



TARGETING HER2-DRIVEN DISEASE BEYOND THE FIRST LINE:

Antibody-Drug Conjugate Therapy in GASTROINTESTINAL CANCERS

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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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Dr. Ajani has received consulting fees from AstraZeneca.

Dr. Dunne has nothing to disclose.

Dr. Hecht has served as a consultant for Actym.

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Douglas Cox, MSN, MHA, RN

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

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Disclosures

- Dr. Ajani receives consulting fees from AstraZeneca.
- During this activity, Dr. Ajani 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.

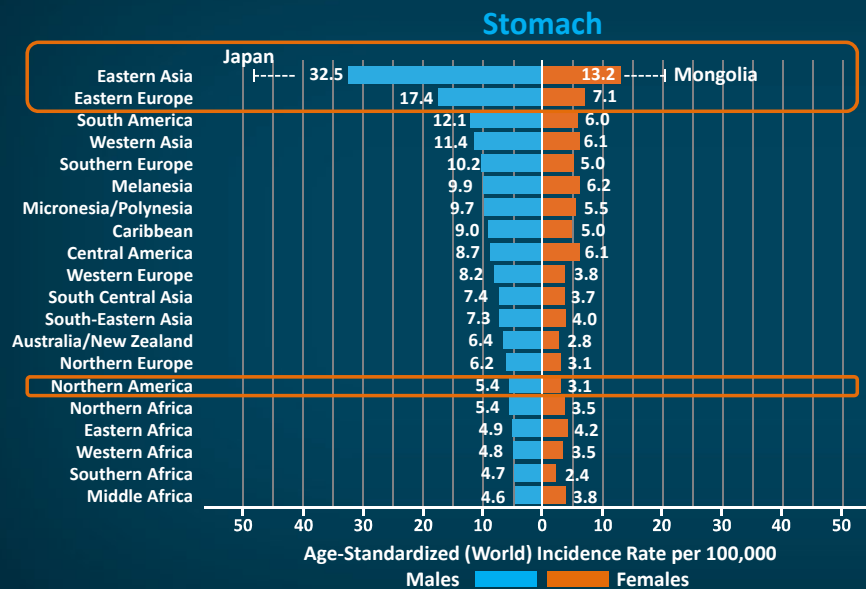
Learning Objectives

- 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



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

- 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

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)

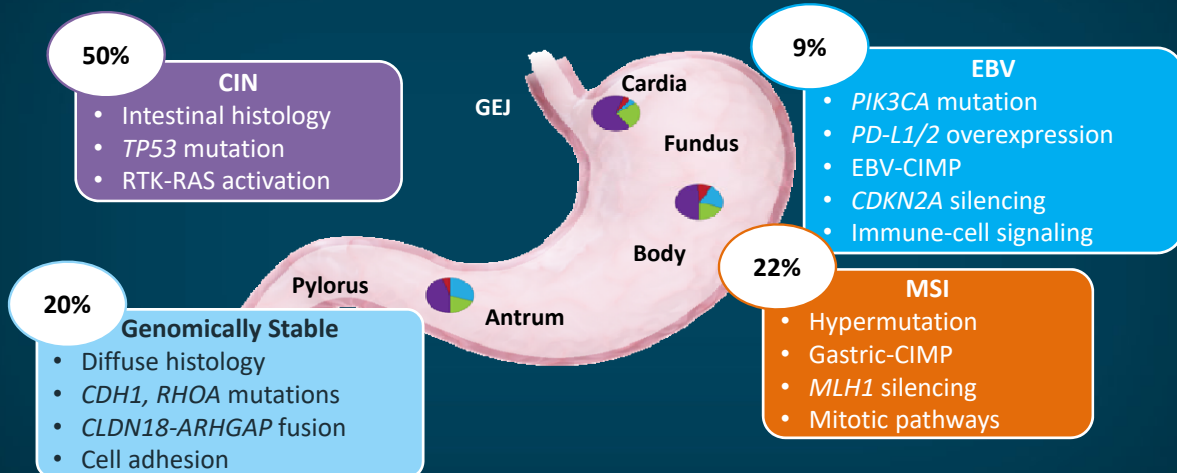
- HER2+ disease
 - Fluoropyrimidine[†] + oxaliplatin + trastuzumab*
 - Fluoropyrimidine + cisplatin + trastuzumab (category 1)
- HER2- disease
 - Fluoropyrimidine + oxaliplatin + nivolumab
 - Fluoropyrimidine + oxaliplatin
 - Fluoropyrimidine + cisplatin

[†] 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.

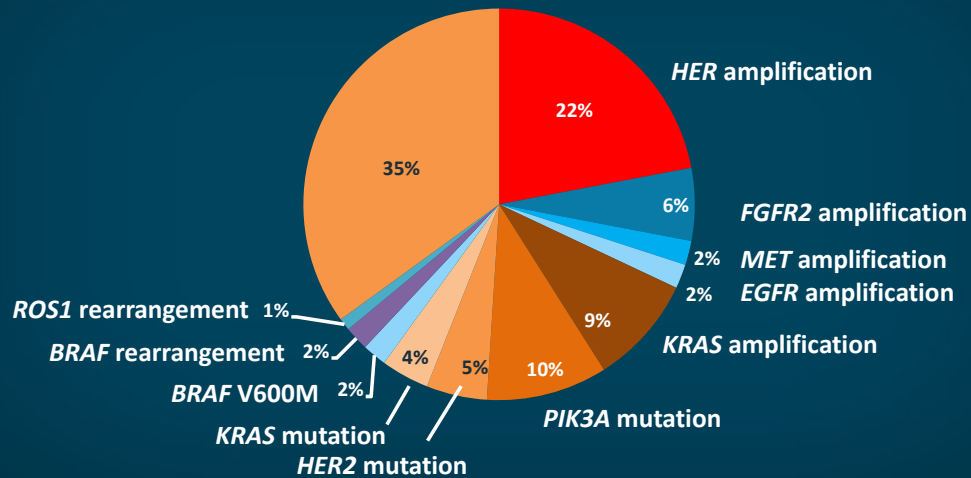
Role of HER2 in Gastric Cancer

- EGFR receptors are associated with tumor cell proliferation, apoptosis, adhesion, migration, and differentiation¹
- HER2* amplified or overexpressed in an average of $\approx 20\%$ of G/GEJ adenocarcinomas¹
- Prognostic significance of HER2 positivity remains controversial²

EGFR = epidermal growth factor receptor.

