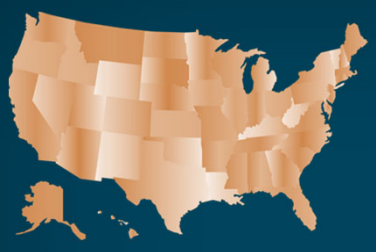
Gastrointestinal Cancers and HER2 Levels of Expression: Application of Biomarker Findings in Patients with Advanced Disease

Pre-read Material

1

Gastric Cancer (GC)



United States[1]

- Estimates for 2023 are that 26,500 people will be diagnosed with GC and 11,130 will die from the disease

Worldwide (2018 data)[2,3]

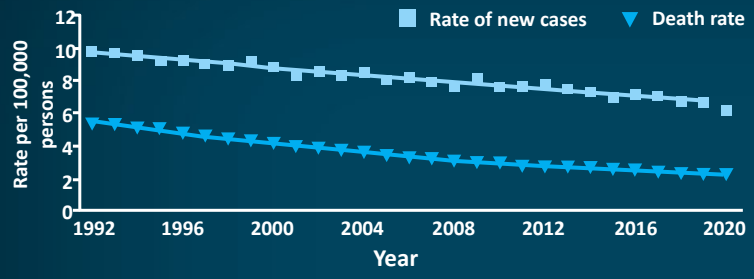
- GC is the 5th most common malignancy, with greater than 1 million incident cases worldwide
- GC is the 4th most common cause of cancer mortality (nearly 782,685 deaths)

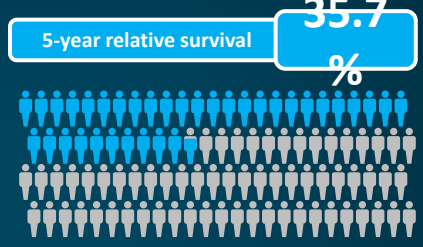
1. American Cancer Society (ACS). *Cancer Facts & Figures*, 2023 (www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2023/2023-cancer-facts-and-figures.pdf). Accessed 11/7/2023. 2. Wong MCS, et al. *JAMA Network Open*. 2021;4:e2118457. 3. Morgan E, et al. *EClinicalMedicine*. 2022;47:101404.

2

Trends in Stomach Cancer Statistics

Incidence and mortality rates (1992–2020)





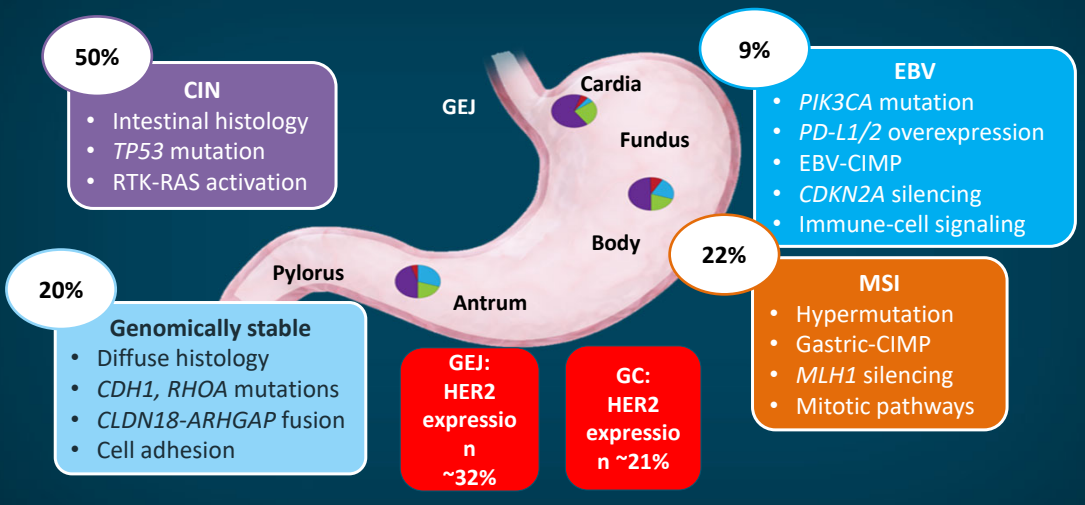
Based on data from SEER 22 (Excluding IL/MA) 2013–2019. Beige figures represent those people who have died from stomach cancer, and blue figures represent those people who have survived 5 years or more.

