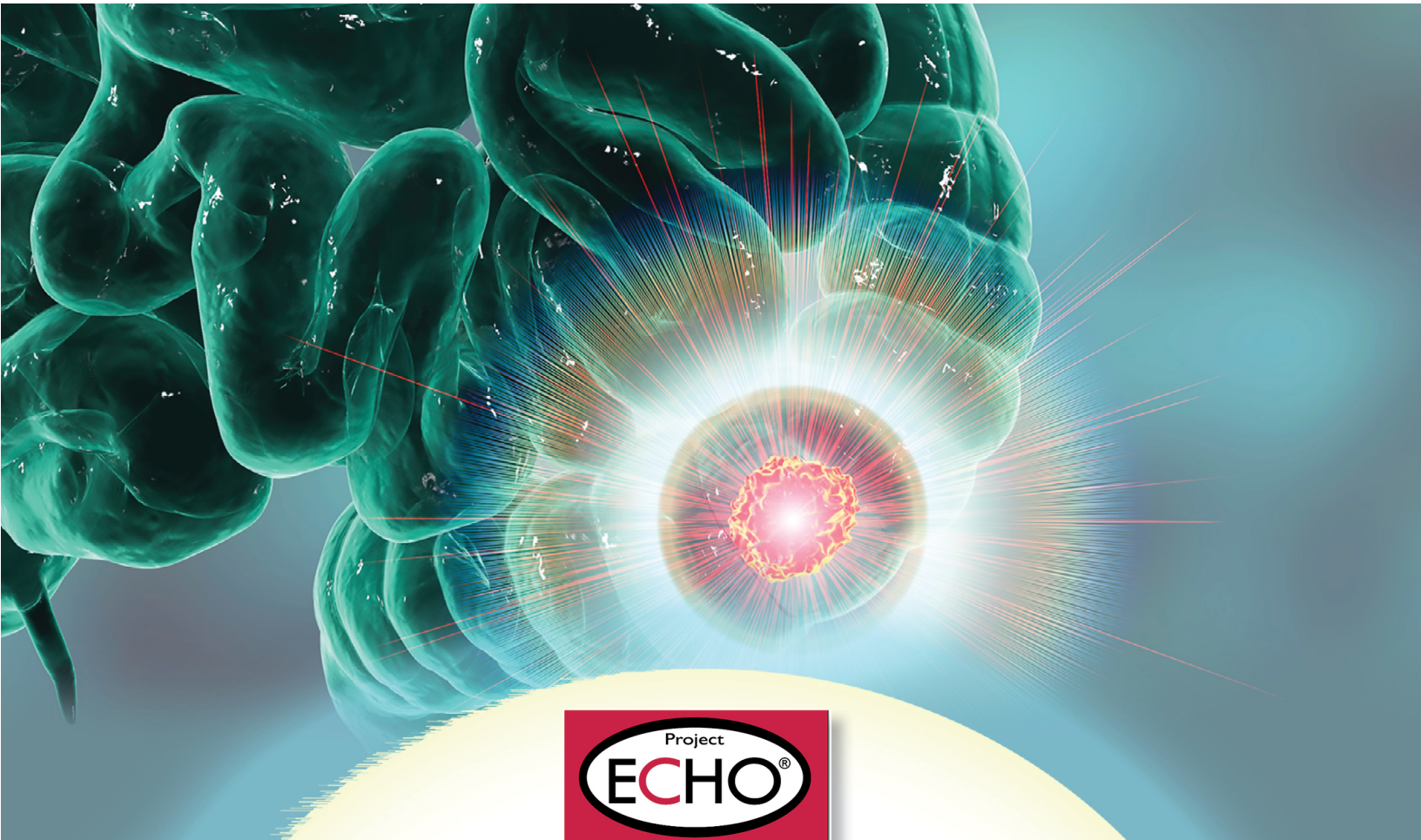

Project ECHO®

TARGETING HER2-DRIVEN DISEASE BEYOND THE FIRST LINE:

Antibody-Drug Conjugate Therapy in GASTROINTESTINAL CANCERS

Richard Dunne, MD
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This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by educational grants from AstraZeneca Pharmaceuticals and Daiichi Sankyo, Inc.

Agenda

I. **Identifying HER2-Driven Gastrointestinal Cancers – Applying Pathology**
   a. Incidence of gastric cancer
   b. NCCN recommendations for treatment
   c. Assessment of Overexpression or Amplification of HER2
      i. When to test for HER2 status in GI cancers
      ii. Laboratory methods to assess HER2 status
         1. Immunohistochemistry
         2. Fluorescence in situ hybridization
         3. Next generation sequencing
         4. Liquid biopsies – when and how to interpret?
      iii. What is HER2-positivity?
   d. Role of HER2 in Solid GI Tumor Treatment
      i. Clinical trials in HER2-positive patients

II. **Leveraging Antibody-Drug Conjugates in HER2-Positive Gastrointestinal Malignancies**
   a. What is an Antibody-Drug Conjugate Anyway?
      i. Characteristics of ADC compounds
         1. Antibody construct, linker technology, payload
   b. How do ADC Compounds Work and Why Should I Care?
      i. Anti-tumor effects
      ii. Unique bystander effect

III. **Evolution of HER2-Targeted Therapy for HER2-Positive GI Cancers After Progression on Trastuzumab**
   a. Clinical Application of ADCs in Advanced HER2-Positive GI Cancers
      i. Trastuzumab emtansine – efficacy and safety data review
      ii. Resistance to anti-HER2 targeted therapy
      iii. Trastuzumab deruxtecan - efficacy and safety data
         1. GATSBY
         2. Destiny –Gastric01
         3. Destiny – CRC01
      iv. Margetuximab
         1. MAHOGANY
      v. Zanidatamab

IV. **HER2 + mCRC**
      i. HERACLES
      ii. MyPathway
      iii. SWOG S1613
      iv. DESTINY-CRC01

V. **Case study**

VI. **Conclusions**

VII. **Adjournment**

Targeting HER2-Driven Disease Beyond the First Line: Antibody-Drug Conjugate Therapy in Gastrointestinal Cancers

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PROGRAM OVERVIEW

These live virtual TeleECHO® sessions will be a faculty-led didactic and case-based lecture focusing on the management of patients with gastric cancer and colorectal cancer.

TARGET AUDIENCE

This activity is designed to meet the educational needs of medical oncologists, internal medicine physicians, gastroenterologists, pathologists and others (e.g. nurse practitioner, pharmacist, physician assistant, oncology nurse) involved in the management of patients with gastric cancer and colorectal cancer.

LEARNING OBJECTIVES

Upon completion of the program, attendees should be able to:

- Identify HER2 methods of biomarker testing and apply them to clinical practice in patients with GI malignancies
- Discuss the unique pharmacodynamics of HER2-directed antibody-drug conjugates and their anti-tumor effects in gastrointestinal cancers
- Apply evidence from HER2-targeted, antibody-drug conjugate clinical trials to personalize treatment of patients with advanced GI malignancies beyond the first-line

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Nursing Credit Information
Purpose: This program would be beneficial for nurses involved in the management of patients with gastric cancer and colorectal cancer.
CNE Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement
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Dr. Ajani has received consulting fees from AstraZeneca.

Dr. Dunne has nothing to disclose.

Dr. Hecht has served as a consultant for Actym.

CME Content Review

The content of this activity was independently peer reviewed.
The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

Douglas Cox, MSN, MHA, RN
Ultimate Medical Academy/CCM – Lead Nurse Planner

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- Remember to direct all questions to the "co-host." There is a toggle button above the typing space that allows you to specify the location of your message delivery.

Targeting HER2-Driven Disease Beyond the First Line: Antibody-Drug Conjugate Therapy in Gastrointestinal Cancers

Richard Dunne, MD
Assistant Professor of Medicine
Wilmot Cancer Institute
University of Rochester Medical Center
Rochester, NY

Disclosures

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- During this activity, Dr. Dunne may mention the use of medications for both FDA-approved and nonapproved indications.

This activity is supported by educational grants from AstraZeneca Pharmaceuticals and Daiichi Sankyo, Inc.

FDA = US Food and Drug Administration.

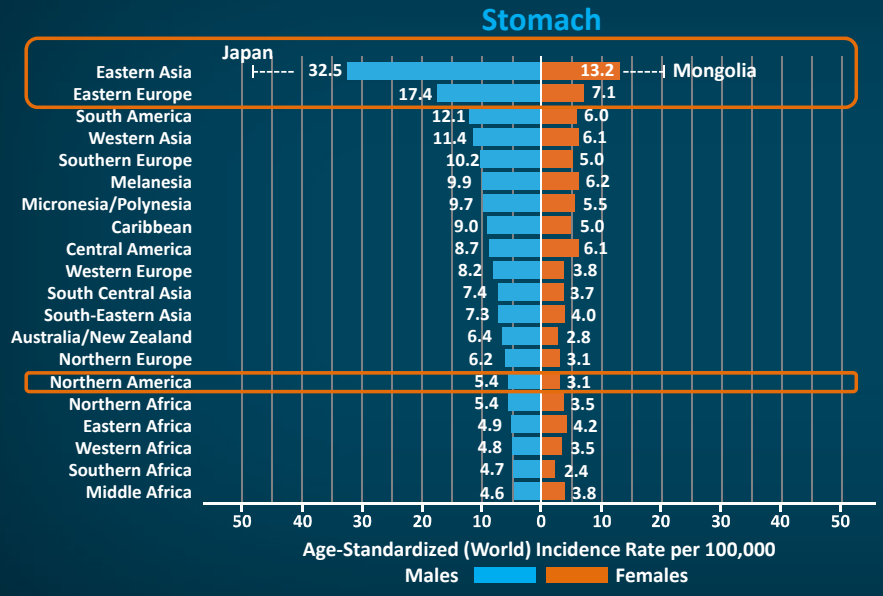
Learning Objectives

- Identify HER2 methods of biomarker testing and apply them to clinical practice in patients with GI malignancies
- Discuss the unique pharmacodynamics of HER2-directed ADCs and their antitumor effects in GI cancers
- Apply evidence from HER2-targeted, ADC clinical trials to personalize treatment of patients with advanced GI malignancies beyond the first line

ADC = antibody-drug conjugates; GI = gastrointestinal; HER2 = human epidermal growth factor receptor 2.