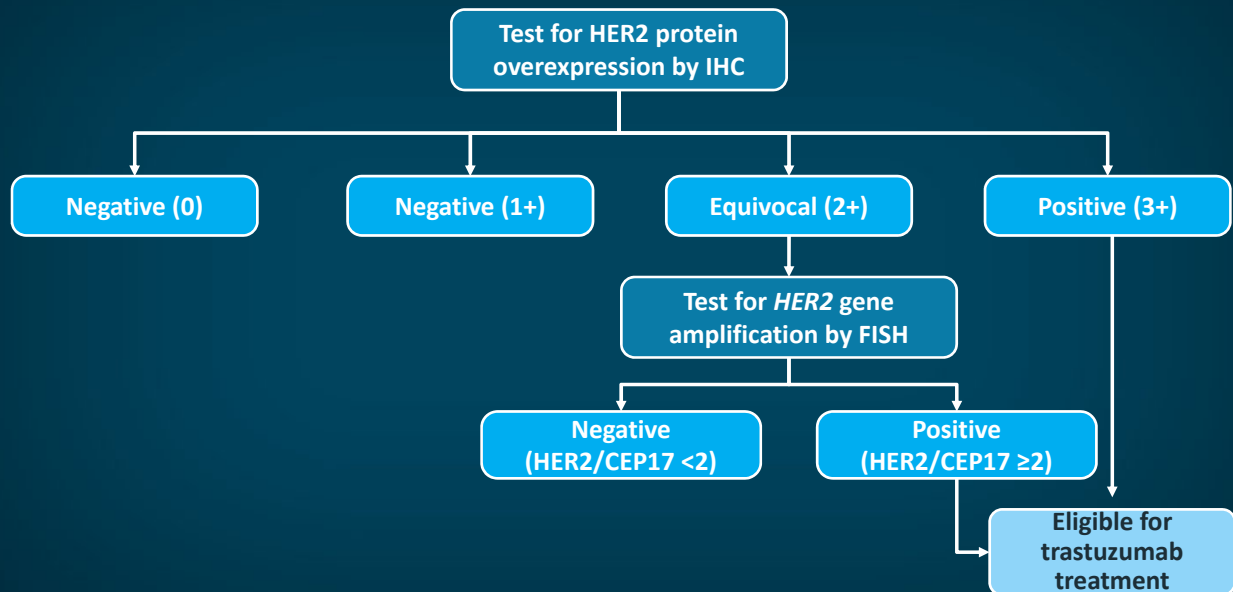
1. Bang YJ, et al. *Lancet*. 2010;376:687-697. 2. Namikawa T, et al. *Mol Clin Oncol*. 2013;1:249-252.

Prevalence of *HER2* Amplification in Gastric Cancer



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

HER2 Testing in Gastric Cancer Algorithm



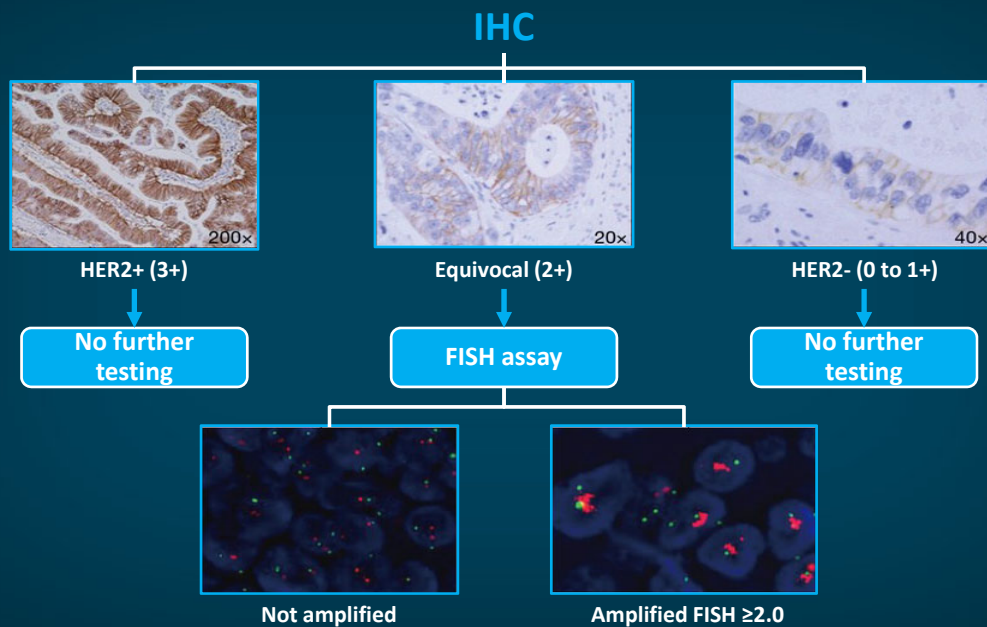
CEP17 = chromosome 17; FISH = fluorescent in situ hybridization; IHC = immunohistochemistry.
 Abrahao-Machado LF, Scapulatempo-Neto C. *World J Gastroenterol.* 2016;22:4619-4625.

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

Rüschhoff 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

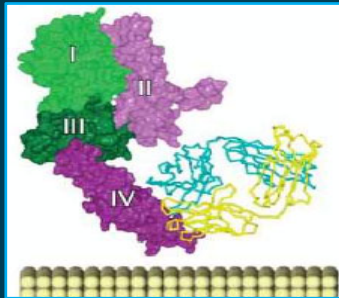
- GC: HER2 positivity varies by histology¹
 - Diffuse or intestinal histologic subtypes
 - Diffuse cancers: 6%-7% HER2+; ≥16% for intestinal cancers
- CRC: HER2 positivity in 2%-7% of patients²
 - More common in left-sided primaries
 - *HER2* amplification predicts resistance to EGFR-targeted therapy
 - 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

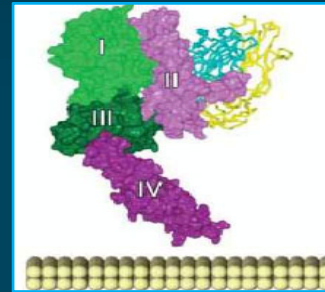
Binding Sites for HER2-Targeted Therapies

Trastuzumab¹



- Activates antibody-dependent cellular cytotoxicity¹
- Enhances HER2 internalization²
- Inhibits shedding and, therefore, formation of p95³
- Inhibits angiogenesis⁴

Pertuzumab¹



- Activates antibody-dependent cellular cytotoxicity⁵
- Prevents HER2/HER3 receptor dimerization¹
- Potent inhibitor of HER-mediated signaling pathways⁵