- 5-year relative rate survival varies by staging:
  - **localized = 74.7%, regional = 34.6%, distant = 6.6%,** and unknown = 31.1%
- Median age at diagnosis is 68 years
- New case incidence per 100,000 persons (of all races) is greater in males (9.0) compared with females (5.2)

National Cancer Institute (NCI). Cancer Stat Facts: Stomach cancer (https://seer.cancer.gov/statfacts/html/stomach.html). Accessed 11/7/23.

3

Comprehensive Molecular Characterization of Gastric Cancer: TCGA

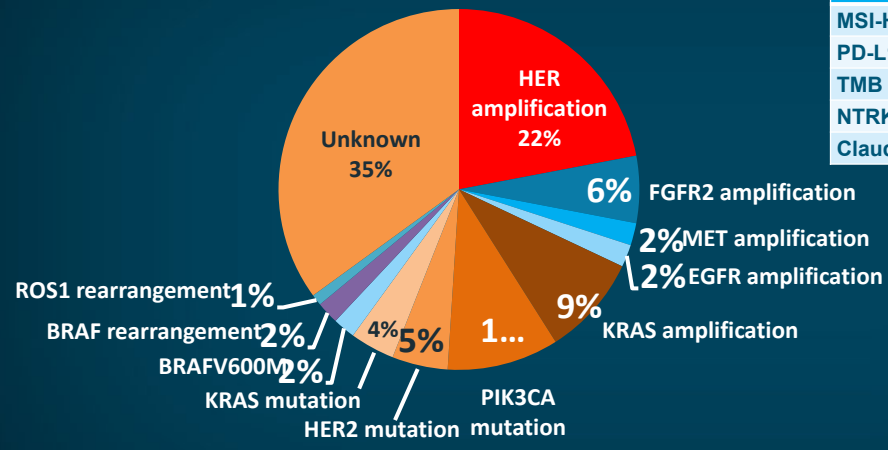


CIMP = CpG island methylator phenotype; CIN = chromosomal instability; EBV = Epstein-Barr virus; GC = gastric cancer; GEJ = gastroesophageal junction; MSI = microsatellite instability; PD-L1/2 = programmed (cell) death ligand 1/2; RTK = receptor tyrosine kinase; TCGA = The Cancer Genome Atlas.

1. Modified from Cancer Genome Atlas Research Network. *Nature.* 2014;513:202-209. 2. Van Custem E, et al. *Gastric Cancer.* 2015;18:476-484.

4

Molecular Profiling in Advanced Gastric Cancer



Additional profiling	Prevalence
MSI-H/dMMR[2]	8–11%
PD-L1[3]	59%
TMB ≥10 mut/Mb[4]	16%
NTRK fusion[5]	<1%
Claudin 18.2[6]	14%

BRAF = B-Raf proto-oncogene, serine/threonine kinase; dMMR = deficient mismatch repair; FGFR = fibroblast growing factor receptor; KRAS = Kirsten rat sarcoma virus; MET = hepatocyte growth factor receptor; MSI-H = microsatellite instability high; ; NTRK = neurotrophic-tropomyosin receptor tyrosine kinase. PIK3CA = phosphatidylinositol-4,5-biphosphate 3-kinase, catalytic subunit alpha; ROS1 = c-ROS kinase; TMB = tumor mutational burden.

1. Image from Lee J, Ou SHI. *Discov Med.* 2013;15:333-341. 2. Amonkar M, et al. *J Clin Oncol.* 2019;37(15 suppl): 3. Liu X, et al. *Pathol Res Pract.* 2020;216:152881. 4. Lee KW, et al. *Clin Cancer Res.* 2022;28:3489-3498. 5. Westphalen CB, et al. *NPJ Precis Oncol.* 2021;5:69. 6. Hong JY, et al. *Transl Cancer Res.* 2020;9:3367-3374.

5

Role of HER2 in Solid GI Tumors

- GC: HER2 positivity varies by histology[1]
  - Diffuse or intestinal histologic subtypes
    - Diffuse cancers: 6–7% HER2+; ≥16% for intestinal cancers
- CRC: HER2 positivity in ~1 to 6% of patients[2]
  - More common in left-sided primaries
    - *HER2* amplification predicts resistance to EGFR inhibitors
  - HER2 therapy benefit limited to *RAS* WT cancers
- Biliary cancer[3,4]
  - Genomic profiling indicates *HER2* amplification is seen
  - More common in gallbladder primaries
  - Potentially targetable by HER2-targeted agents

HER2 testing	Gastric or esophageal /GEJ[5]	Colon[6]	Pancreatic[7]	Biliary tract[3]
When	All patients	All patients unless known *RAS/RAF* mutation positive	When therapy targeting uncommon mutations is considered	All patients
How	IHC and ISH first (NGS may be considered)	IHC, ISH, or NGS	NGS	IHC, FISH, or NGS

CRC = colorectal cancer; EGFR = epidermal growth factor receptor; FISH = fluorescence in situ hybridization; GI = gastrointestinal; IHC = immunohistochemistry; ISH = in situ hybridization; NGS = next-generation sequencing; WT = wild type.

