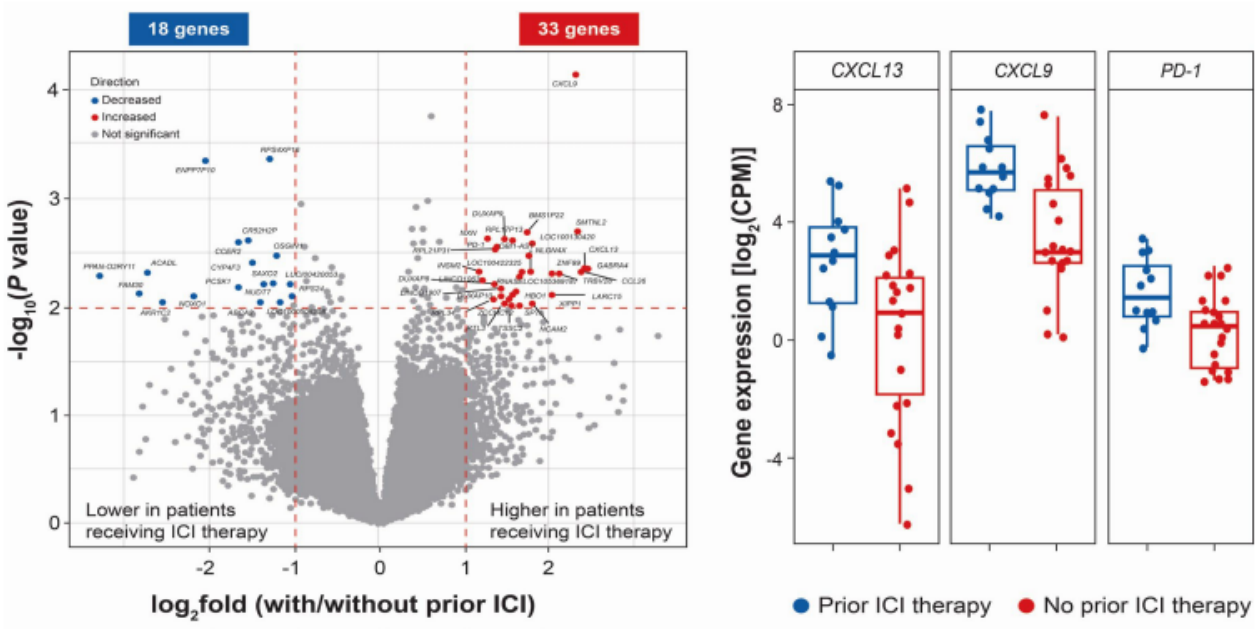


- Tissue collection before or after/during Tmab didn’t influence the outcome of TDxd

Shitara et al. Nat Med (2024).

Efficacy of T-DXd and exposure to previous **Anti-PD1** exploratory analysis from DSGC01

	Prior ICI Therapy		No Prior ICI Therapy	
Efficacy[a]	**T-DXd n = 44**	**PC Chemotherapy n = 17**	**T-DXd n = 81**	**PC Chemotherapy n = 45**
ORR, %	**65.9** (29/44)	25.0 (4/16)	**42.7** (32/75)	10.0 (4/40)
Confirmed ORR,[b] %	**56.8** (25/44)	18.5 (3/16)	**34.7** (26/75)	10.0 (4/40)
Median OS, months	16.6	8.6	10.3	8.4
95% CI	12.1-21.2	3.6-10.7	8.1-13.0	6.9-13.6
	HR, 0.31 (95% CI, 0.15-0.63)		HR, 0.83 (95% CI, 0.50-1.35)	



- Prior ICI therapy was received by 35.2% of patients in the T-DXd arm and 27.4% of patients in the PC chemotherapy arm
- Patients treated with T-DXd had significantly higher ORRs and confirmed ORRs than those who received PC chemotherapy, regardless of whether they had prior ICI therapy
- 33 genes had a trend for higher expression in patients who had received prior ICI
- Differentially expressed genes included those for immuno-oncology related molecules such as CXCL13, CXCL9, and PD-1

Shitara K, et al. ASCO-GI 2022

Phase 1/2 Study: T-DXd plus chemo +/- anti-PD1 (DESTINY-Gastric03)

Part 1 – Dose escalation (3 + 3)[a]

Population

- Metastatic or unresectable HER2-positive (IHC 3+ or 2+/ISH positive per local assessment) GC or GEJ adenocarcinoma[b]
- ≥2L following trastuzumab-containing therapy

Allocate

- Arm 1A: T-DXd + 5-FU q3w
- Arm 1B: T-DXd + Cap q3w
- Arm 1D(a): T-DXd + 5-FU + oxaliplatin q3w
  Arm 1D(b): T-DXd + Cap + oxaliplatin q3w
- Arm 1C: T-DXd + durvalumab q3w
- Arm 1E(a): T-DXd + 5-FU + durvalumab q3w
  Arm 1E(b): T-DXd + Cap + durvalumab q3w

Endpoints

- **Primary:** Safety and RP2D
- **Secondary:** Confirmed ORR per RECIST v1.1, DoR, PFS, OS, PK
- **Exploratory:** ctDNA and tissue samples for candidate biomarkers

Part 2 – Dose expansion: RP2D from Part 1 (N≈40 patients/arm)