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

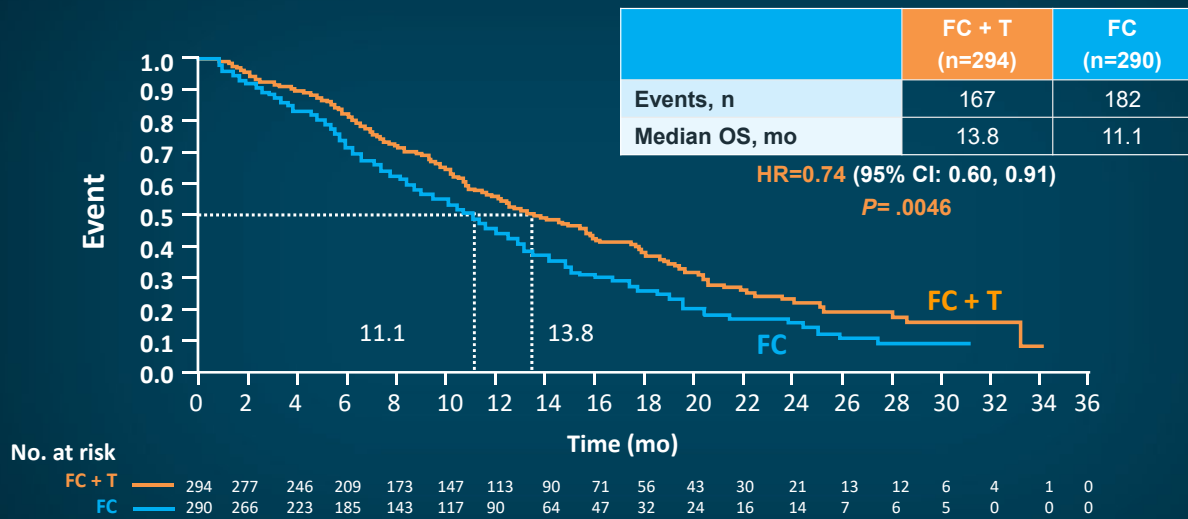
Clinical Trial	Regimen	Stratification
ToGA¹ HER2+ (n=594)	5-FU or capecitabine + cisplatin + trastuzumab	• Advanced vs metastatic • GC vs GEJ cancer • Measurable vs nonmeasurable • ECOG PS 0-1 vs 2 • Capecitabine vs 5-FU
	5-FU or capecitabine + cisplatin	
TRIO-013/LOGIC² HER2+ (FISH+ or IHC 3+) (n=545)	Capecitabine + oxaliplatin + lapatinib*	• Geographic region of the world • Prior neoadjuvant and/or adjuvant chemotherapy
	Capecitabine + oxaliplatin	
JACOB³ HER2+ (ISH+ and IHC 2+ or 3+) (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+)
	Capecitabine or 5-FU + cisplatin + trastuzumab	

*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.

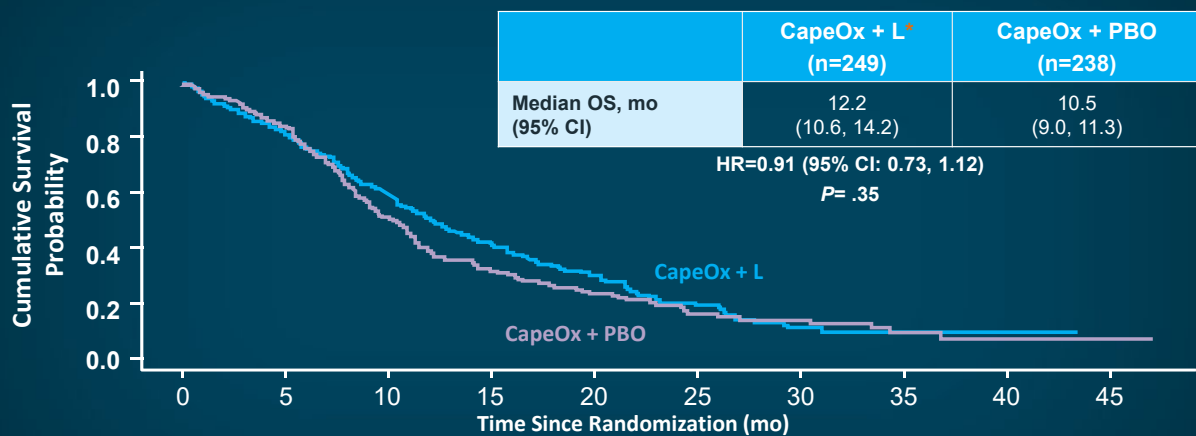
ToGA Primary Endpoint: Overall Survival



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

TRIO-013/LOGiC Trial

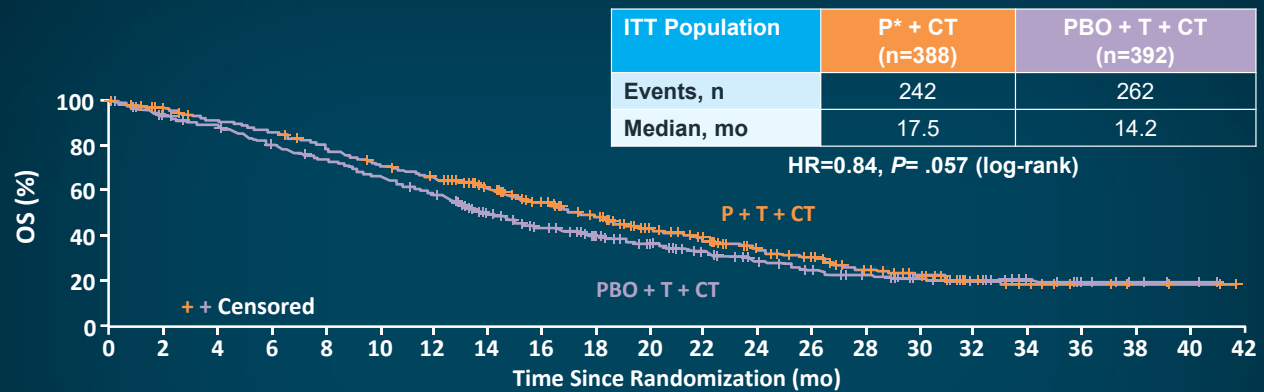
Primary Endpoint: OS in Primary Efficacy Population



CapeOx + L = 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



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.