1. Gravalos C, Jimeno A. *Ann Oncol.* 2008;19:1523-1529. 2. De Cuyper A, et al. *Clin Colorectal Cancer.* 2020;19:65-72. 3. Dika IE, Ilson DH. *Expert Rev Anticancer Ther.* 2018;18:1085-1092. 4. Javle M, et al. *Lancet Oncol.* 2021;22: 1290-1300. 5.Ajani JA, et al. *JNCCN.* 2022;20(2):167-192. 6. Cercek A, et al. *J Clin Oncol.* 2023;41(4)_suppl 198. 7. Tempero MA, et al. *JNCCN.* 2021;19(4):439-457.

6

HER2 Targeted Therapy Plus Chemotherapy

Key Trials

7

First-Line HER2-Directed Clinical Trials

Clinical trial	Regimen	Stratification	mOS mo	HR (95% CI)	*P*-value
ToGA[1] HER2+ (n = 594)	5-FU or capecitabine + cisplatin + trastuzumab	• Advanced vs metastatic • GC vs GEJ cancer • Measurable vs nonmeasurable • ECOG PS 0–1 vs 2 • Capecitabine vs 5-FU	13.8	0.74 (0.60–0.91)	.0046
	5-FU or capecitabine + cisplatin		11.1		
TRIO-013/LOGiC[2] HER2+ (FISH+ or IHC 3+) (n = 545)	Capecitabine + oxaliplatin + lapatinib*	• Geographic region (North America, Asia, or ROW) • Prior neoadjuvant and/or adjuvant chemotherapy	12.2	0.91 (0.73–1.12)	.3492
	Capecitabine + oxaliplatin		10.5		
JACOB[3] HER2+ (IHC 3+ or IHC 2+ and ISH+) (n = 780)	Capecitabine or 5-FU + cisplatin + trastuzumab + pertuzumab*	• Geographic region (Japan vs North America/Western Europe/Australia vs Asia [excluding Japan] vs South America/Eastern Europe) • Prior gastrectomy • HER2+ (IHC 3+ vs IHC 2+ and ISH+)	17.5	0.84 (0.71–1.00)	.057
	Capecitabine or 5-FU + cisplatin + trastuzumab		14.2		

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FDA = United States Food and Drug Administration; HR = hazard ratio; mOS = median OS; OS = overall survival; PS = performance status; ROW = rest of world.

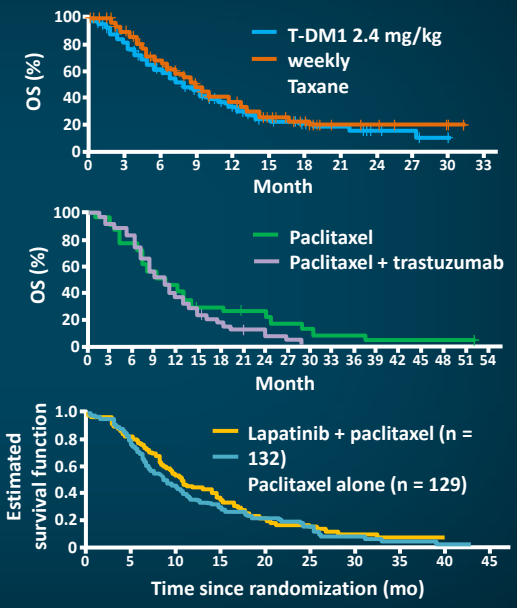
1. Bang YJ, et al. *Lancet*. 2010;376:687-697. 2. Hecht JR, et al. *J Clin Oncol*. 2016;34:443-451. 3. Tabernero J, et al. *Lancet Oncol*. 2018;19:1372-1384.