Identifying HER2-Driven Gastrointestinal Cancers: Applying Pathology

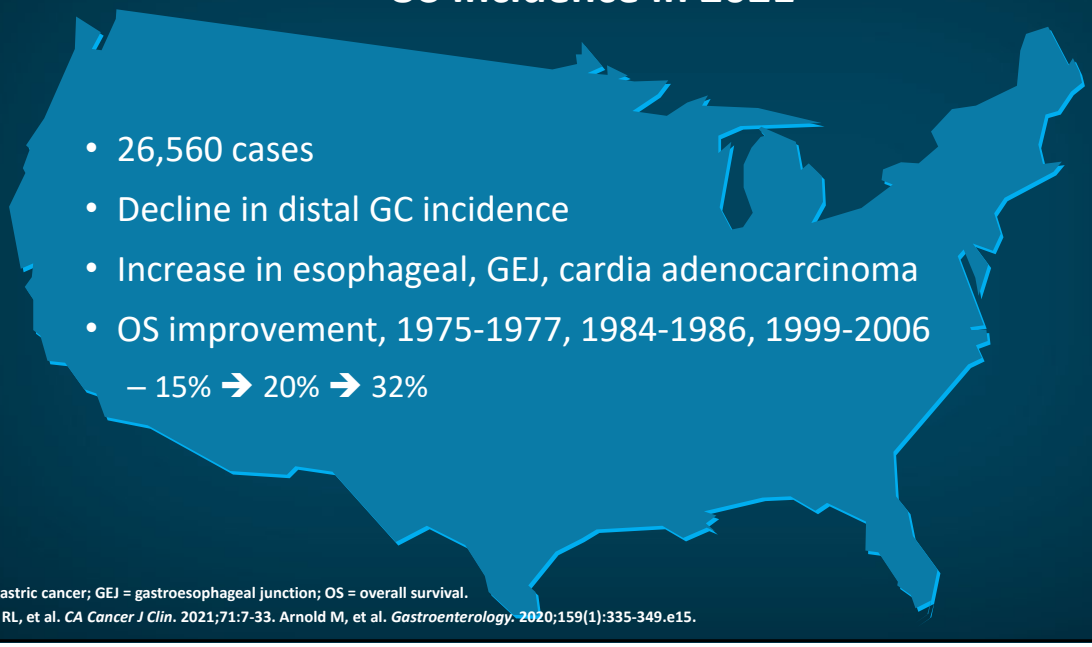
Gastric Cancer—Global Incidence: 2021



- 5th leading cause of cancer
- 4th leading cause of cancer-related death
- Uncommon in the United States and Europe
- Esophageal, 6th leading cause of cancer death

Sung H, et al. *CA Cancer J Clin*. 2021;71:209-249.

Gastric Carcinoma US Incidence in 2021



- 26,560 cases
- Decline in distal GC incidence
- Increase in esophageal, GEJ, cardia adenocarcinoma
- OS improvement, 1975-1977, 1984-1986, 1999-2006
  - 15% → 20% → 32%

GC = gastric cancer; GEJ = gastroesophageal junction; OS = overall survival.
Siegel RL, et al. *CA Cancer J Clin*. 2021;71:7-33. Arnold M, et al. *Gastroenterology*. 2020;159(1):335-349.e15.

Moving Toward Evidence-Based Management of Advanced G/GEJ Cancer: NCCN Recommendations

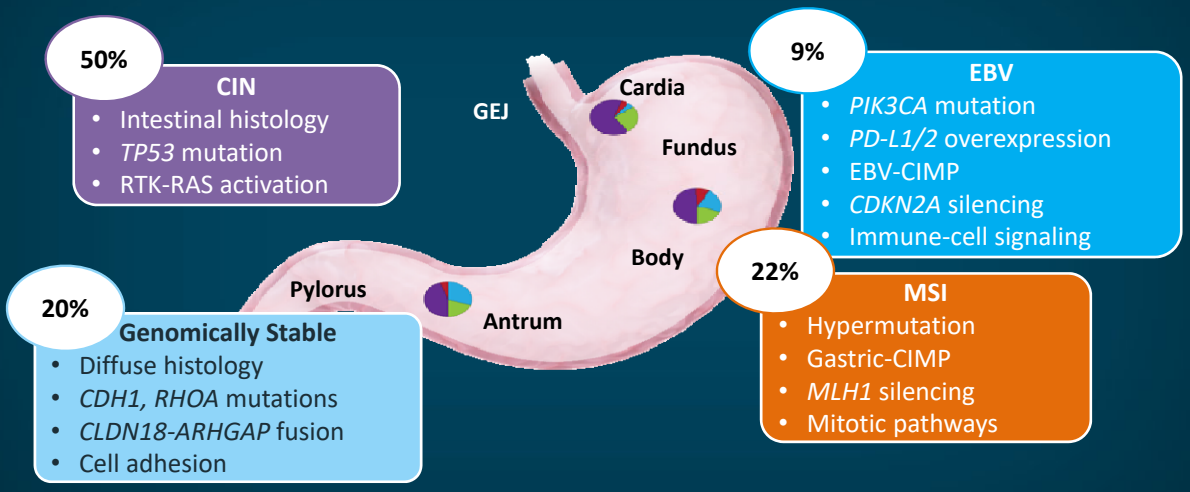
NCCN Guidelines for first-line therapy recommend (preferred regimens)

- HER2+ disease
  - Fluoropyrimidine† + oxaliplatin + trastuzumab*
  - Fluoropyrimidine + cisplatin + trastuzumab (category 1)
- HER2- disease
  - Fluoropyrimidine + oxaliplatin + nivolumab
  - Fluoropyrimidine + oxaliplatin
  - Fluoropyrimidine + cisplatin

† Fluorouracil or capecitabine G = gastric.
*NCCN guidelines support an FDA-approved biosimilar as an appropriate substitute for trastuzumab.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Gastric cancer. Version 4.2021 (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1434). Accessed 8/19/21.

Comprehensive Molecular Characterization of Gastric Cancer: TCGA



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

Adapted from Cancer Genome Atlas Research Network. *Nature.* 2014;513:202-209.

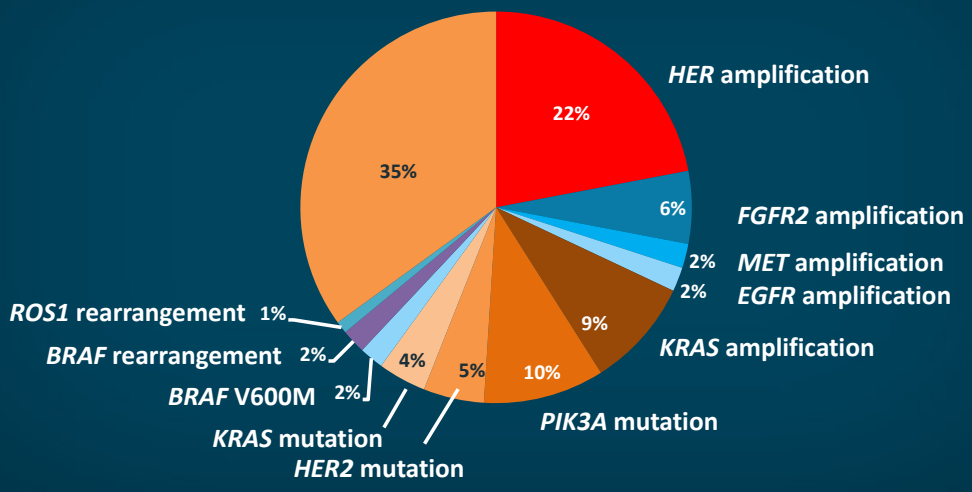
Role of HER2 in Gastric Cancer

- EGFR receptors are associated with tumor cell proliferation, apoptosis, adhesion, migration, and differentiation[1]
- *HER2* amplified or overexpressed in an average of ≈20% of G/GEJ adenocarcinomas[1]
- Prognostic significance of HER2 positivity remains controversial[2]

EGFR = epidermal growth factor receptor.

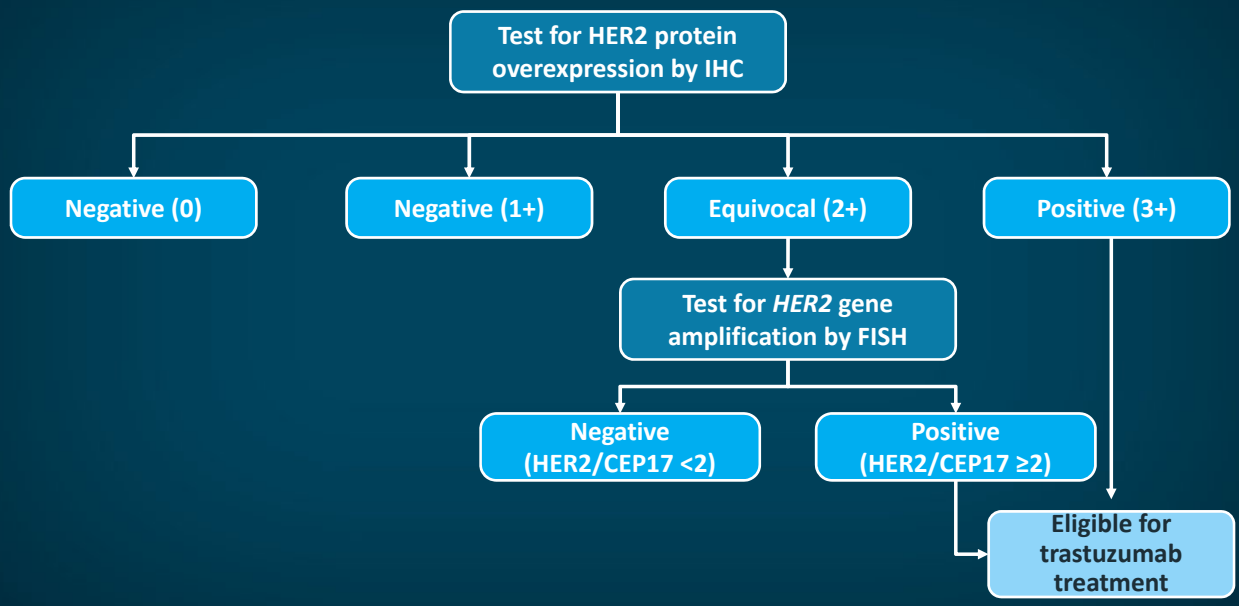
1. Bang YJ, et al. *Lancet*. 2010;376:687-697. 2. Namikawa T, et al. *Mol Clin Oncol*. 2013;1:249-252.