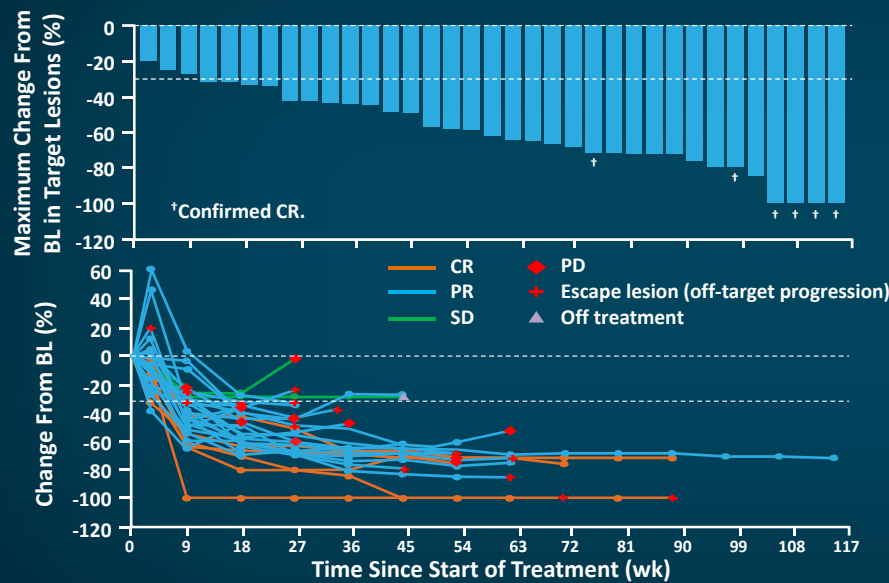
First-Line HER2-Directed Clinical Trials: OS

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 + oxaliplatin + lapatinib*	12.2	0.91 (0.73, 1.12)	.3492
	Capecitabine + oxaliplatin	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 YI, 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)

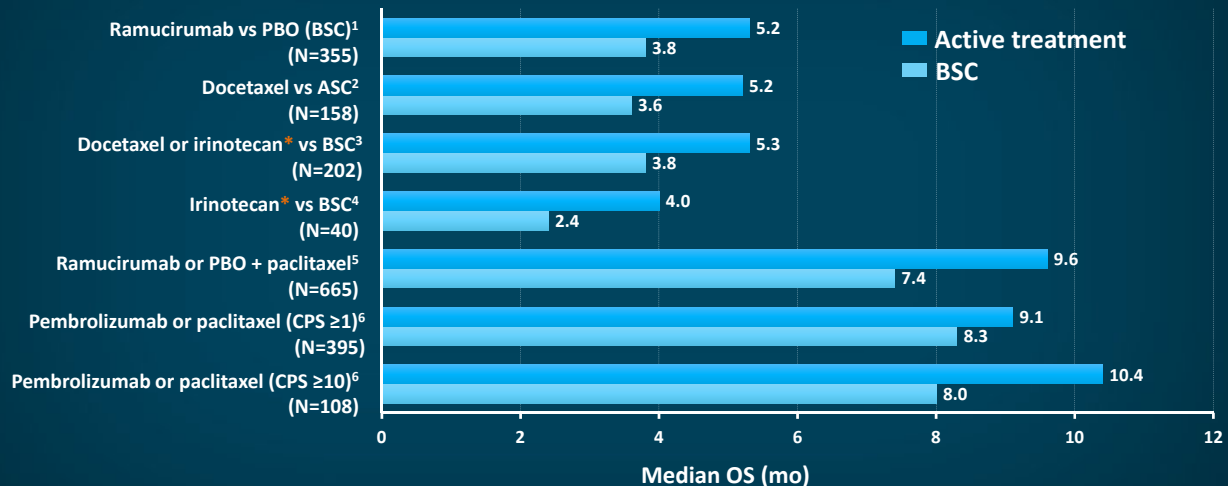
Best Response, n (%)	Pembrolizumab (n=133)	Placebo (n=131)
CR	15 (11)	4 (3)
PR	84 (63)	64 (49)
SD	29 (22)	49 (37)
PD	5 (4)	7 (5)
Not evaluable	0	2 (2)
Not assessed	0	5 (4)

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/m², 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.

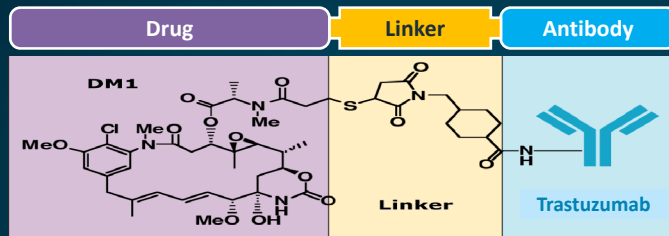
Makiyama A, et al. *J Clin Oncol*. 2020;38:1919-1927.

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

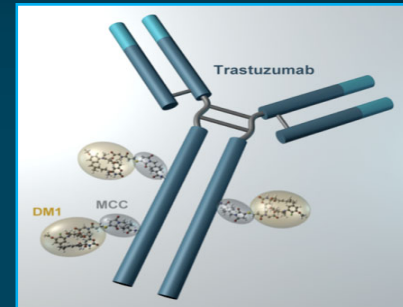
- Continuing trastuzumab past first-line progression has not shown significant improvement in outcomes
- Treatment options inline with HER2- disease options
- Treatment choices based on patient/provider decision
 - Toxicity profile of regimen
 - Patient PS
 - Patient goals
 - Patient comorbidities
-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

Leveraging Antibody-Drug Conjugates in HER2-Positive Gastrointestinal Malignancies