Population

- Previously untreated metastatic or unresectable HER2-positive (IHC 3+ or 2+/ISH positive per local assessment) GC or GEJ adenocarcinoma[b]
- Stratified by HER2 status (IHC 3+ or IHC 2+/ISH positive)

Randomize

- Arm 2A[c]: SOC (trastuzumab + FP[d] + platinum[e])
- Arm 2B[c]: T-DXd monotherapy[f] q3w
- Arm 2C: T-DXd + chemo (FP[d] ± oxaliplatin)
- Arm 2D: T-DXd + chemo (FP[d]) + pembrolizumab q3w
- Arm 2E: T-DXd + pembrolizumab q3w

Endpoints

- **Primary:** Confirmed ORR per RECIST v1.1
- **Secondary:** Safety, DoR, PFS, OS, PK
- **Exploratory:** ctDNA and tissue samples for candidate biomarkers

Arm 1A and Arm 1B

Figure 3. Best percentage change in target lesion size from baseline

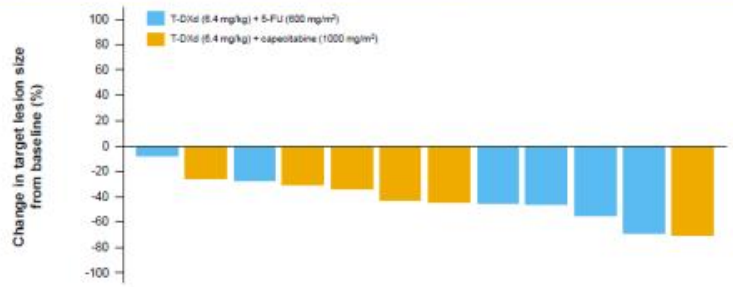
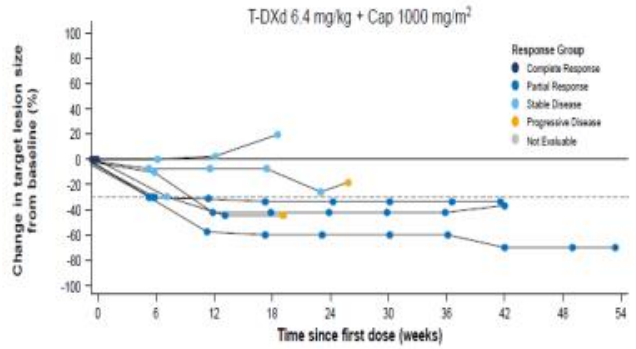


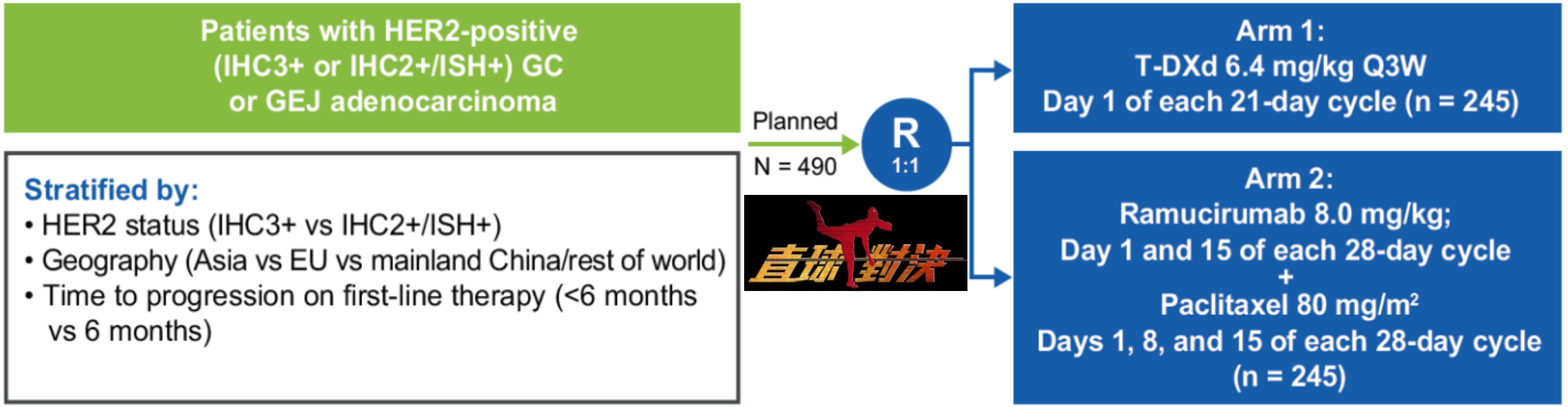
Figure 4. Percentage change in target lesion size from baseline over



- The RP2D dose was determined to be T-DXd 6.4 mg/kg + Cap 1000 mg/m2 BID
- ORR 71%/confirmed ORR 43% with RP2D with Cape+T-DXd
- ORR 67%/Confirmed ORR 50% with 5FU+T-DXd

Jajigian Y, et al. ASCO-GI 2022

Phase 3 Study: T-DXd vs. paclitaxel+ramucirumab (DESTINY-Gastric04)



EU, European Union; GC, gastric cancer; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.

Major difference between Gastric01 and Gastric04

- Global trial vs Asian trial
- Second-line trial vs third or later line
- HER2 + by fresh biopsy after PD on Trastuzumab is required

Shitara K, et al. ESMO 2021. NCT04704934.