Prevalence of *HER2* Amplification in Gastric Cancer



Lee J, Ou SHI. *Discov Med.* 2013;15:333-341.

HER2 Testing in Gastric Cancer Algorithm



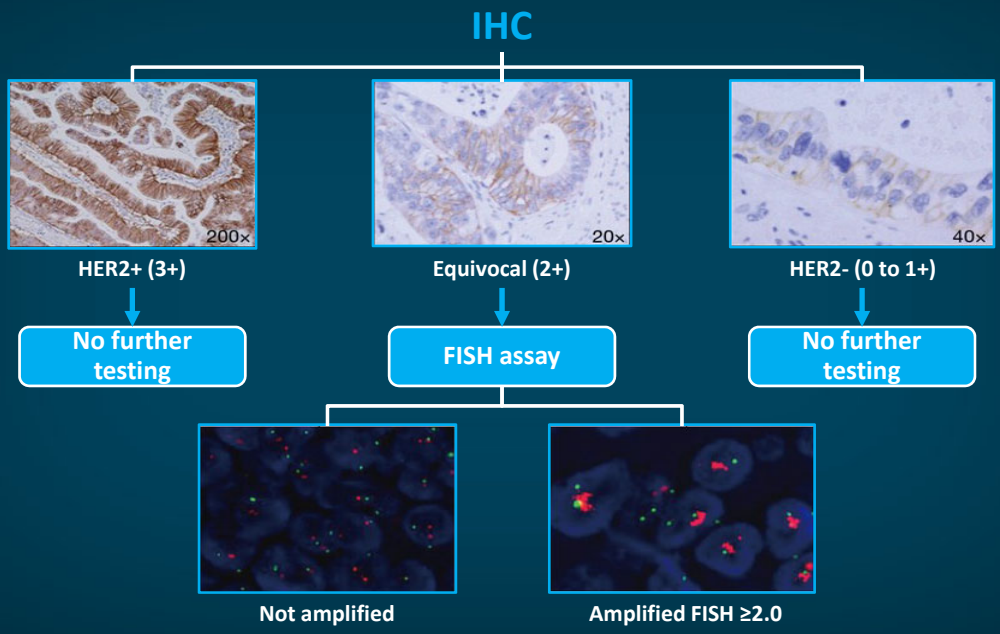
CEP17 = chromosome 17; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry.
Abrahao-Machado LF, Scapulatempo-Neto C. *World J Gastroenterol.* 2016;22:4619-4625.

HER2 Testing in Gastric vs Breast Cancer

Analysis	Parameter	GC	Breast Cancer
IHC scoring	Extent	Biopsy specimens ≥5 cells	≥10%
	(Area cut-off)	Resection specimens ≥10%	Resection specimens ≥10%
	Circularity	Mostly absent (often only lateral in IHC 2+/3+)	Required in IHC 2+/3+
FISH	Cell number	20 cohesive tumor cells showing highest gene count	20 cohesive tumor cells showing highest gene count
	Amplification	Ratio ≥2.0	Ratio ≥2.0
Patient selection	IHC vs FISH	IHC more predictive than FISH	IHC and FISH equally predictive

Rüschoff J, et al. *Virchows Arch.* 2010;457:299-307.

HER2 Expression vs Amplification



Kelly CM, Janjigian YY. *J Gastrointest Oncol.* 2016;7:750-762.

Intratumor HER2 Heterogeneity

Testing for HER2 on single section may miss HER2+ clone

- ≈20% of HER2+ esophageal/GEJ adenocarcinomas have intertumor HER2 heterogeneity
- Patients with HER2+ GC respond differently according to concomitant genomic aberrations beyond ERBB2
- High *ERBB2* amplification by NGS or cfDNA can be a positive predictor for patient selection
- Tumor genomic alterations change significantly during targeted agent therapy

cfDNA = cell-free DNA; NGS = next-generation sequencing.
Kim ST, et al. *Ann Oncol*. 2018;29:1037-1048. Courtesy of Axel Grothey.

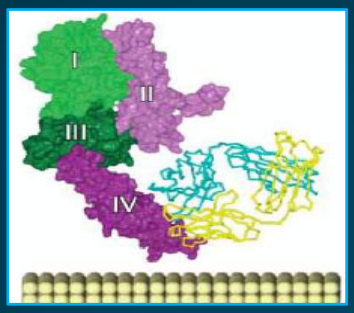
Role of HER2 in Solid GI Tumors

- 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 2%-7% of patients[2]
  - More common in left-sided primaries
    - *HER2* amplification predicts resistance to EGFR-targeted therapy
  - 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

CRC = colorectal cancer; WT = wild type.
1. Gravalos C, Jimeno A. *Ann Oncol.* 2008;19:1523-1529. 2. De Cuyper A, et al. *Clin Color Can*. 2020;19:65-72. 3. Dika IE, Ilson DH. *Expert Rev Anticancer Ther.* 2018;18:1085-1092; 4. Javle et al Lancet Oncology 22: 1290; 2021

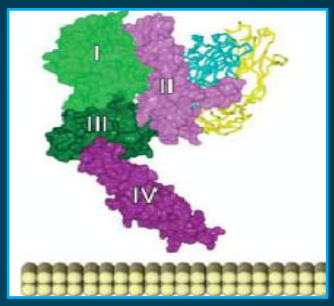
Binding Sites for HER2-Targeted Therapies

Trastuzumab[1]



- Activates antibody-dependent cellular cytotoxicity[1]
- Enhances HER2 internalization[2]
- Inhibits shedding and, therefore, formation of p95[3]
- Inhibits angiogenesis[4]

Pertuzumab[1]



- Activates antibody-dependent cellular cytotoxicity[5]
- Prevents HER2/HER3 receptor dimerization[1]
- Potent inhibitor of HER-mediated signaling pathways[5]

1. Reprinted from Hubbard SR. *Cancer Cell*. 2005;7:287-288 (with permission from Elsevier). 2. zum Büschenfelde CM, et al. *Cancer Res*. 2002;62:2244-2247. 3. Molina MA, et al. *Cancer Res*. 2001;61:4744-4749. 4. Petit AM, et al. *Am J Pathol*. 1997;151:1523-1530. 5. Scheuer W, et al. *Cancer Res*. 2009;69:9330-9336.

First-Line HER2-Directed Clinical Trials

Clinical Trial	Regimen	Stratification
ToGA[1] **HER2+** **(n=594)**	5-FU or capecitabine + cisplatin + trastuzumab 5-FU or capecitabine + cisplatin	• Advanced vs metastatic • GC vs GEJ cancer • Measurable vs nonmeasurable • ECOG PS 0-1 vs 2 • Capecitabine vs 5-FU
TRIO-013/LOGiC[2] **HER2+** **(FISH+ or IHC 3+)** **(n=545)**	Capecitabine + oxaliplatin + lapatinib* Capecitabine + oxaliplatin	• Geographic region of the world • Prior neoadjuvant and/or adjuvant chemotherapy
JACOB[3] **HER2+** **(ISH+ and IHC 2+ or 3+)** **(n=780)**	Capecitabine or 5-FU + cisplatin + trastuzumab + pertuzumab* Capecitabine or 5-FU + cisplatin + trastuzumab	• 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+)

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

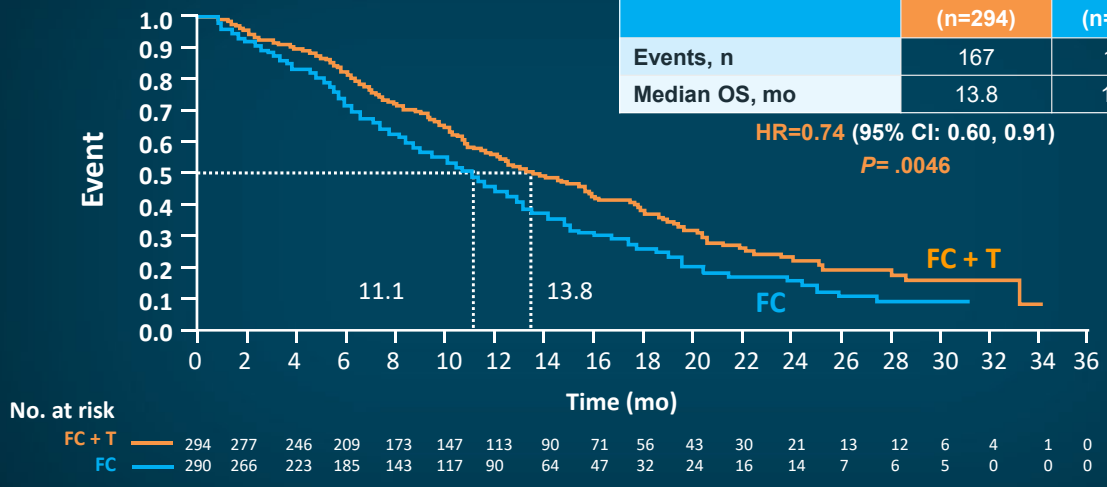
ECOG = Eastern Cooperative Oncology Group; ISH = in situ hybridization; PS = performance status.

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.