Trastuzumab Emtansine (T-DM1) Structure



T-DM1 is a novel ADC



Target expression: HER2

mAb: trastuzumab

Cytotoxic agent: DM1

Highly potent cytotoxic agent

Linker: MCC

Systemically stable

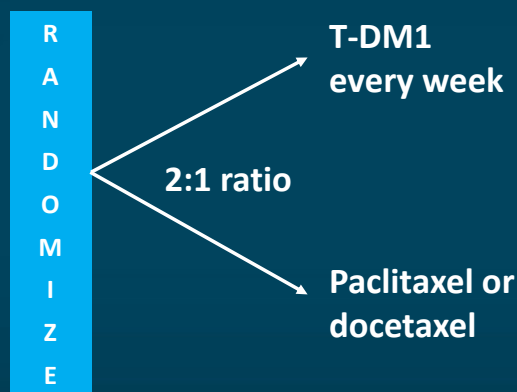
T-DM1

Average drug has an antibody ratio $\cong 3.5:1$

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

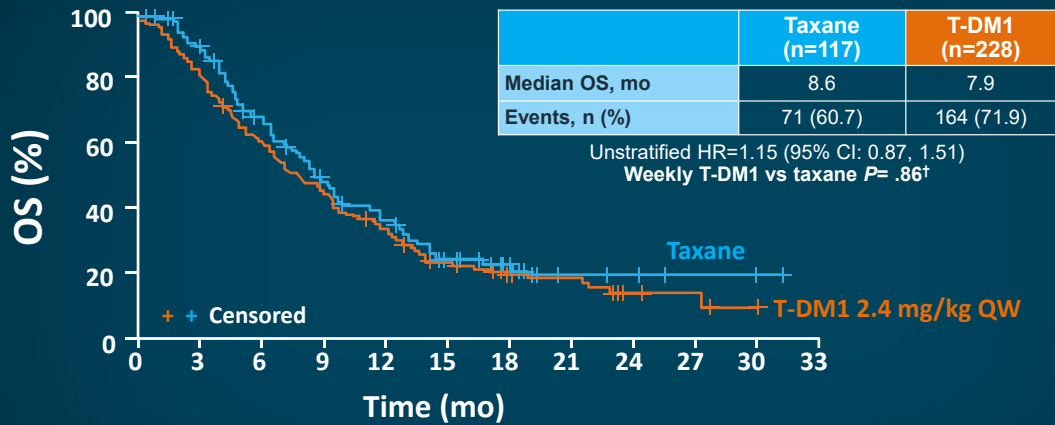
345 patients with HER2+ disease following first-line therapy



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



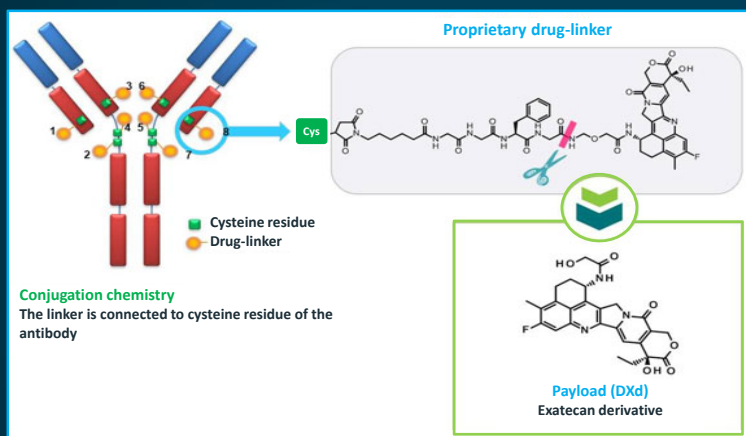
T-DM1	228	181	134	92	57	30	21	12	4	3	1	0
Taxane	117	96	68	43	26	16	8	6	5	3	2	0

† 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

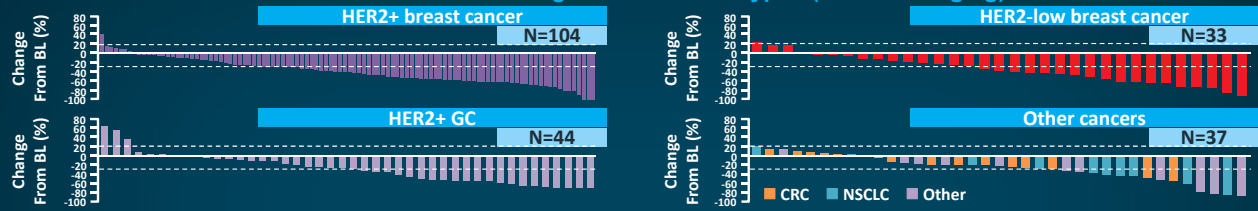
Tumor-selective cleavable linker

High drug-to-antibody ratio

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

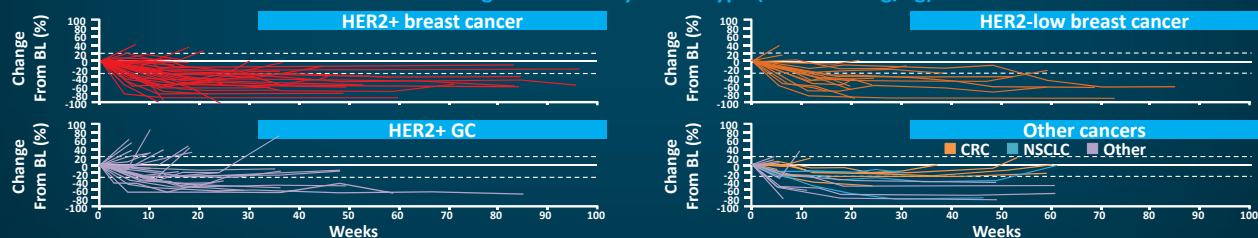
Antitumor Activity of Trastuzumab Deruxtecan

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)



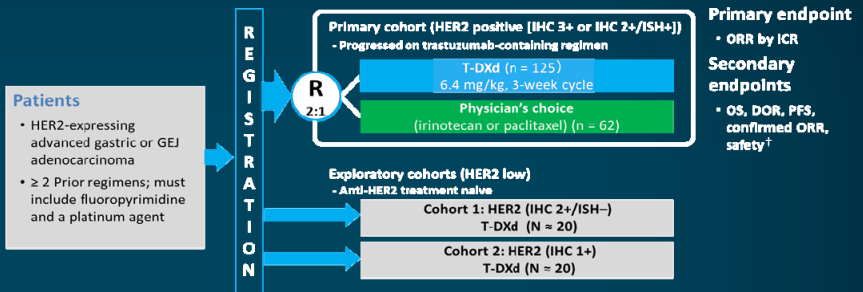
- Overall, 86.3% of subjects experienced tumor shrinkage
- 91.5% of these subjects experienced shrinkage at time of first imaging assessment at 6 weeks

NSCLC = non-small cell lung cancer. Iwata H. ASCO 2020. Abstract 2501. US Oncology Research is supported by McKesson Specialty Health.
© 2018 McKesson Specialty Health. All rights reserved.

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

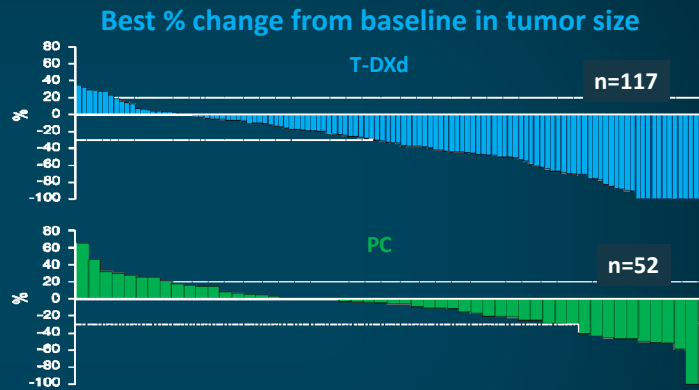
ICR = independent central review.