Real-World Evidence

Retrospective cohort study to evaluate the efficacy and safety of T-DXd in human epidermal growth factor receptor (HER2)-positive unresectable advanced or recurrent gastric or gastroesophageal junction cancer: EN-DEAVOR study

Koki Nakanishi

Results

About a third of patients (34.9%) received <4 cycles of T-DXd

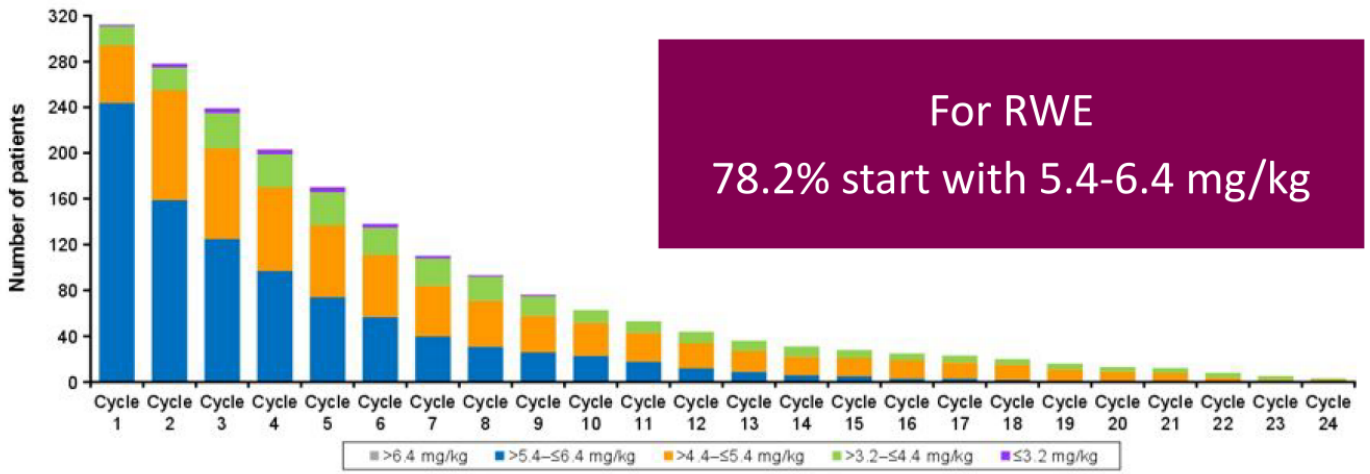
- A **total of 312 patients** were eligible for the analysis[a]
- **Median patient age** was 70.0 years (range, 27–89 years)
- A total of 38 patients (12.2%) had **ECOG PS ≥2**, and 135 (43.3%) has **ascites**

Baseline patient characteristics

		All eligible patients (n=312)
Male sex, n (%)		235 (75.3)
Age (years), median (range)		70.0 (27–89)
ECOG PS ≥2, n (%)		38 (12.2)
HER2 status at initial diagnosis–IHC3+, n (%)		217 (69.6)
Site of primary lesions–stomach, n (%)		264 (84.6)
Any surgeries for primary lesions, n (%)		107 (34.3)
Histological type of primary lesions, n (%)	Diffuse	79 (25.3)
	Intestinal	170 (54.5)
	Others/unknown	63 (20.2)
≥2 metastatic organs, n (%)		192 (61.5)
Ascites–yes, n (%)		135 (43.3)
Number of previous lines, n (%)	≤2	161 (51.6)
	3	73 (23.4)
	≥4	78 (25.0)
Previous therapies, n (%)	Taxane	290 (92.9)
	Trastuzumab	288 (92.3)
	Immune checkpoint inhibitor	131 (42.0)
	Ramucirumab	256 (82.1)
	Platinum	280 (89.7)
	Irinotecan	49 (15.7)
	Pyrimidine fluoride	296 (94.9)
	Others	42 (13.5)
Trastuzumab-free interval (months, n=286), median (range)		6.8 (0.1–70.6)

- In total, **34.9% of patients received less than 4 cycles of T-DXd**
- T-DXd dose in Cycle 1 was:
  - **>5.4–≤6.4 mg/kg in 244 patients (78.2%)**
  - >4.4–≤5.4 mg/kg in 50 patients (16.0%)
  - >3.2–≤4.4 mg/kg in 17 patients (5.4%)

T-DXd dose in each treatment cycle (all eligible patients)



For RWE

78.2% start with 5.4-6.4 mg/kg

[a]A total of 6 patients were excluded due to incorrect enrollment (from the total 318 patients that were enrolled). A total of 226 patients had target lesions.

ASCO-GI 2024, Abstract #274

Retrospective cohort study to evaluate the efficacy and safety of T-DXd in human epidermal growth factor receptor (HER2)-positive unresectable advanced or recurrent gastric or gastroesophageal junction cancer: EN-DEAVOR study

Koki Nakanishi

Results

Treatment with T-DXd was efficacious in real world setting

OS, rwPFS, and TTF (all eligible patients)

Endpoint	
Median OS	**8.90 months** (95% CI, 7.95–11.04)
6-month OS	**67.9%** (95% CI, 62.4–72.9)
12-month OS	**40.0%** (95% CI, 34.3–45.5)
Median rwPFS	**4.57 months** (95% CI, 4.04–5.09)
6-month rwPFS	**37.5%** (95% CI, 32.1–43.0)
12-month rwPFS	**13.2%** (95% CI, 9.5–17.5)
Median TTF	**3.94 months** (95% CI, 3.42–4.17)
6-month treatment success rate	**27.5%** (95% CI, 22.7–32.6)
12-month treatment success rate	**8.0%** (95% CI, 5.3–11.4)

Response rate (patients with target lesions)

Response rate	Patients with target lesions (n=226)
ORR, n (%)	97 (42.9) [95% CI, 36.4–49.7]
Best overall response, n (%)	
CR	5 (2.2)
PR	92 (40.7)
SD	87 (38.5)
PD	31 (13.7)
NE	11 (4.9)

The 95% CI was estimated using the Clopper-Pearson method.