ToGA Primary Endpoint: Overall Survival

	FC + T (n=294)	FC (n=290)
Events, n	167	182
Median OS, mo	13.8	11.1

HR=0.74 (95% CI: 0.60, 0.91)
P= .0046



No. at risk

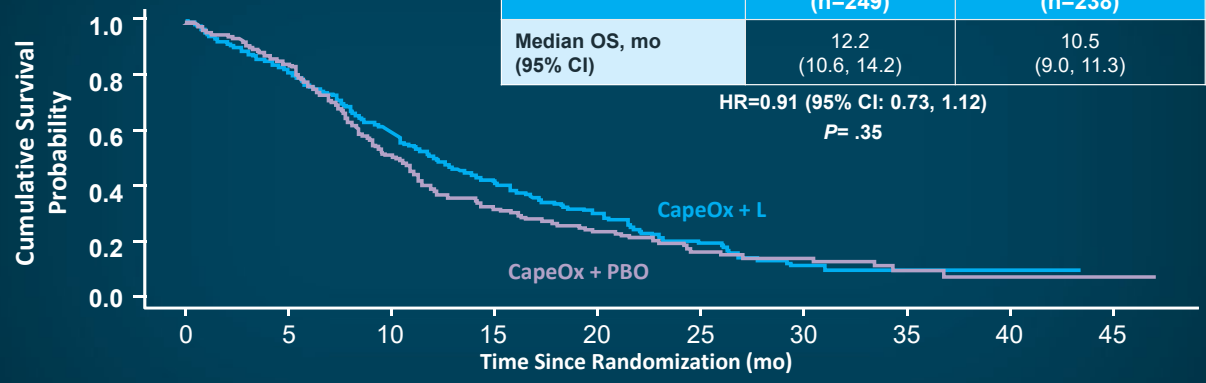
FC + T	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0
FC	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0

FC = 5-FU or capecitabine + cisplatin; HR = hazard ratio; T = trastuzumab.
Bang YJ, et al. *Lancet.* 2010;376:687-697.

TRIO-013/LOGiC Trial
Primary Endpoint: OS in Primary Efficacy Population

	CapeOx + L* (n=249)	CapeOx + PBO (n=238)
Median OS, mo (95% CI)	12.2 (10.6, 14.2)	10.5 (9.0, 11.3)

HR=0.91 (95% CI: 0.73, 1.12)
P= .35



Subjects at risk

CapeOx + L	249	199	133	83	47	24	9	3	3	
CapeOx + PBO	238	189	106	53	34	17	11	7	2	2

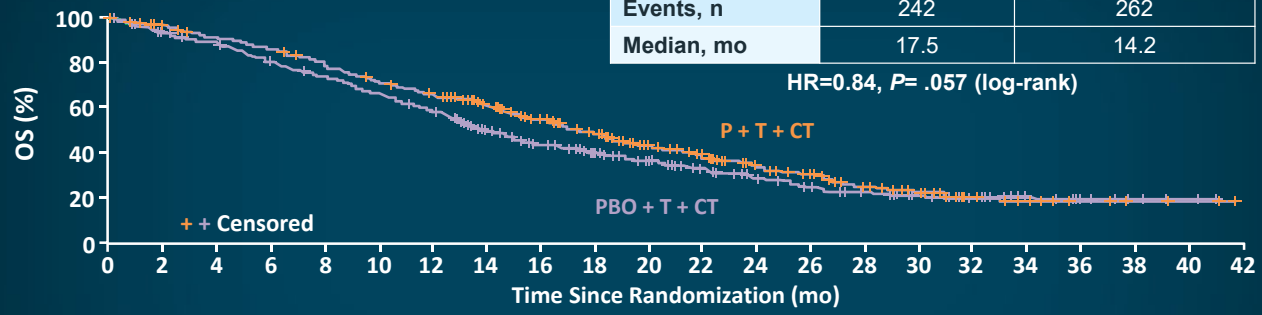
CapeOx + L = oxaliplatin/capecitabine + lapatinib; CapeOX + PBO = oxaliplatin/capecitabine + placebo; PBO = placebo.
Hecht JR, et al. *J Clin Oncol*. 2016;34:443-451.

**Lapatinib is not FDA approved for use in GC.*

JACOB: Primary Endpoint—OS

ITT Population	P* + CT (n=388)	PBO + T + CT (n=392)
Events, n	242	262
Median, mo	17.5	14.2

HR=0.84, *P*= .057 (log-rank)



Secondary Endpoints	P + T + CT (n=388)	PBO + T + CT (n=392)	HR (*P*)
Median PFS, mo	8.5	7.0	0.73 (0.62-0.85)
ORR	56.7%	48.3%	—

CT = chemotherapy; ITT = intention-to-treat; NR = not reported; ORR = objective/overall response rate; P = pertuzumab; T=trastuzumab

Tabernero J, et al. *Lancet Oncol.* 2018;19:1372-1384.

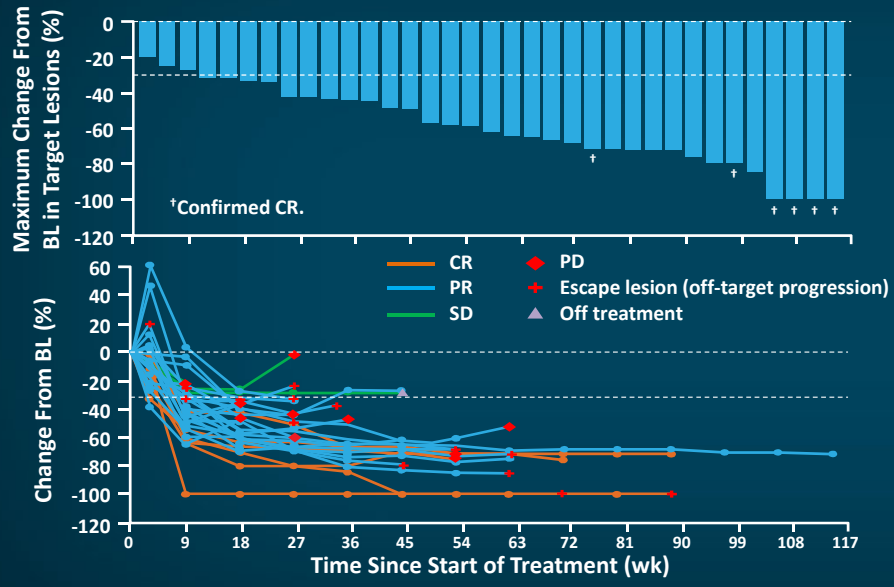
First-Line HER2-Directed Clinical Trials: OS

Clinical Trial	Regimen	Median OS, mo	HR (95% CI)	*P*
ToGA[1]	5-FU or capecitabine + cisplatin + trastuzumab	13.8	0.74 (0.60, 0.91)	.0046
	5-FU or capecitabine + cisplatin	11.1		
TRIO-013/ LOGiC[2]	Capecitabine + oxaliplain + lapatinib*	12.2	0.91 (0.73, 1.12)	.3492
	Capecitabine + oxaliplain	10.5		
JACOB[3]	Capecitabine or 5-FU + cisplatin + trastuzumab + pertuzumab	17.5	0.84 (0.71, 1.00)	.057
	Capecitabine or 5-FU + cisplatin + trastuzumab	14.2		

**Lapatinib is not FDA approved for use in GC.*

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.

First-Line Capecitabine/Oxaliplatin/Pembrolizumab/Trastuzumab



Best Response (n=37)	Patients, n (%)
ORR [95% CI]	32 (91) [78, 97]
CR	6 (17)
PR	26 (74)
SD	3 (9)
PD	0
DCR	100%

BL = baseline; CR = complete response; DCR = disease control rate; PD = progressive disease; PR = partial response; SD = stable disease.

Janjigian YY, et al. *Lancet Oncol.* 2020;21:821-831.

KEYNOTE-811 Global Cohort: Randomized, Double-Blind, Phase 3 Study

APPROVAL FOR FIRST-LINE PEMBROLIZUMAB

Key Eligibility Criteria

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

Stratification Factors

- Geographic region (Australia/Europe/Israel/North America vs Asia vs rest of world)
- PD-L1 CPS (≥1 vs <1)
- Chemotherapy choice (FP vs CAPOX)

R 1:1
N ≈ 692

HER2+

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

Placebo IV Q3W + Trastuzumab and FP or CAPOX* for up to 35 cycles

Endpoints

- **Dual primary:** OS and PFS per RECIST v1.1 by BICR
- **Key secondary:** ORR and DOR per RECIST v1.1 by BICR and safety

*Trastuzumab: 6 mg/kg IV Q3W following an 8-mg/kg loading dose. FP: 5-FU 800 mg/m²/d IV on days 1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX: capecitabine 1,000 mg/m² BID on days 1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.

BICR = blinded independent central review; BID = twice daily; CPS = combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); DOR = duration of response; IV = intravenous; Q3W = every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumours.

KEYNOTE-811. (https://clinicaltrials.gov/ct2/show/NCT03615326). Chung HC, et al. *Future Oncol.* 2021;17:491-501.