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.



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

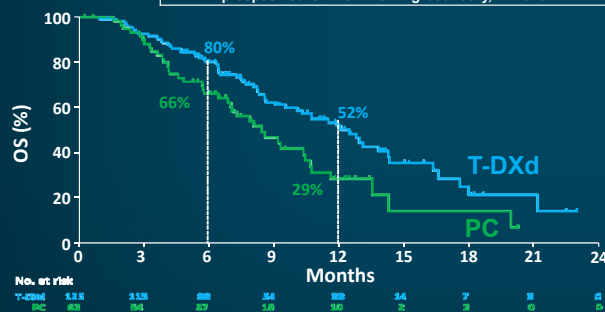
Shitara K, et al. *N Engl J Med.* 2020;381:2419-2430.

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)

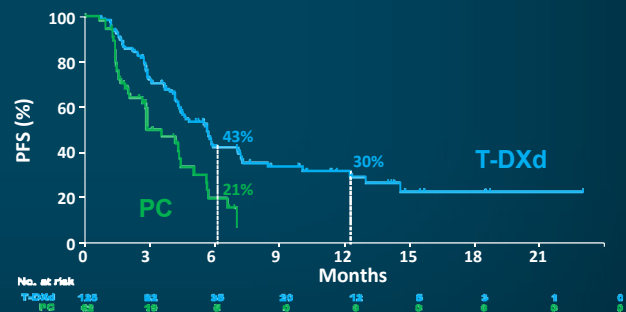
HR=0.59 (95% CI: 0.39, 0.88); $P = .01$
prespecified O'Brien-Fleming boundary, $P = .0202$



Progression-Free Survival

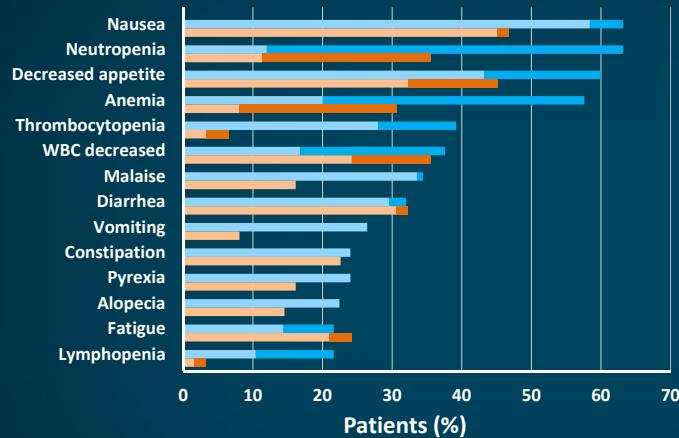
	Events/n	Median PFS
T-DXd	73/125	5.6 months (95% CI: 4.3, 6.9)
PC	36/62	3.5 months (95% CI: 2.0, 4.3)

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

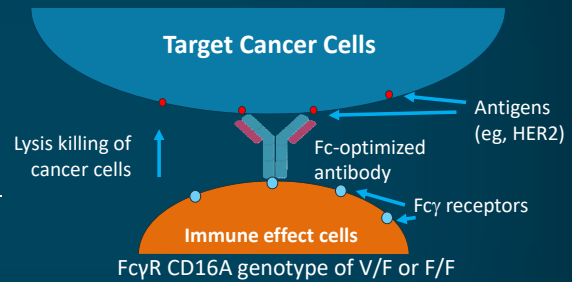
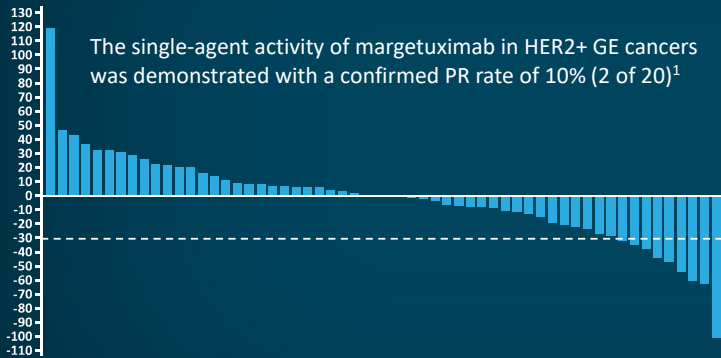
- Centrally confirmed HER2-low via IHC 2+/ISH- (n=20) or IHC 1+ (n=24)
- Progressed on ≥2 prior lines of therapy; excluded if prior HER2 therapy
- Safety profile similar to HER2+ primary cohort

	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 trastuzumab¹



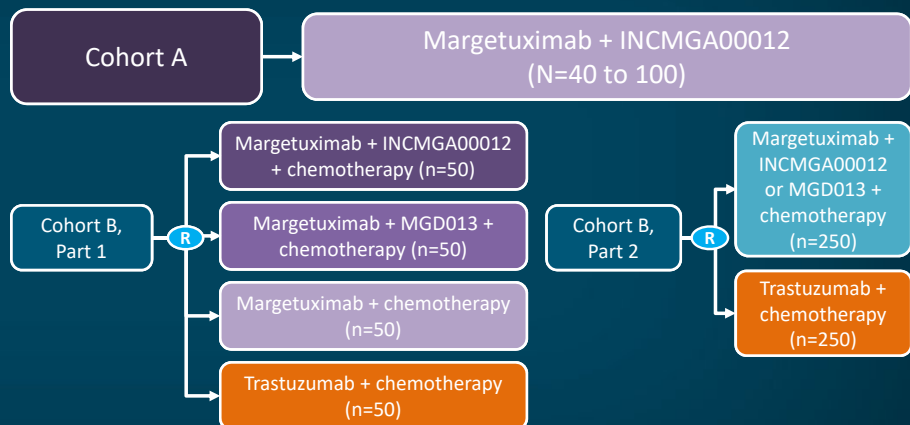
Phase 2/3 MAHOGANY: Combination margetuximab*, INCMGA00012*, MGD013*, and chemotherapy in HER2+ G/GEJ cancer²

* 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 LAG3 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

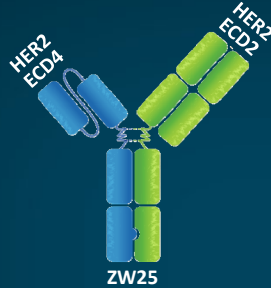
- Previously untreated advanced disease
 - Cohort A: HER2+ (by IHC 3+) and PD-L1+ (CPS ≥1%)
 - Cohort B: HER2+ (by IHC 3+ or IHC 2+/FISH+)
- ECOG PS 0 or 1