- **ORR was 42.9%** (95% CI, 36.4−49.7) and **DCR was 81.4%** (95% CI, 75.7−86.3) in patients with target lesions (n=226)
- Most patients with target lesions recorded PR (40.7%) or SD (38.5%) as BOR
- Median best percentage of change in the sum of diameters for all target lesions was -24.7% (range: -100.0−127.7)

ASCO-GI 2024, Abstract #274

Retrospective cohort study to evaluate the efficacy and safety of T-DXd in human epidermal growth factor receptor (HER2)-positive unresectable advanced or recurrent gastric or gastroesophageal junction cancer: EN-DEAVOR study

Koki Nakanishi

Results

No new safety signals were identified with T-DXd treatment based on this study

Most common (>4%) Grade ≥3 TEAEs (all eligible patients)

Patients with CTCAE grade ≥3 TEAEs, n (%)	All eligible patients (n=312)[a]
Any grade ≥3 TEAEs	151 (48.4)
Hematotoxicity TEA	(28.5)
Neutrophil count	(19.6)
Anemia	9 (9.3)
Platelet count de	3 (4.2)
Non-hematotoxicity	(28.2)
Anorexia	9 (9.3)
Malaise	4 (4.5)
Interstitial pneum	4 (4.5)
Nausea	3 (4.2)

TEAEs were coded usi

For RWE

≥ G3 neutropenia: 19.6%

≥ G3 nausea : 4.2%

≥ G3 ILD: 4.5%

Most common (>5%) TEAEs leading to dose reduction, interruption, or discontinuation (all eligible patients)

Patients with TEAEs, n (%)	All eligible patients (n=312)			
	Dose reduction,	Dose	Dose interruption[a]	Discontinuation[a]
Ar			106 (34.0)	74 (23.7)
He			72 (23.1)	4 (1.3)
			60 (19.2)	1 (0.3)
			9 (2.9)	3 (1.0)
Nc			48 (15.4)	74 (23.7)
			16 (5.1)	19 (6.1)
			15 (4.8)	11 (3.5)
			8 (2.6)	10 (3.2)
Interstitial pneumonia	29 (9.3)	0 (0.0)	0 (0.0)	29 (9.3)

TEAEs were coded using MedDRA version 26.0. AEs leading to dose reduction, interruption, or discontinuation with an incidence of >5% are listed.

For clinical trial (6.4mg/kg)

≥ G3 neutropenia: **35.8%**

≥ G3 nausea : 6.8%

≥ G3 ILD: 2.4%

- **Grade ≥5 TEAEs** were seen in **8 patients**
  - Interstitial pneumonia (n=5)
  - Febrile neutropenia (n=1)
  - Pneumonia (n=1)
  - Pneumonia cytomegaloviral (n=1)

- The most common **hematotoxicity TEAE** that led to dose reduction, interruption, or discontinuation was **decrease in neutrophil counts** (24.4%)
- The most common **non-hematotoxicity TEAE** that led to dose reduction, interruption, or discontinuation was **anorexia** (17.6%)

[a]Multiple selections were possible when reporting TEAEs.

ASCO-GI 2024, Abstract #274

Novel Therapy in HER2 Positive GC

Novel **HER2**-Directed Strategies

Combination with PD-1 blockade

- With durvalumab, nivolumab, and pembrolizumab
- KN811 study

Tyrosine kinase inhibitor

- Tucatinib (+chemotherapy, tras, and ramucirumab)

Antibody-drug conjugate

- Trastuzumab deruxtecan (T-Dxd)
- RC48-ADC, Trastuzumab duocarmazine etc.
- NJH 395 and SBT6050 with toll-kike receptor agonists

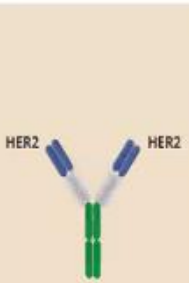
Monoclonal/bispecific antibodies

- Margetuximab (+ PD-1 inhibitor):enhanced ADCC
- ZW25 or KN026; targets two epitopes on HER2
- CD47 inhibition with trastuzumab
- HER2-41BB (PRS-343)or HER2-CD3 bispecific (BTRC4017A)

Newer Immunotherapy

- Cellular therapy for HER2: CT-0508 and CYNK-101
- Vaccination against Her-2/neu

Margetuximab: Fc region optimized anti-HER2 mab to enhance ADCC



MARGETUXIMAB[3,5]