Confirmed Response at IA1, Efficacy Population

ORR and DCR, % (95% CI)	Pembrolizumab (n=133)	Placebo (n=131)
ORR	**74.4 (66.2, 81.6)**	**51.9 (43.0, 60.7)**
ORR difference*	**22.7 (11.2, 33.7) *P*= .00006**	
DCR	96.2 (91.4, 98.8)	89.3 (82.7, 94.0)

Best Response, n (%)	Pembrolizumab (n=133)	Placebo (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)

DOR†	Pembrolizumab (n=99)	Placebo (n=68)
Median (range), mo	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

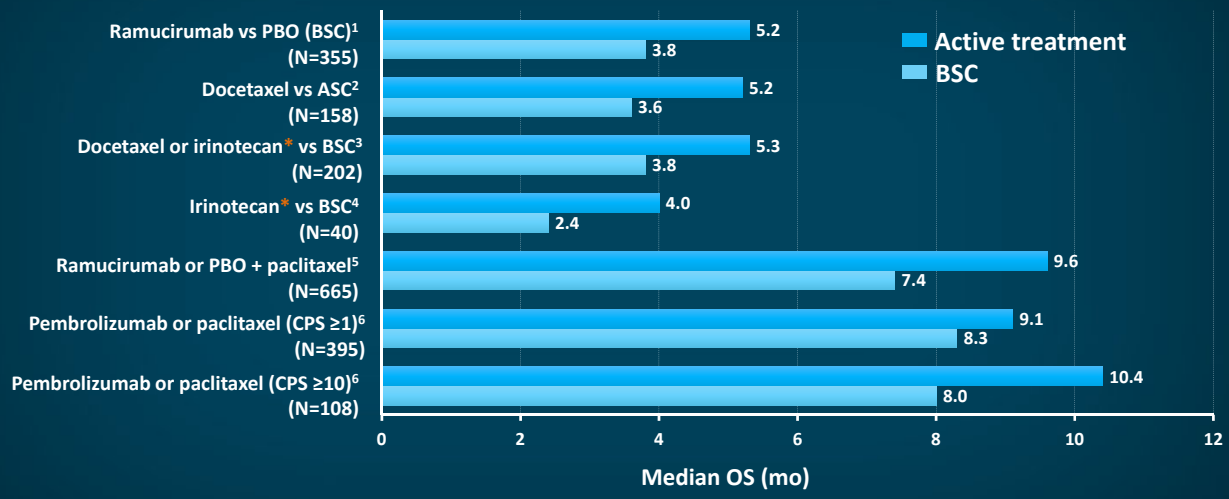
*Calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors. †Calculated in participants with best response of CR or PR; medians and ≥6-mo and ≥9-mo durations estimated using the Kaplan-Meier method. The treatment regimen in both arms included trastuzumab and chemotherapy. Data cutoff date: June 17, 2020.

Janjigian YY, et al. *J Clin Oncol*. 2021;39(15 suppl):4013. Janjigian YY, et al. CCO Oncology Presentation. (https://www.clinicaloptions.com/oncology/conference-coverage/2021/clinical-oncology-2021/gastrointestinal-cancers/capsule-summary-slidesets/4013). Accessed 8/24/21.

Pembrolizumab is now FDA-approved for this indication

Evolution of HER2-Targeted Therapy for HER2+ GI Cancers After Progression on Trastuzumab

What Are Treatment Options After First-Line Progression for Patients With HER2+ Gastric Cancer?



**Irinotecan is not FDA approved in GC.*

ASC = active symptom control; BSC = best supportive care.

1. Fuchs CS, et al. *Lancet.* 2014;383:31-39. 2. Ford H, et al. *J Clin Oncol.* 2013;31(suppl 4):LBA4. 3. Kang JH, et al. *J Clin Oncol.* 2012;30:1513-1518. 4. Thuss-Patience PC, et al. *Eur J Cancer.* 2011;47:2306-2314. 5. Wilke H, et al. *Lancet Oncol.* 2014;15:1224-1235. 6. Fuchs C, et al. *J Clin Oncol.* 2020;38(15 suppl):4503.

T-ACT: Paclitaxel ± Trastuzumab

- Phase 2 (N=91)
- Patients with HER2+ advanced G/GEJ cancer progressing during first-line chemotherapy with trastuzumab + 5-FU + platinum were randomized to receive either paclitaxel (80 mg/m^2, day 1, 8, 15, Q4W) or paclitaxel + trastuzumab (PT) (initial trastuzumab 8 mg/kg followed by 6 mg/kg, Q3W)
- Median PFS (primary endpoint) = 3.2 and 3.7 months in the paclitaxel and PT arms, respectively; HR=0.91 (95% CI: 0.67, 1.22), *P*= .33
- Secondary endpoints (OS, ORR, DCR) also not significantly different between arms
- Safety was comparable between arms
- 69% (11/16) lost their HER2+ status

Q4W = every 4 weeks.

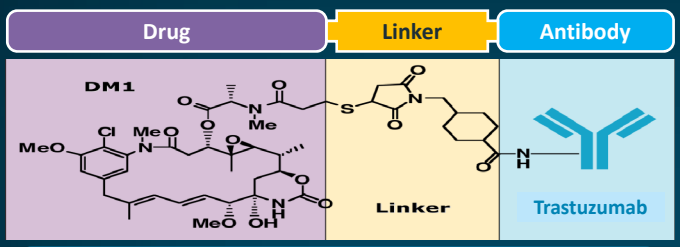
Makiyama A, et al. *J Clin Oncol*. 2020;38:1919-1927.

Current Treatment Options for Second-Line Therapy in Patients With HER2+ Disease

- Continuing trastuzumab past first-line progression has not shown significant improvement in outcomes
- Treatment options inline with HER2- disease options
- Treatment choices based on patient/provider decision
  - Toxicity profile of regimen
  - Patient PS
  - Patient goals
  - Patient comorbidities
- More options are clearly needed

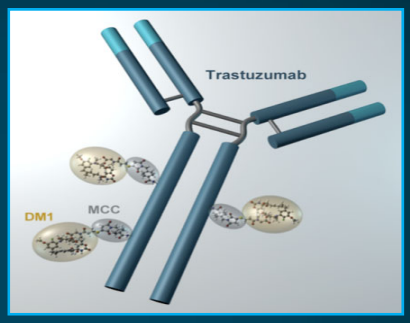
Leveraging Antibody-Drug Conjugates in HER2-Positive Gastrointestinal Malignancies

Trastuzumab Emtansine (T-DM1) Structure



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

T-DM1 is a novel ADC



T-DM1

Average drug has an antibody ratio ≅ 3.5:1

mAb = monoclonal antibody; MCC = [*N*-maleimidomethyl]cyclohexane-1-carboxylate; T-DM1 = trastuzumab emtansine.

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

GATSBY: Phase 3 Study of T-DM1 vs Taxane in Patients With HER2+ GC

345 patients with HER2+ disease following first-line therapy

RANDOMIZE

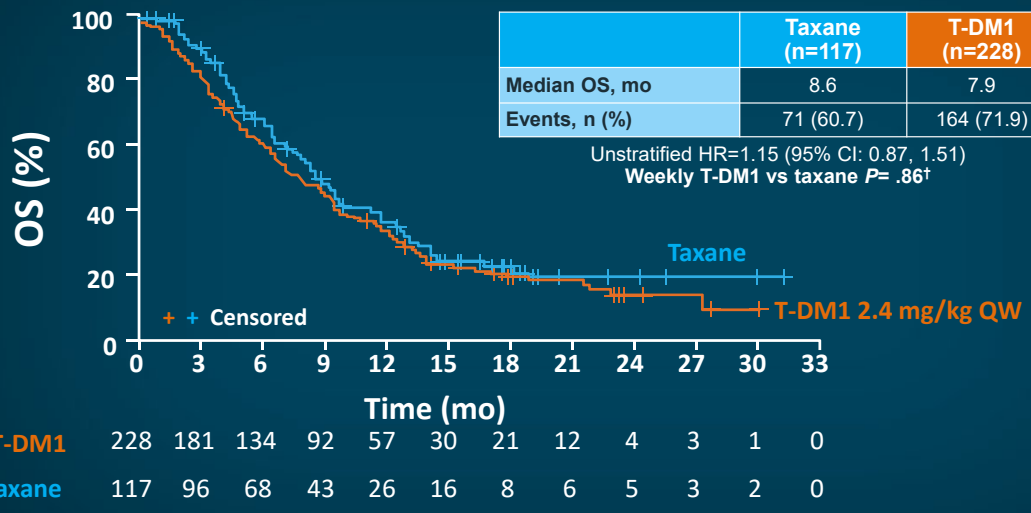
2:1 ratio

- T-DM1 every week
- Paclitaxel or docetaxel

Primary endpoint: OS

Shah MA, et al. *Gastric Cancer.* 2019;18:803-816. Kang Y-K, et al. *J Clin Oncol.* 2016;34(4 suppl):5.

GATSBY: Overall Survival



	Taxane (n=117)	T-DM1 (n=228)
Median OS, mo	8.6	7.9
Events, n (%)	71 (60.7)	164 (71.9)

Unstratified HR=1.15 (95% CI: 0.87, 1.51)
Weekly T-DM1 vs taxane *P*= .86†

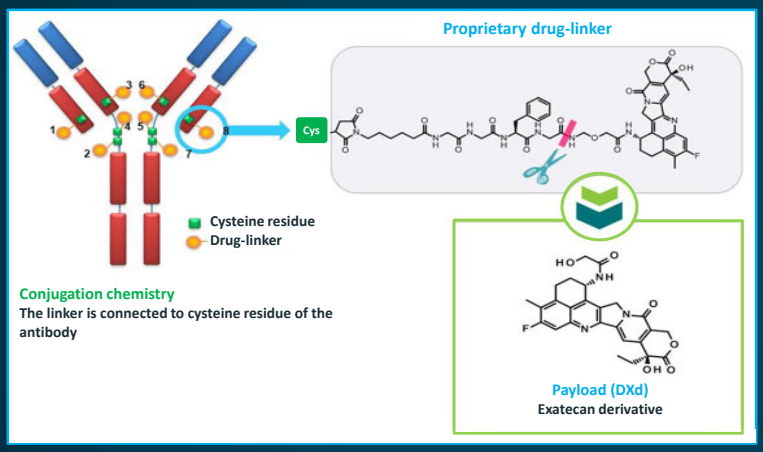
T-DM1	228	181	134	92	57	30	21	12	4	3	1	0
Taxane	117	96	68	43	26	16	8	6	5	3	2	0

†1-sided *P* value with correction for interim treatment selection, due to adaptive seamless design.

QW = every week.

Thuss-Patience PC, et al. *Lancet Oncol.* 2017;18:640-653. Kang Y-K, et al. *J Clin Oncol.* 2016;34(4 suppl):5.