- 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

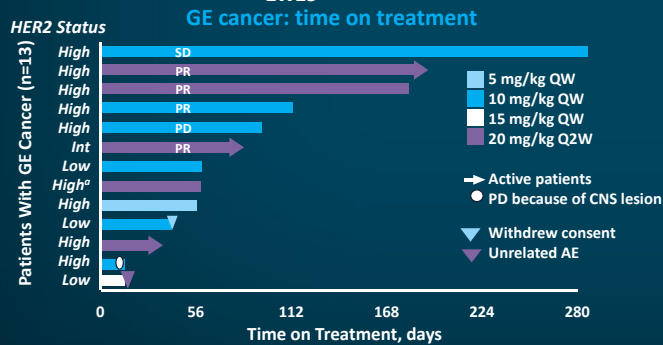


Biparatopic binding targets 2 distinct HER2 epitopes

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

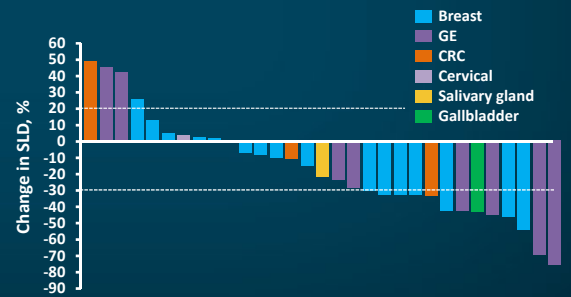
Unique mechanisms of action designed to expand activity

- 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



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 trial¹: trastuzumab + lapatinib
- MyPathway trial²: pertuzumab + trastuzumab
- TRIUMPH trial³: pertuzumab + trastuzumab
- HERACLES-B trial⁴: T-DM1
- DESTINY trial⁵: T-DXd (also anti-HER2 pretreated)

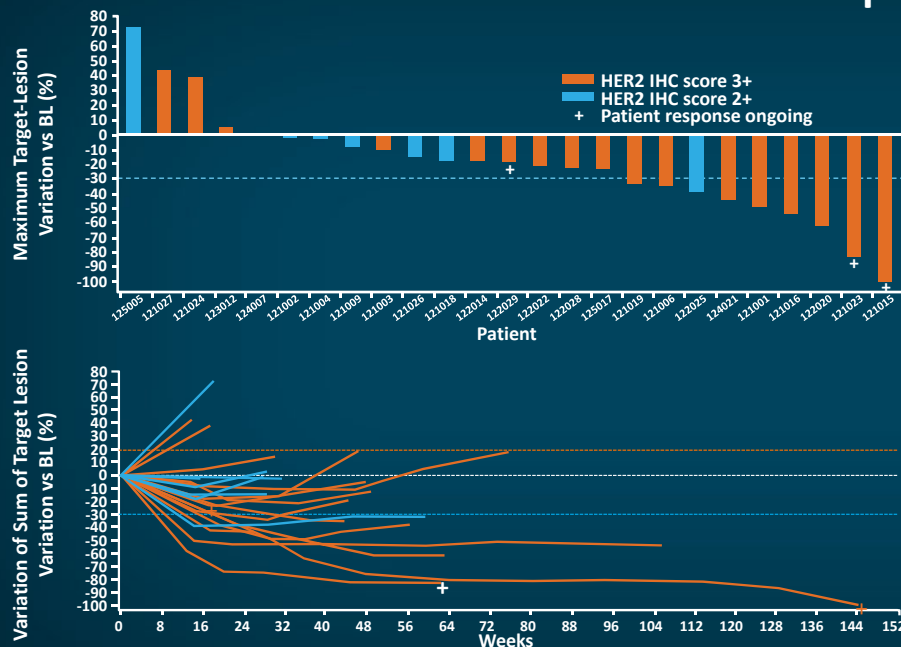
→ Only 2%-5% have *HER2* amplification²

→ 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

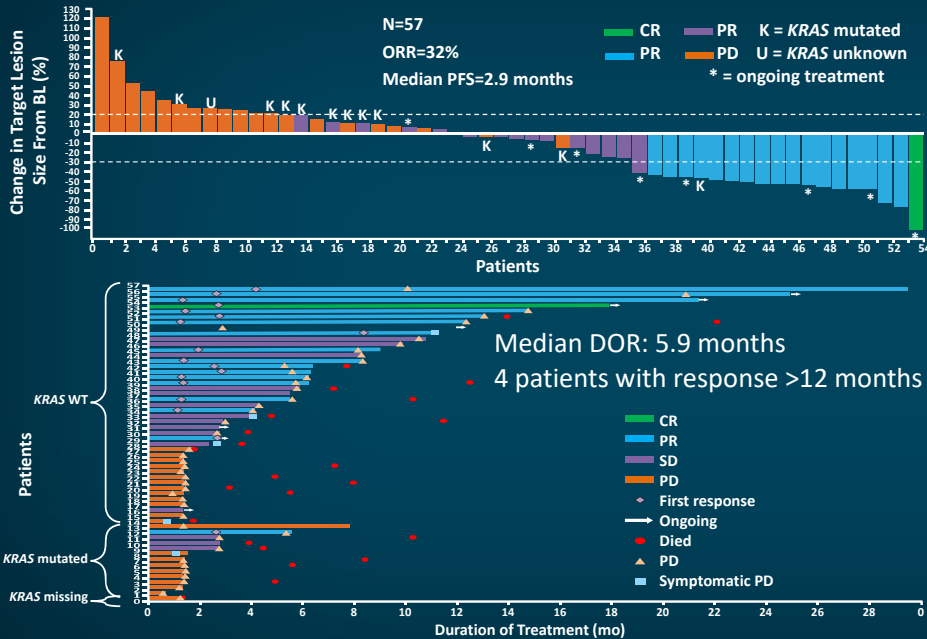


Sartore-Bianchi A, et al. *Lancet Oncol.* 2016;17:738-746.