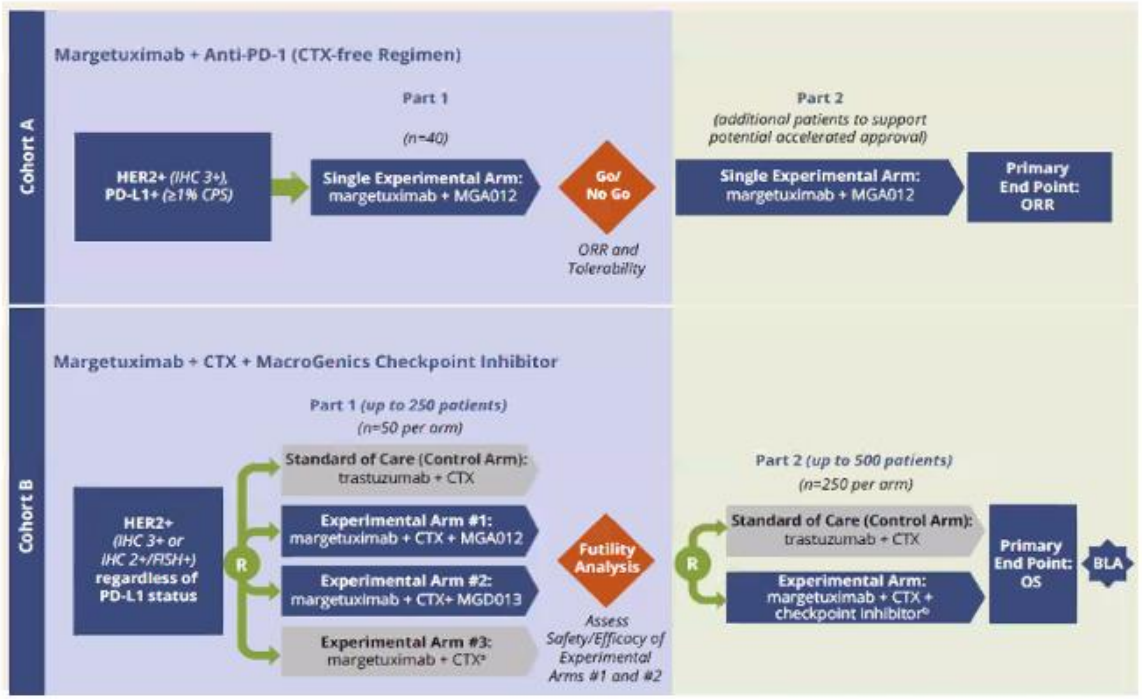
Fab
- Same specificity and affinity as trastuzumab
- Similarly disrupts signaling as trastuzumab

Fc
- ↑Affinity for activating FcγRIIIA (CD16A)
- ↓Affinity for inhibitory FcγRIIB (CD32B)

Margetuximab Binding to FcγR Variants

Receptor Type	Receptor	Allelic Variant	Relative Binding	Affinity Fold-Change
Activating	CD16A	158F	Lower	6.6 × ↑
		158V	Higher	4.7 × ↑
	CD32A	131R	Lower	6.1 × ↓
		131H	Higher	↔
Inhibitory	CD32B	232I/T	Equivalent	8.4 × ↓

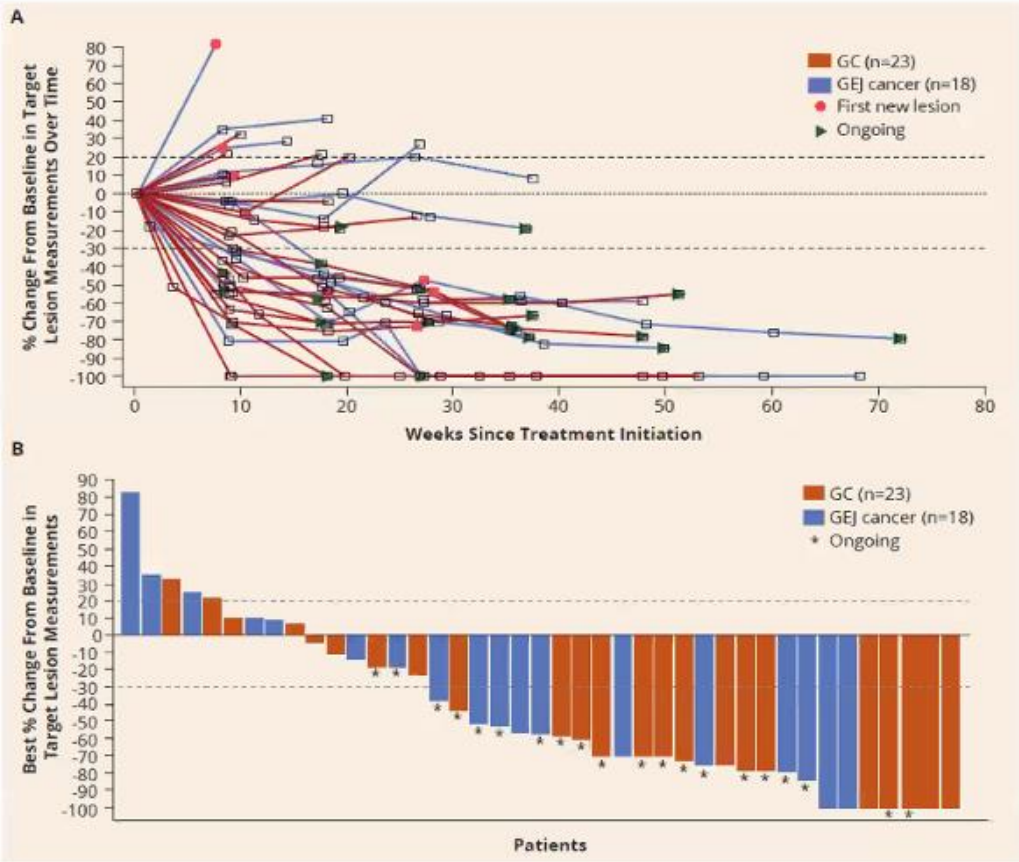
MAHOGANY Study: a Randomized, Open-label Phase 2/3 Study