**Lapatinib and pertuzumab are not FDA approved for use in GC.*

8

Older HER2 Targeting Agents as 2nd-Line Treatment

- GATSBY[1]: T-DM1 vs taxane (N = 345)
  - OS = 7.9 vs 8.6 mo; HR = 1.15 (95% CI: 0.87–1.51; *P* = .86)
- WJOG7112G (T-ACT study)[2]: Paclitaxel ± trastuzumab in patients refractory to trastuzumab + CT (N = 91)
  - No difference in PFS, OS
    - OS HR = 1.23 (95% CI: 0.76–1.99; *P* = .20)
  - Loss of HER2-amplified ctDNA in >60%
- TyTAN[3]: lapatinib + paclitaxel vs paclitaxel alone in second-line HER2 amplified (N = 261)
  - No benefit for lapatinib + second-line paclitaxel
    - OS HR = 0.84 (95% CI: 0.64–1.11; *P* = .1044)
  - De novo and acquired HER2 resistance are likely; loss of HER2 expression may occur[4]



CT = chemotherapy; ctDNA = circulating tumor deoxyribonucleic acid; PFS = progression-free survival; T-DM1 = ado-trastuzumab emtansine.

1. Thuss-Patience PC, et al. *Lancet Oncol*. 2017;18:640-653. 2. Makiyama A, et al. *J Clin Oncol*. 2020;38:1919-1927. 3. Satoh T, et al. *J Clin Oncol*. 2014;32:2039-2049. 4. Seo S, et al. *Gastric Cancer*. 2019;22(3):527-535.

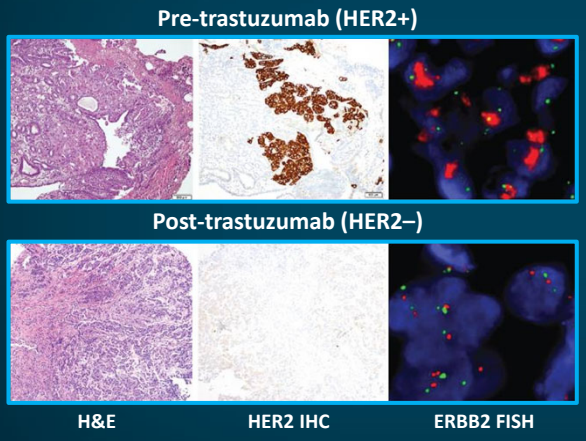
9

Resistance Mechanisms to HER2 Targeted Drugs

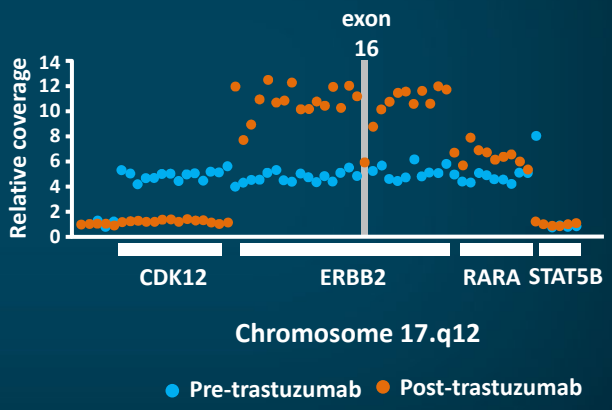
10

Loss of HER2 Upon Disease Progression After Trastuzumab

Loss of ERBB2 amplification and HER2 expression



Structure of acquired ERBB2 Exon 16 deletion



H&E = hematoxylin and eosin (stain).

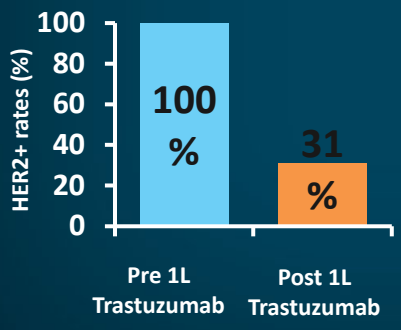
Janjigian YY, et al. *Cancer Discov*. 2018;8:49-58.