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

MyPathway: Trastuzumab + Pertuzumab



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

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

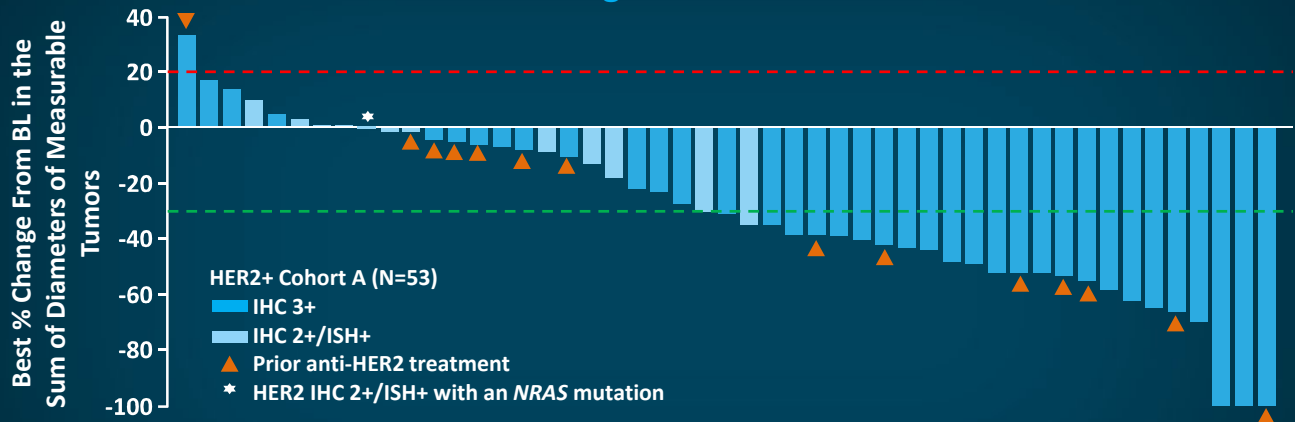
SWOG S1613 (NCT03365882)

- 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 primaries¹

Javle et al Lancet Oncology 22: 1290; 2021

Thank you!



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

TOOLKIT

Resources	Web Address
Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: An update. <i>World J Gastroenterol</i> . 2016;22(19):4619-4625.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4870069/
Arnold M, Abnet CC, Neale RE, et al. Global burden of 5 major types of gastrointestinal cancer. <i>Gastroenterology</i> . 2020;159(1):335-349.e15.	https://pubmed.ncbi.nlm.nih.gov/32247694/
Bang YJ, Giaccone G, Im SA, et al. First-in-human phase 1 study of margetuximab (MGAH22), an Fc-modified chimeric monoclonal antibody, in patients with HER2-positive advanced solid tumors. <i>Ann Oncol</i> . 2017;28(4):855-861.	https://pubmed.ncbi.nlm.nih.gov/28119295/
Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial. <i>Lancet</i> . 2010;376(9742):687-697.	https://pubmed.ncbi.nlm.nih.gov/20728210/
Chung HC, Bang YJ, S Fuchs C, et al. First-line pembrolizumab/placebo plus trastuzumab and chemotherapy in HER2-positive advanced gastric cancer: KEYNOTE-811. <i>Future Oncol</i> . 2021;17(5):491-501.	https://pubmed.ncbi.nlm.nih.gov/33167735/
Clinicaltrials.gov. DS-8201a in Human Epidermal Growth Factor Receptor 2 (HER2)-Expressing Gastric Cancer [DESTINY-Gastric01]. Last updated February 23, 2021.	https://clinicaltrials.gov/ct2/show/NCT03329690
Clinicaltrials.gov. Pembrolizumab/Placebo Plus Trastuzumab Plus Chemotherapy in Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE-811). Last updated August 6, 2021.	https://clinicaltrials.gov/ct2/show/NCT03615326
Clinicaltrials.gov. Combination Margetuximab, INCMGA00012, MGD013, and Chemotherapy	https://clinicaltrials.gov/ct2/show/NCT04082364

Phase 2/3 Trial in HER2+ Gastric/GEJ Cancer (MAHOGANY). Last updated May 3, 2021.	
De Cuyper A, Van Den Eynde M, Machiels JP. HER2 as a predictive biomarker and treatment target in colorectal cancer. <i>Clin Colorectal Cancer</i> . 2020;19(2):65-72.	https://pubmed.ncbi.nlm.nih.gov/32229076/
El Dika I, Ilson DH. Current and future therapies for targeting HER2 mutations in gastrointestinal cancer. <i>Expert Rev Anticancer Ther</i> . 2018;18(11):1085-1092.	https://pubmed.ncbi.nlm.nih.gov/30092682/
Ford H, Marshall A, Wadsley J, et al. COUGAR-02: A randomized phase III study of docetaxel versus active symptom control in advanced esophagogastric adenocarcinoma. <i>J Clin Oncol</i> . 2013;31(4 suppl):LBA4.	https://ascopubs.org/action/showCitFormats?doi=10.1200/jco.2013.31.4_suppl.lba4
Fuchs CS, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated patients with PD-L1–positive advanced gastric or gastroesophageal junction cancer (GC): Update from the phase III KEYNOTE-061 trial. <i>J Clin Oncol</i> . 2020;38:(15 suppl):4503.	https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.15_suppl.4503
Fuchs CS, Tomasek J, Yong CJ, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. <i>Lancet</i> . 2014;383(9911):31-39.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61719-5/fulltext
Gravalos C, Jimeno A. HER2 in gastric cancer: A new prognostic factor and a novel therapeutic target. <i>Ann Oncol</i> . 2008;19(9):1523-1529.	https://pubmed.ncbi.nlm.nih.gov/18441328/
Hecht JR, Bang YJ, Qin SK, et al. Lapatinib in combination with capecitabine plus oxaliplatin in human epidermal growth factor receptor 2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: TRIO-013/LOGiC—A randomized phase III trial. <i>J Clin Oncol</i> . 2016;34(5):443-451.	https://ascopubs.org/doi/10.1200/JCO.2015.62.6598
Iwata H, Tamura K, Doi T, et al. Trastuzumab deruxtecan (DS-8201a) in subjects with HER2-expressing solid tumors: Long-term results of a large phase 1 study with multiple expansion cohorts. <i>J Clin Oncol</i> . 2018;36(15 suppl):2501.	https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.2501
Janjigian YY, Kawazoe A, Yanez PE, et al. Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or	https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.4013

gastroesophageal junction (G/GEJ) cancer: Initial findings of the global phase 3 KEYNOTE-811 study.. <i>J Clin Oncol</i> . 2021;39(15 suppl):4013.	
Janjigian YY, Maron SB, Chatila WK, et al. First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: An open-label, single-arm, phase 2 trial. <i>Lancet Oncol</i> . 2020;21(6):821-831.	https://pubmed.ncbi.nlm.nih.gov/32437664/
Kang JH, Lee SI, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: A randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. <i>J Clin Oncol</i> . 2012;30(13):1513-1518.	https://ascopubs.org/doi/pdf/10.1200/JCO.2011.39.4585
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