Trastuzumab Deruxtecan (T-DXd; DS-8201a): Structure and Mechanism of Action



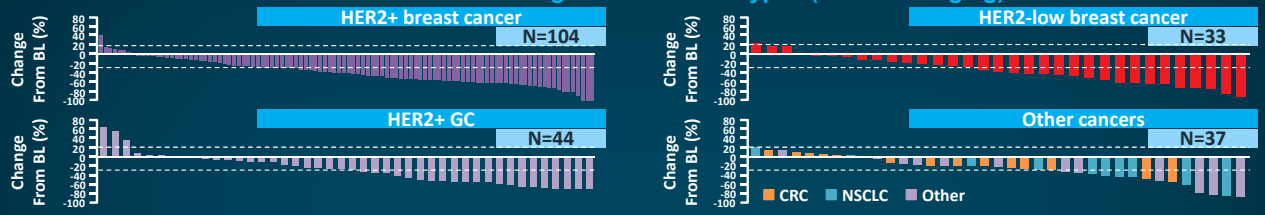
- Payload with a different mechanism of action
- High potency of payload
- Payload with short systemic half-life
- Bystander effect
- Stable linker-payload
- Tumor-selective cleavable linker
- High drug-to-antibody ratio

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

Iwata H. ASCO 2020. Abstract 2501. US Oncology Research is supported by McKesson Specialty Health.

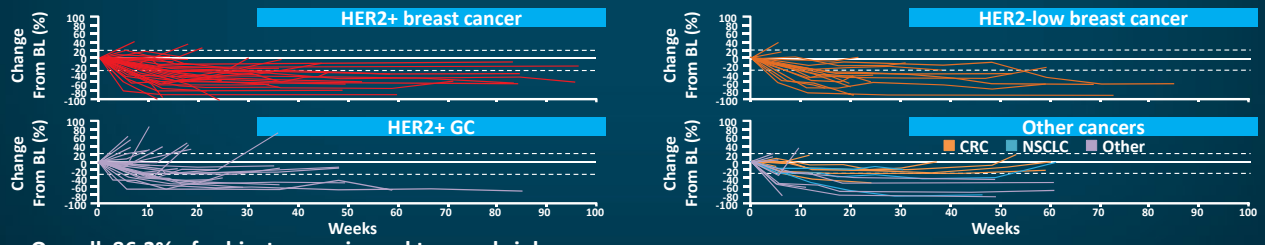
Antitumor Activity of Trastuzumab Deruxtecan

Consistent tumor shrinkage across tumor types (5.4 or 6.4 mg/kg)



- Overall, 86.3% of subjects experienced tumor shrinkage
- Confirmed ORR in overall population is 49.3%

Tumor shrinkage over time by tumor type (5.4 or 6.4 mg/kg)



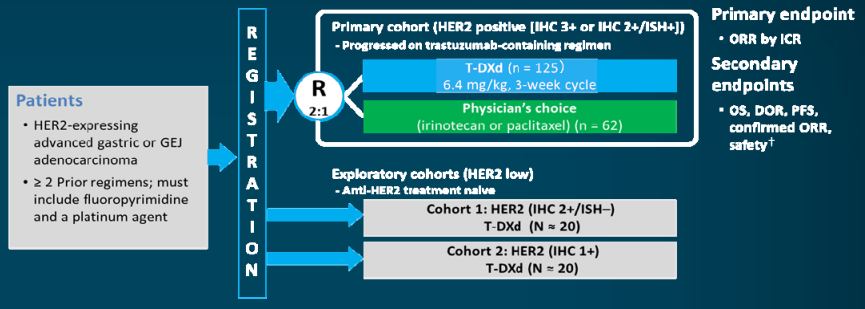
- Overall, 86.3% of subjects experienced tumor shrinkage
- 91.5% of these subjects experienced shrinkage at time of first imaging assessment at 6 weeks

NSCLC = non-small cell lung cancer. Iwata H. ASCO 2020. Abstract 2501. US Oncology Research is supported by McKesson Specialty Health.

DESTINY-Gastric01

An Open-Label, Multicenter, Randomized Phase 2 Study

- T-DXd is an ADC consisting of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and cytotoxic topoisomerase I inhibitor payload
- Previously, T-DXd 5.4 or 6.4 mg/kg in a phase 1 study demonstrated an ORR of 43.2% and median PFS of 5.6 months in 44 patients with HER2+ G/GEJ cancer previously treated with trastuzumab (NCT02564900)
- Shown is the schema for the primary cohort of DESTINY-Gastric01 (NCT03329690)



†OS was key secondary endpoint to be statistically evaluated hierarchically if primary endpoint statistically significant (familywise type I error controlled at 0.05 for ORR and OS).

- 187 patients were randomized (T-DXd=125; PC=62)
- 77% of patients had HER2 IHC 3+
- Median number of prior systemic therapies was 2 (range, 2-9)
- 86% previously received taxanes, 72% ramucirumab, and 33% anti–PD1/-PD-L1
- At data cut-off (November 8, 2019), 22% and 5% of patients in the T-DXd and PC arms remained on treatment

ICR = independent central review.

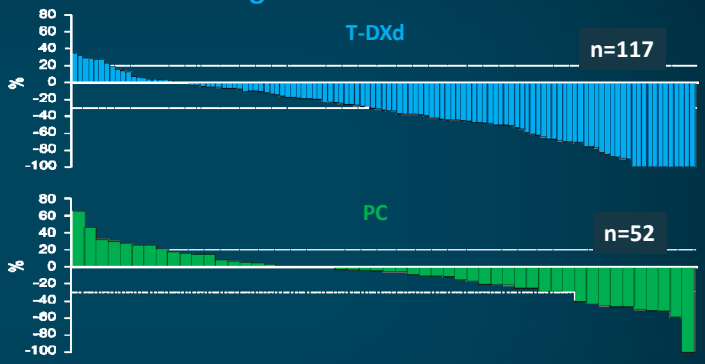
Shitara K, et al. *N Engl J Med*. 2020;381:2419-2430. DESTINY-Gastric01. (https://clinicaltrials.gov/ct2/show/NCT03329690).

DESTINY-Gastric01: Primary Endpoint—ORR

	T-DXd (n=119)	PC (n=56)
ORR by ICR (CR + PR)	51% (n=61) 95% CI: 42, 61 *P*< .001	14% (n=8) 95% CI: 6, 26
Confirmed ORR by ICR (CR + PR)	43% (n=51) 95% CI: 34, 52	12% (n=7) 95% CI: 5, 24
CR	8% (n=10)	0
PR	34% (n=41)	12% (n=7)
SD	43% (n=51)	50% (n=28)
PD	12% (n=14)	30% (n=17)
Not evaluable	3% (n=3)	7% (n=4)
Confirmed DCR (CR + PR + SD)	86% (n=102) 95% CI: 78, 91	62% (n=35) 95% CI: 49, 75
Median confirmed DOR	11.3 months 95% CI: 5.6, NE	3.9 months 95% CI: 3.0, 4.9

Includes data for the response-evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on ICR at baseline.

Best % change from baseline in tumor size



Line at 20% indicates progressive disease; line at -30% indicates PR. Includes patients who had both baseline and postbaseline target lesion assessments by ICR in both treatment arms.

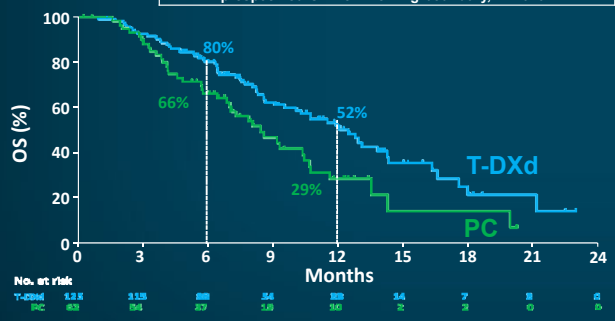
NE = not estimable; PC = physician's choice (of chemotherapy).

Shitara K, et al. *N Engl J Med*. 2020;381:2419-2430.

DESTINY-Gastric01: OS and PFS

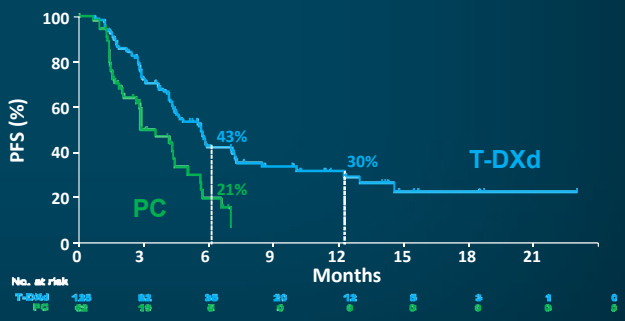
Overall Survival

	Events/n	Median OS
T-DXd	62/125	12.5 months (95% CI: 9.6, 14.3)
PC	39/62	8.4 months (95% CI: 6.9, 10.7)
HR=0.59 (95% CI: 0.39, 0.88); *P*= .01 prespecified O'Brien-Fleming boundary, *P*= .0202		



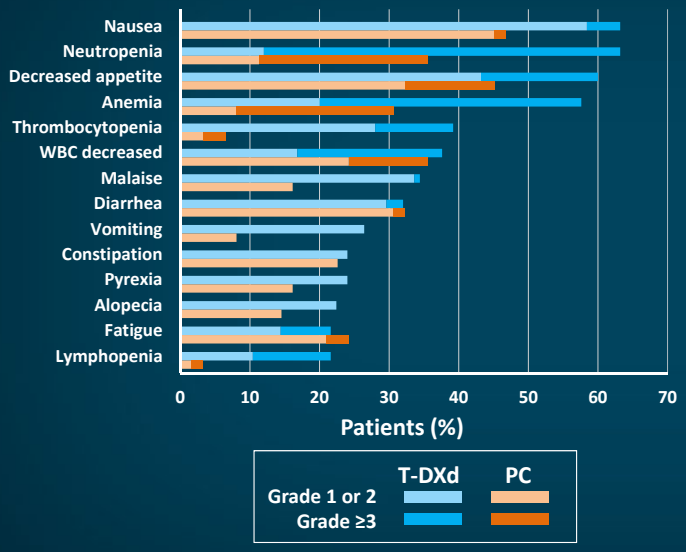
Progression-Free Survival

	Events/n	Median PFS
T-DXd	73/125	5.6 months (95% CI: 4.3, 6.9)
PC	36/62	3.5 months (95% CI: 2.0, 4.3)
HR=0.47 (95% CI: 0.31, 0.71)		



Shitara K, et al. *N Engl J Med*. 2020;381:2419-2430.