11

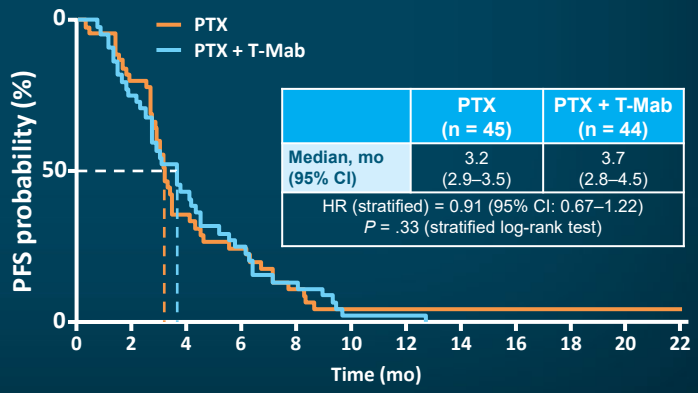
Loss of HER2 on Disease Progression After Trastuzumab
2L Trial Options

Patients with HER2+ mGC refractory following prior 1L treatment with trastuzumab + platinum-based chemotherapy who received 2L trastuzumab + paclitaxel in T-ACT study

HER2+ rates pre and post 1L trastuzumab (N = 16)



PFS on 2L paclitaxel + trastuzumab



	PTX (n = 45)	PTX + T-Mab (n = 44)
Median, mo (95% CI)	3.2 (2.9–3.5)	3.7 (2.8–4.5)
HR (stratified) = 0.91 (95% CI: 0.67–1.22) *P* = .33 (stratified log-rank test)		

2L = second line; PTX = Paclitaxel; T-Mab = trastuzumab.

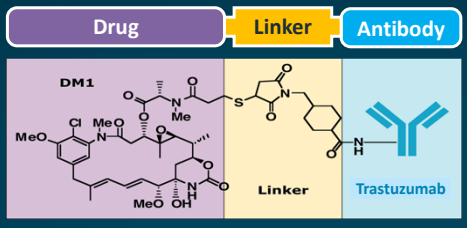
1. Makiyama A, et al. *J Clin Oncol*. 2018;36(suppl): abstract 4011. 2. Makiyama A, et al. *J Clin Oncol*. 2020;38:1919-1927.

12

Antibody-Drug Conjugates (ADCs) in HER2-Positive Gastrointestinal Malignancies

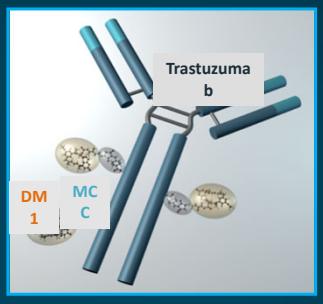
13

Trastuzumab Emtansine (T-DM1) Structure



- Target expression: HER2
- Monoclonal antibody: trastuzumab
- Cytotoxic agent: DM1
- Highly potent cytotoxic agent
- Linker: MCC
- Systemically stable

T-DM1 is a novel ADC



T-DM1

T-DM1 has drug to antibody ratio ≅ 3.5:1

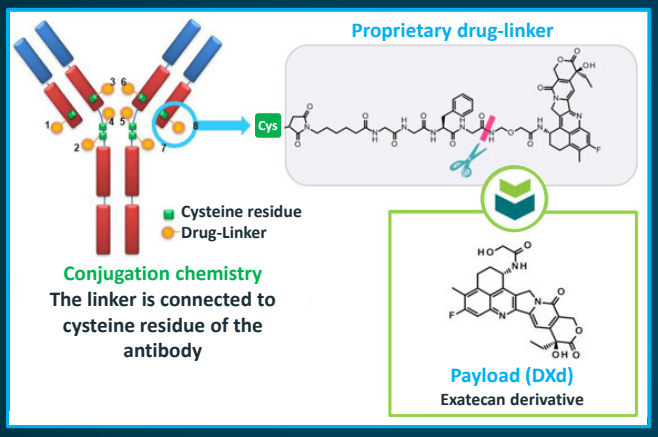
ADC = antibody-drug conjugate; MCC = N-maleimidomethyl]cyclohexane-1-carboxylate.

1. Mahato R, et al. *Adv Drug Deliv Rev.* 2011;63:659-670. 2. Krop IE, et al. *J Clin Oncol.* 2010;28:2698-2704.

*T-DM1 is not FDA-approved for use in GC.

14

Trastuzumab Deruxtecan (T-DXd/DS-8201a): Structure and MOA



- Payload with a different MOA
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio

DS-8201a was designed with goal of improving critical attributes of an ADC

DXd = trastuzumab deruxtecan; MOA = mechanism of action.

Noguchi Y. ADC seminar slides (www.daiichisankyo.com/files/investors/library/materials/2019/pdf/DS-1062%20Seminar%20Slides_EN.pdf). Accessed 11/7/23.

15