Catenacci DVT, et al. ESMO GI 2020; ESMO 2021

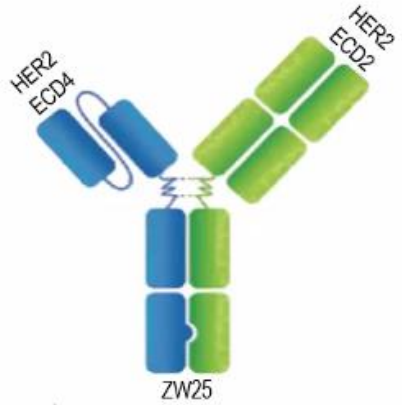
Margetuximab+Retifanlimab

MAHOGANY Cohort A part 1: Chemo free regimen
N=41 (HER2 IHC3+, PD-L1+, and non–MSI-H)



- ORR 52.5%, mDOR 10.3ms, mPFS 6.4ms, mOS not reached
- Enrollment for cohort A and cohort B (randomization part) is stopped because of change in treatment landscape

Zanidatamab: HER2-Targeted Bispecific mab

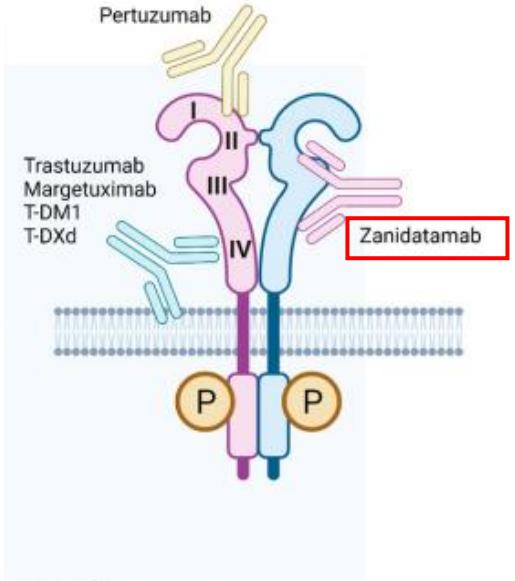


Biparatopic binding targets two distinct HER epitopes

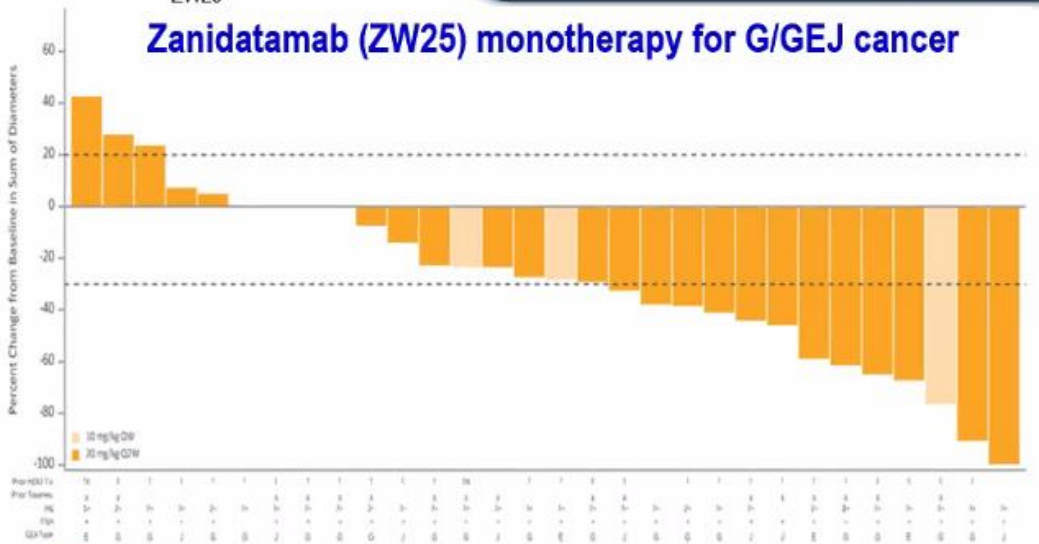
- Same domains as trastuzumab (ECD4) and pertuzumab (ECD2)

Unique mechanisms of action designed to expand activity

- Extended chain formation and dense HER2 receptor clustering
- Enhanced HER2 internalization and downregulation
- Increased tumor cell binding density and potent effector-mediated cytotoxicity
- Enhanced blockade of ligand-dependent and ligand-independent tumor growth