DESTINY-Gastric01: Safety Summary



Treatment-Emergent AEs Associated With:	T-DXd (n=125)	PC (n=62)
Drug discontinuation	15%	6%
Dose reduction	32%	34%
Dose interruption	62%	37%

- 1 drug-related death due to pneumonia with T-DXd and none with PC
- 12 patients (10%) had T-DXd–related ILD/pneumonitis as determined by an independent adjudication committee
  - Median time to first onset, 84.5 days (range, 36-638 days)
  - Most were grade 1 or 2 (3 grade 1, 6 grade 2, 2 grade 3, 1 grade 4, and no grade 5)

AE = adverse event; ILD = interstitial lung disease; WBC = white blood count.

Shitara K, et al. *N Engl J Med*. 2020;381:2419-2430.

DESTINY-Gastric01: HER2-Low Exploratory Cohorts

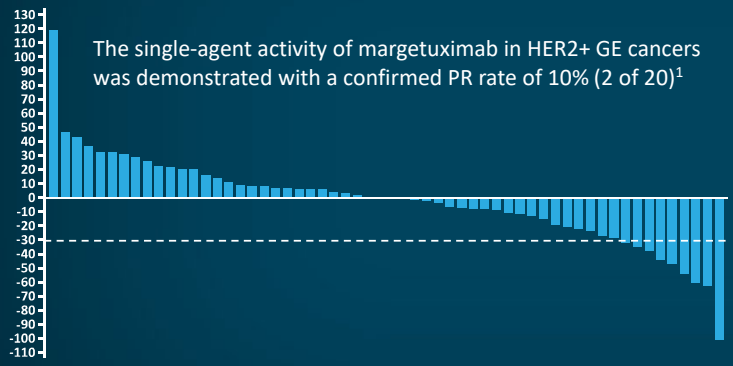
- Centrally confirmed HER2-low via IHC 2+/ISH- (n=20) or IHC 1+ (n=24)
- Progressed on ≥2 prior lines of therapy; excluded if prior HER2 therapy
- Safety profile similar to HER2+ primary cohort

	IHC 2+/ISH-	IHC 1+
PR	5/19	2/21
SD	12/19	
Confirmed ORR, % (95% CI)	26.3 (5, 19)	9.5 (2, 21)
DCR, % (95% CI)	89.5	71.4
Median PFS, mo (95% CI)	4.4 (2.7, 7.1)	2.8 (1.5, 4.3)
Median OS, mo (95% CI)	7.8 (4.7, NE)	8.5 (4.3, 10.9)
12-month OS rate, %	40	25.7

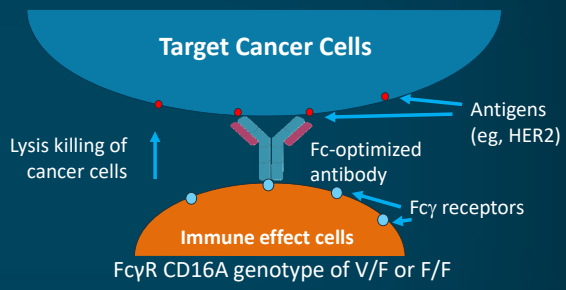
Yamaguchi K, et al. *Ann Oncol*. 2020;31(suppl 4):S899-S900.

Margetuximab

- Margetuximab had enhanced antibody-dependent cell-mediated cytotoxicity compared with trastuzumab[1]



The single-agent activity of margetuximab in HER2+ GE cancers was demonstrated with a confirmed PR rate of 10% (2 of 20)[1]



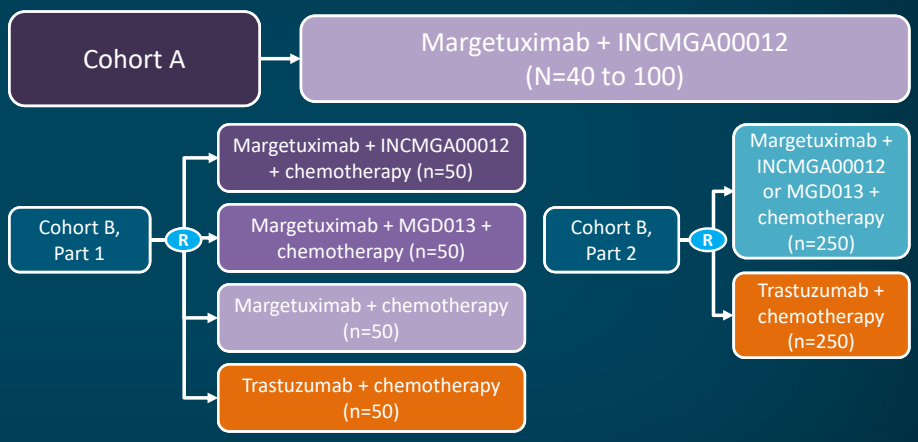
Phase 2/3 MAHOGANY: Combination margetuximab*, INCMGA00012*, MGD013*, and chemotherapy in *HER2*+ G/GEJ cancer[2]

* Margetuximab, INCMGA00012, MGD013 are not FDA-approved for the treatment of G/GEJ cancers. INCMGA as an anti PD-1 antibody ; MGD013 is a bispecific antibody targeting LAG32 and PD-1; 1. Bang YJ, et al. *Ann Oncol*. 2017;28:855-861. 2. MAHOGANY. (https://clinicaltrials.gov/ct2/show/NCT04082364).

MAHOGANY Phase 2/3 Trial in HER2+ G/GEJ Cancer

Inclusion Criteria

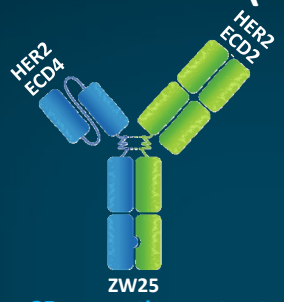
- Previously untreated advanced disease
  - Cohort A: HER2+ (by IHC 3+) and PD-L1+ (CPS ≥1%)
  - Cohort B: HER2+ (by IHC 3+ or IHC 2+/FISH+)
- ECOG PS 0 or 1



- Primary outcomes: AE incidence (Cohort A), ORR (Cohorts A and B), OS (Cohort B)

* Margetuximab, INCMGA00012, MGD013 are not FDA-approved for the treatment of G/GEJ cancers. MAHOGANY. (https://clinicaltrials.gov/ct2/show/NCT04082364).

Zanidatamab* (ZW25), a HER2-Targeted Bispecific mAb



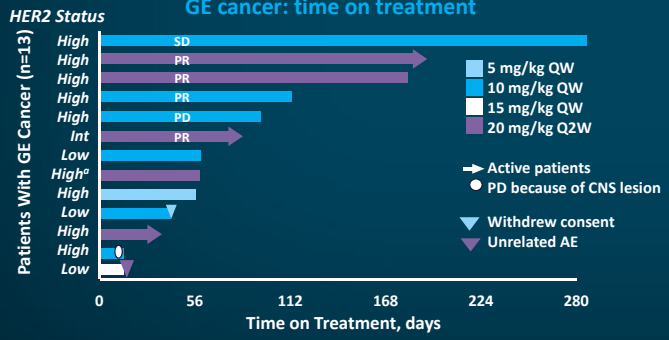
Biparatopic binding targets 2 distinct HER2 epitopes

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

Unique mechanisms of action designed to expand activity

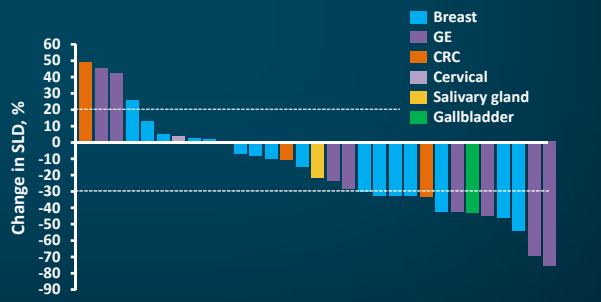
- Extended chain formation and dense HER2 receptor clustering
- Enhanced HER2 internalization and downregulation
- Increased tumor cell binding density and potent effector-mediated cytotoxicity
- Enhanced blockade of ligand-dependent and ligand-independent tumor growth

GE cancer: time on treatment



Change in target lesions across cancer types

Decrease in target lesions in majority of patients with measurable disease



*Zanidatamab is not FDA-approved for G/GEJ cancer; CNS = central nervous system; GE = gastroesophageal; Q2W = every 2 weeks; SLD = sum of longest diameters.

ASCO Post. 2018 (https://ascopost.com/News/59508). Accessed 8/20/21. Meric-Bernstam F, et al. *J Clin Oncol*. 2018;36(15 suppl):2500. Weisser N, et al. AACR; Abstract 1005;2021.