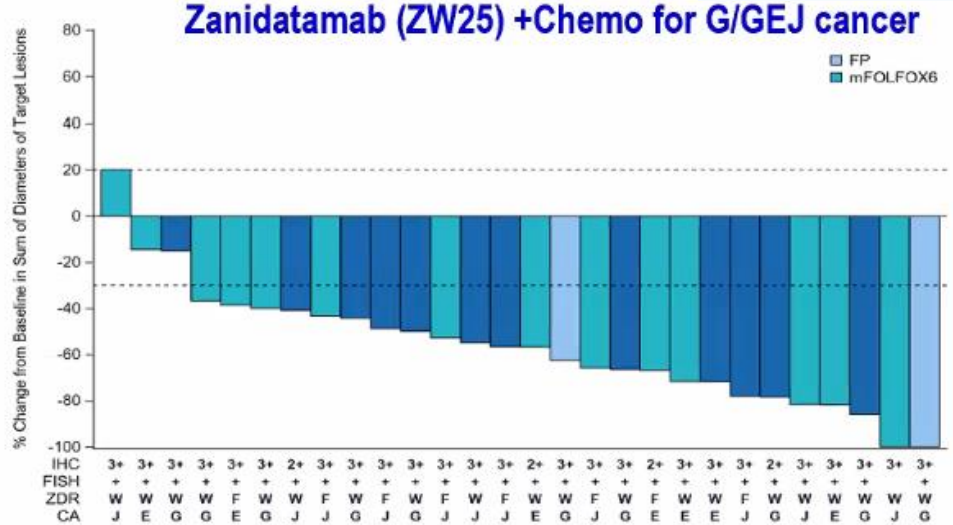


Zanidatamab (ZW25) monotherapy for G/GEJ cancer



- N=33, ORR 33%, mDoR 6 months, mPFS 3.6ms
- Any grade diarrhea 46% (G3 or higher 3%)
- Phase1 of ZW49 as ADC is also ongoing (NCT03821233)

Zanidatamab (ZW25) +Chemo for G/GEJ cancer



- ORR 75%, mPFS 12months
- Global phase 3 study (HERIZON-GEA-01) is ongoing to evaluate chemo+Zanitadamab ± tislelizumab

Meric-Bernstam F et al. ASCO-GI 2021; Ku G, et al. ESMO 2021

Systemic Treatment of GC

Chemotherapy

Fluoropyrimidine

Platinum

Taxane

Irinotecan

Epirubicin

FTD/TPI

Target Therapy

HER2

Trastuzumab

Trastuzumab deruxtecan

VEGFR2

Ramucirumab(VEGFR2)

CLDN 18.2

Zolbetuximab

(FGFR2b)

Immunotherapy

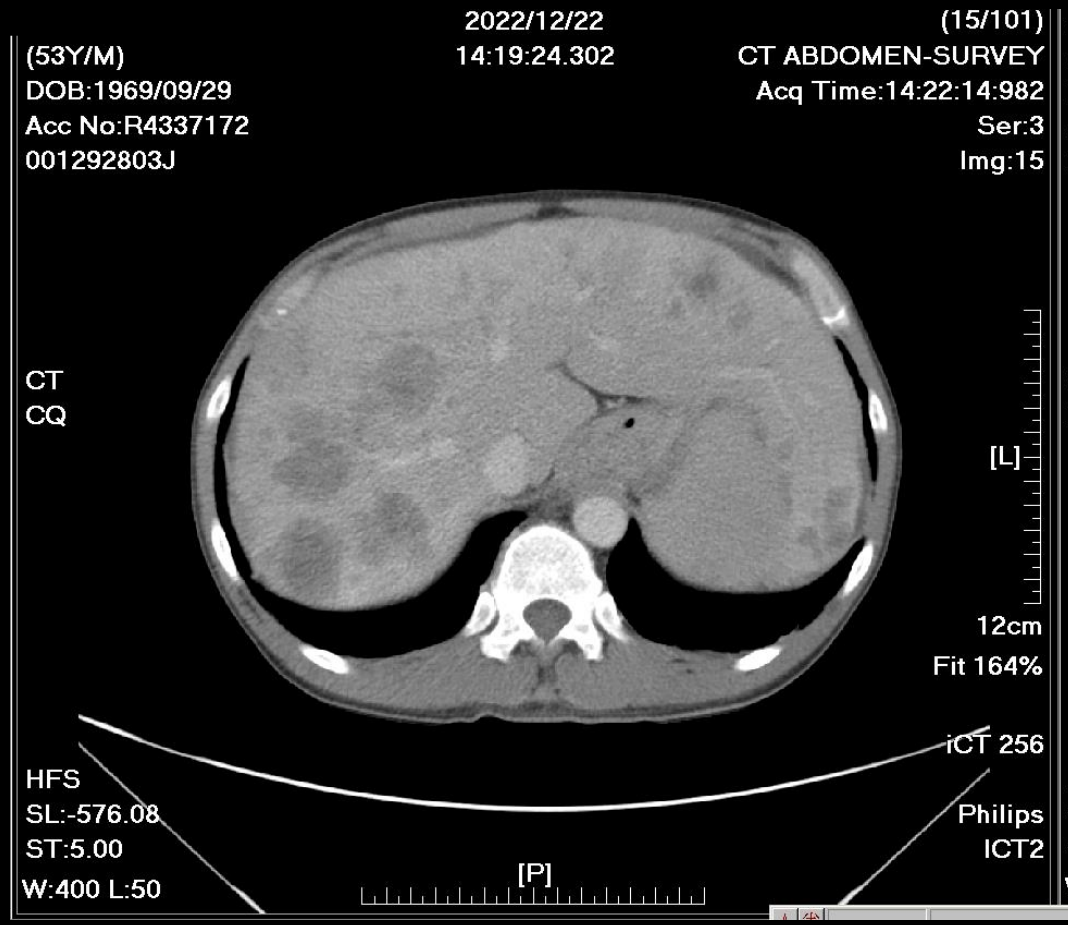
PD-1 inhibitor

Nivolumab

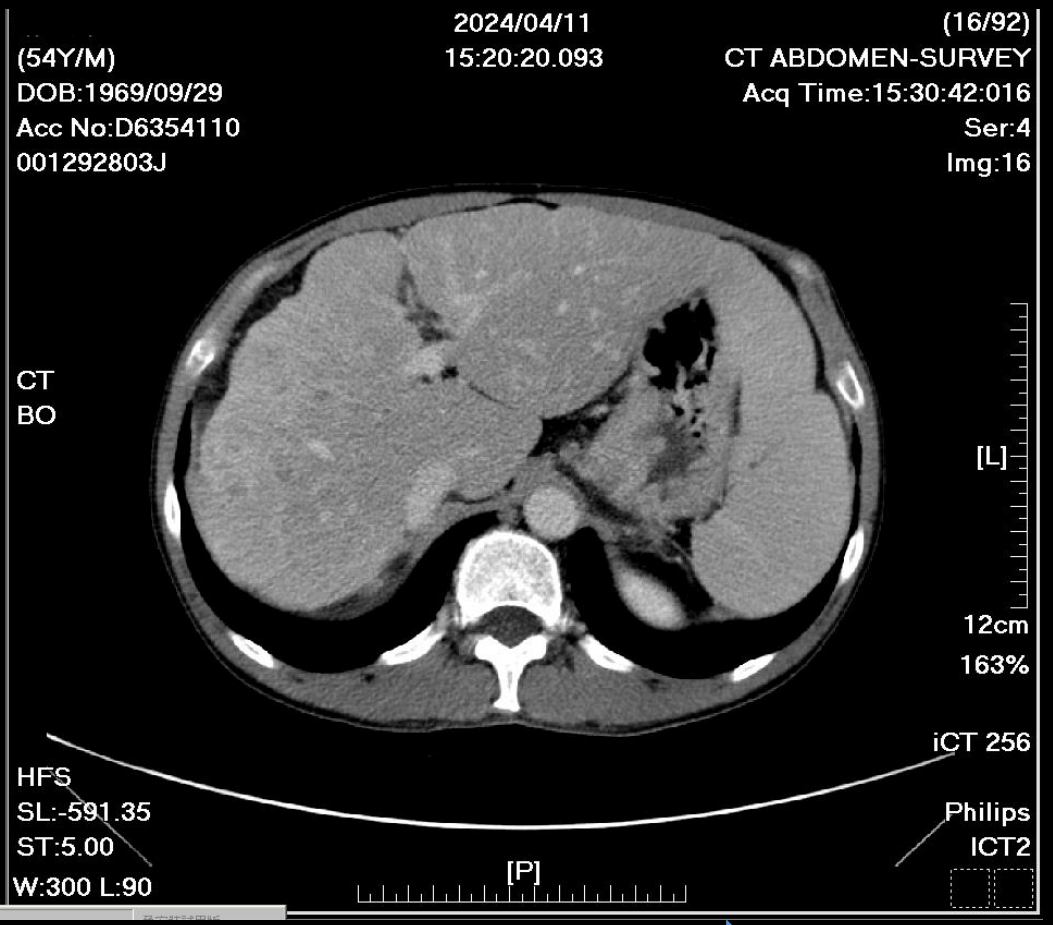
Pembrolizumab

53y/o Male EG junction cancer, adenocarcinoma, liver metastasis
T4bN+M1, stage IV. HER2 IHC:2+, ISH: amplification, PDL1 CPS:1

2022/12/22



2024/4/11



Pembrolizumab + Trastuzumab + Cisplatin + 5-FU

GC HER2 IHC 2+ → 2024/7/1健保可給付HER2 ISH

2024/07/01	2910/12/31	Her-2/neu in situ hybridization（ISH）	第二型人類表皮生長因子受體(Her-2/neu)原位雜合檢驗	適應症：1.乳癌之invasive carcinoma(侵襲性癌)、轉移性胃腺癌（或胃食道接合處腺癌）。2.本法為IHC染色結果之輔助檢查方法，不可單獨使用。3.此法僅適用於Her-2/neu IHC score為2+之乳癌或胃腺癌（或胃食道接合處腺癌）患者。

Treatment of Advanced Gastric Cancer

First line

Nivo/Pembro + Fluoropyrimidine + Platinum (CPS)
HER2(+) → Trastuzumab+Pembrolizumab + Chemotherapy (CPS≥1)
Claudin 18.2(+) → Zolbetuximab + Chemotherapy

Second line

Ramucirumab + Paclitaxel
Taxane
Irinotecan
MSI-H/dMMR, TMB-H → Pembrolizumab
HER2(+) → Trastuzumab Deruxtecan (recheck HER2)

Third line

Nivolumab
TAS-102 Trifluridine/tipiracil
Irinotecan
HER2(+) → Trastuzumab Deruxtecan (recheck HER2)

Thank you!!