HER2+ mCRC

NOTE: There are currently no FDA-approved therapies for HER2+ mCRC, although they are listed in NCCN recommendations

HER2+ mCRC: Very Consistent Data

- HERACLES trial[1]: trastuzumab + lapatinib
- MyPathway trial[2]: pertuzumab + trastuzumab
- TRIUMPH trial[3]: pertuzumab + trastuzumab
- HERACLES-B trial[4]: T-DM1
- DESTINY trial[5]: T-DXd (also anti-HER2 pretreated)

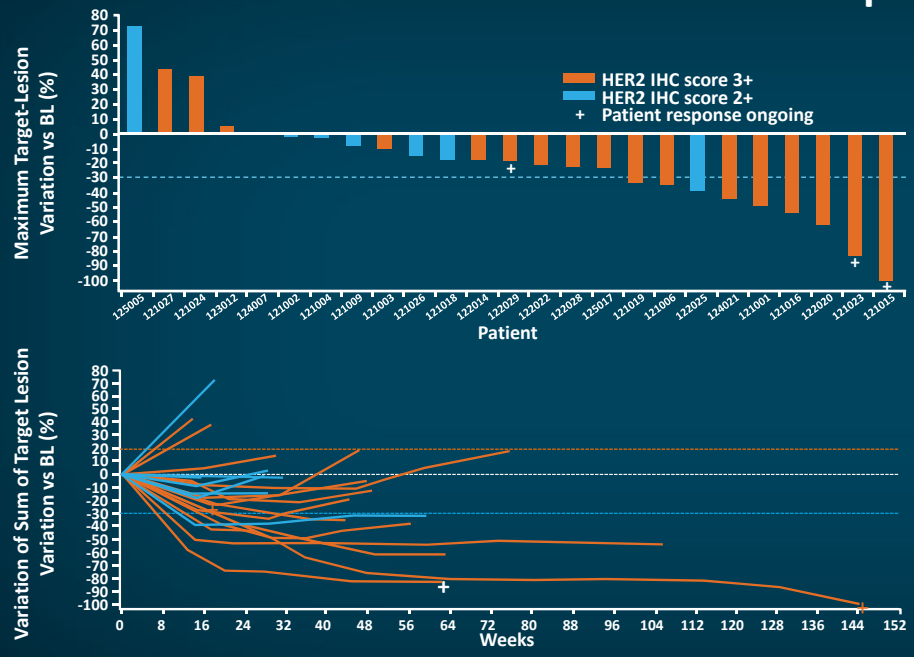
→ Only 2%-5% have *HER2* amplification[2]

→ How and when should we test?

→ What is the best treatment?

1. Sartore-Bianchi A, et al. *Lancet Oncol*. 2016;17:738-746. 2. Meric-Bernstam F, et al. *Lancet Oncol.* 2019;20:518-530. 3. Okamoto W, et al. J Clin Oncol. 2021;39(suppl 15):3555.
4. Sartore-Bianchi A, et al. *ESMO Open*. 2020;5:e000911. 5. Siena S, et al. *Lancet Oncol*. 2021;22:779-789.

HERACLES: Trastuzumab + Lapatinib

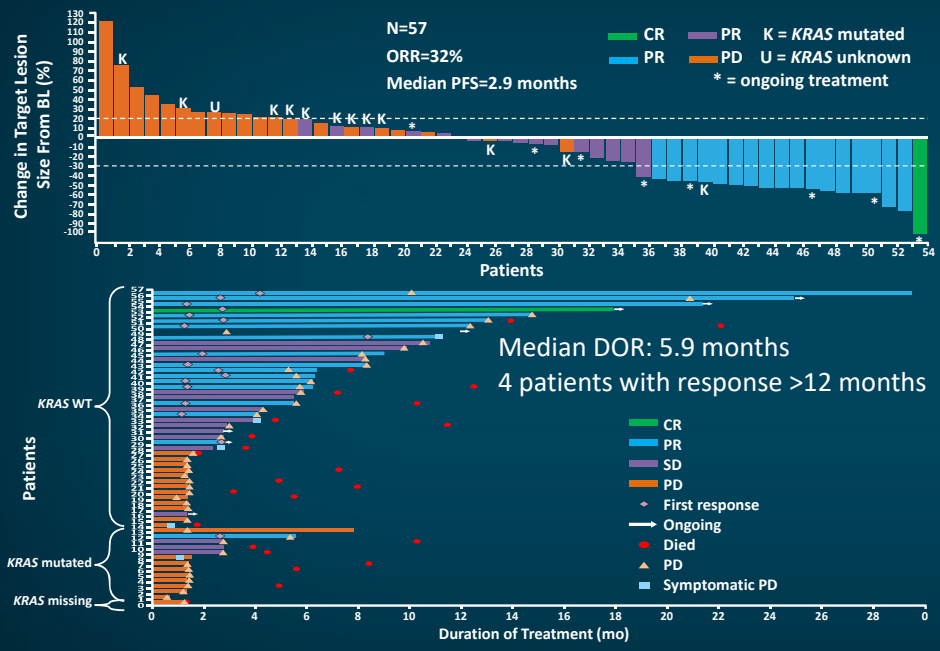


Patient selection (n=27):

- IHC: 3+ HER2 score in >50% of cells
- IHC: 2+ and a HER2:CEP17 ratio >2 in >50% of cells by FISH
- Responses in 30% of patients

Sartore-Bianchi A, et al. *Lancet Oncol*. 2016;17:738-746.

MyPathway: Trastuzumab + Pertuzumab



Patient selection (n=57):

- FISH or CISH + (*HER2/CEP17* >2 or *HER2 copy number* >6)
- NGS: *HER2* amplification based on copy number gain
- IHC 3+
- 32% response rate

CISH = chromogenic in situ hybridization. Meric-Bernstam F, et al. *Lancet Oncol.* 2019;20:518-530.

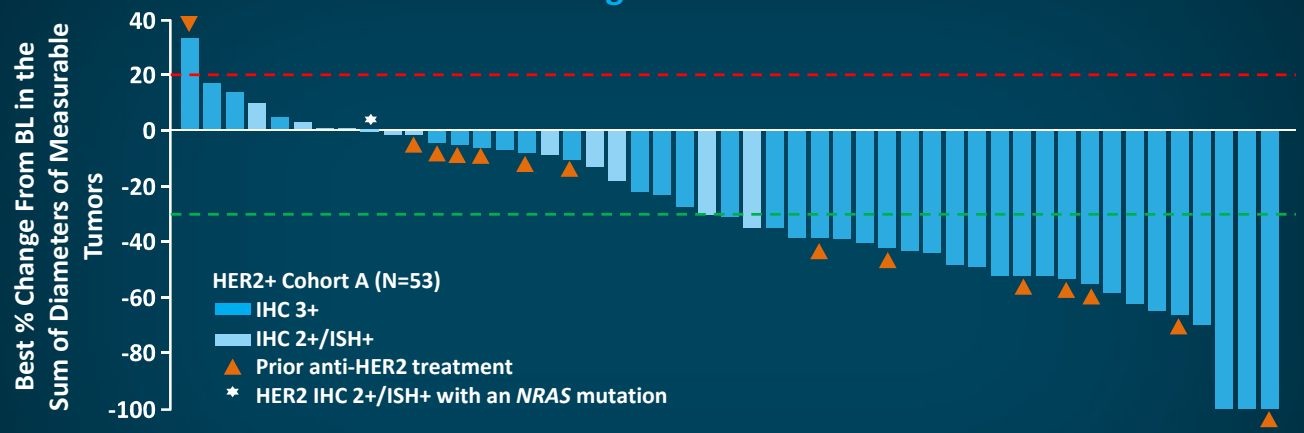
SWOG S1613 (NCT03365882)

- HER2+ CRC
- Phase 2 trial
  - Trastuzumab + pertuzumab vs irinotecan + cetuximab
- Primary endpoint: PFS
- Secondary endpoints: response, OS

Raghav KPS, et al. *J Clin Oncol.* 2018;36(15 suppl):TPS3620. S1613. (https://clinicaltrials.gov/ct2/show/NCT03365882).

DESTINY-CRC01: Trastuzumab Deruxtecan

Best change in tumor size



- Phase 2
- 78 patients with HER2+ mCRC who progressed on ≥2 regimens
- Enrolled by HER2+ level of expression
- 45% response rate

mCRC = metastatic CRC.

Siena S, et al. *Lancet Oncol*. 2021;22:779-789.

Case Study

72-year-old woman with dysphagia, belching, and early satiety

Past Medical History: asthma, hypertension, elevated cholesterol, 14 pack year smoking

- EGD: obstructing circumferential mass in the GEJ, Barrett's, biopsy adenocarcinoma
- CT and PET: upper paratracheal, paraesophageal, GH nodes, primary, small liver metastases
- Tumor tissue tests positive for HER2, IHC 3+, PD-L1 CPS 1%
- Genomic profiling: MSS, *p53* mutation, mutations in *ARID1A* and *B*, *ERBB3* cyclin D, *ALK*, *CSF1R*, *PREX2*, *PIK3R1* deletion, amplification of *HER2* (8.4) and *RARA*, loss *TGFBR2*
- Therapy initiated on study with infusional 5-FU, oxaliplatin, trastuzumab, and pembrolizumab
- Infusional 5-FU is dose reduced for mucositis
- Reflux and dysphagia improve
- Serial CT shows a response in the liver and other disease sites

CT = computed tomography; EGD = esophagogastroduodenoscopy; GH = growth hormone; MSS = microsatellite stable; PET = positron emission tomography.

Case Study (continued)

- 5-FU dose reduction due to conjunctivitis; oxaliplatin stopped at 4 months due to neuropathy
- Infusional 5-FU, trastuzumab, and pembrolizumab continued
- CTs show ongoing response at 8 months; no visible liver lesion
- Changed to trastuzumab and pembrolizumab but developed nephritis
- Continued trastuzumab maintenance therapy, EGD shows residual GEJ mass

17 Months

- Nausea, fevers, and seizure
- MRI of the brain indicates a right temporo-occipital and left cerebellar metastasis
- Resection of the larger lesion, SRS to smaller lesion
- Repeat genomic profiling of the brain lesion: *HER2* now 15-fold amplified
- Resumes trastuzumab maintenance

SRS = stereotactic radiosurgery.

Years 3 and 4

- For progressive dysphagia: capecitabine and radiotherapy at year 3 with improvement
- At 4 years with further local progression, she starts T-DXd
- Local tumor continues to progress on endoscopy; feeding tube placed and later-line therapy considered
- Currently on supportive care

Conclusions

- HER2 is targetable in GI cancers
- High rate of positivity in GC
  - Trastuzumab approved with first-line chemotherapy, now + pembrolizumab
  - Second- or later-line: T-DXd is now approved
- *HER2* amplification in CRC from NGS
  - Left-sided, *RAS* WT cancers
  - Promise for T-DXd and trastuzumab combination therapies
- Biliary cancer
  - *HER2* amplification in gallbladder primaries[1]

Javle et al Lancet Oncology 22: 1290; 2021

Thank you!

Project ECHO®

Med Learning Group - Gastrointestinal Cancers

Targeting HER2-Driven Disease Beyond the First Line: Antibody-Drug Conjugate Therapy in Gastrointestinal Cancers

TOOLKIT

Resources	Web Address
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