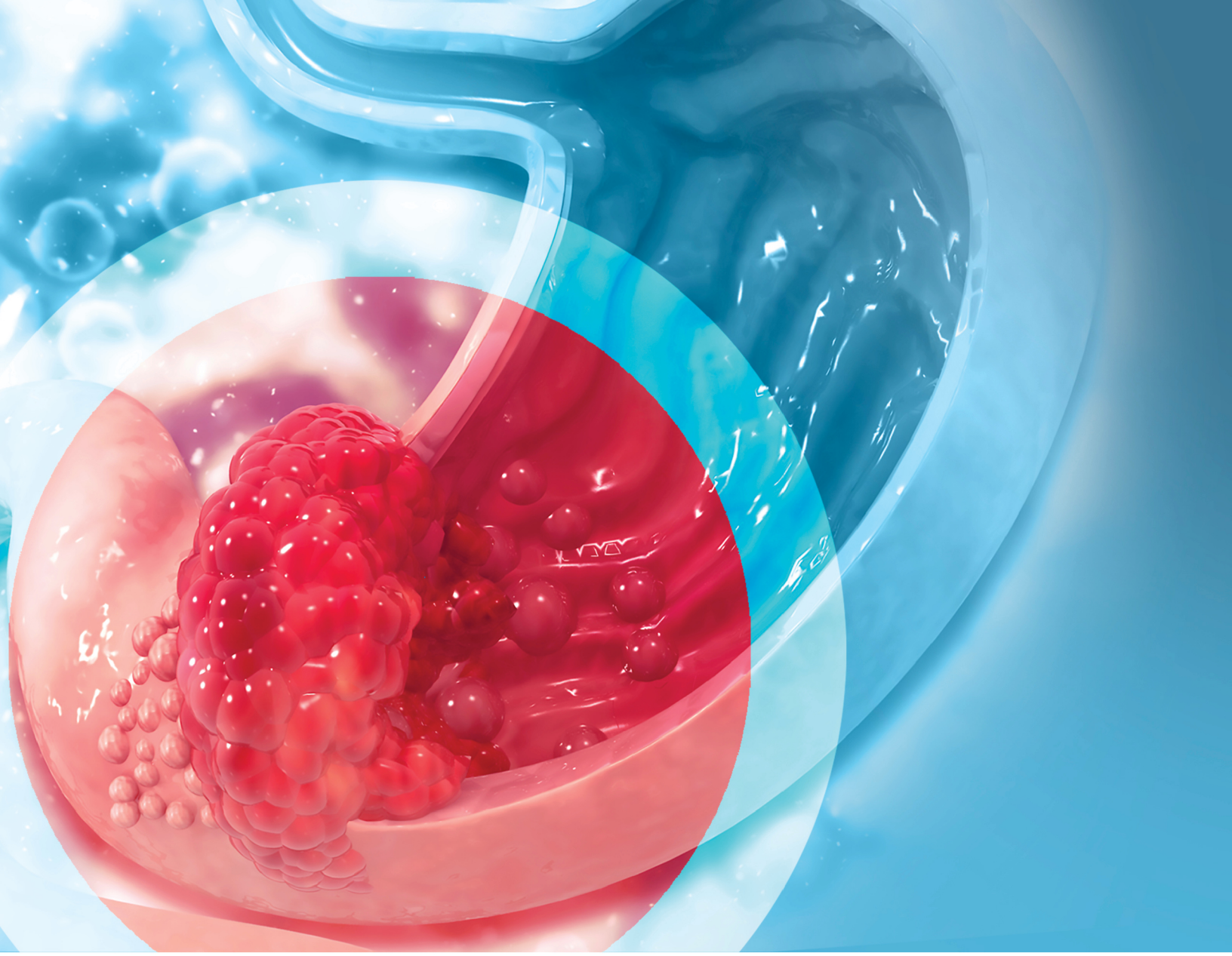

GOING BEYOND the TREATMENT GUIDELINES:

Optimizing Therapy in Patients Progressing Through Trastuzumab With Advanced, HER2-Positive Gastric Cancer - A WHITEBOARD ANIMATION VIEW

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.

Going Beyond the Treatment Guidelines: Optimizing Therapy in Patients Progressing Through Trastuzumab With Advanced, HER2-Positive Gastric Cancer- A Whiteboard Animation View

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PROGRAM OVERVIEW

This program will review current and emerging therapies for the management of HER2-positive gastric cancer.

TARGET AUDIENCE

This activity is designed to educate community oncologists, oncology nurses and other healthcare providers involved in the care of patients with advanced/metastatic gastric cancer and gastroesophageal junction adenocarcinoma.

LEARNING OBJECTIVES

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

- Review HER2-status in advanced gastric cancers and associated biomarker interpretation and clinical application
- Discuss current clinical practice guideline recommendations for HER2-directed therapy for those patients with HER2-positive advanced gastric cancer
- Describe clinical trial data for emerging options in heavily treated patients with HER2-positive advanced gastric cancer

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Purpose: This program would be beneficial for nurses involved in the care of patients with advanced/metastatic gastric cancer and gastroesophageal junction adenocarcinoma.
Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Therapeutics, Scholar Rock, NGM Biopharma, Stemcentrx, BeiGene, CALGB, Cyteir Therapeutics, Foundation Bio, Innate Pharma, Morphotex, Ongologie, and NuMab. **She reports consulting/advisory role to her institution**: Gilead, Genentech/Roche, BMS, Five Prime, Lilly, Merck, Med Immune, Celgene, Taiho, Macrogenics, GSK, Novartis, OncoMed, LEAP, TG Therapeutics, AstraZeneca, Bl, Daiichi Sankyo, Bayer, lncyte, Apexigen, Array, Sanofi, ARMO, Ipsen, Merrimack, Oncogenex, FORMA, Arch Oncology, Prelude Therapeutics, Phoenix Bio, Cyteir, Molecular Partners, Innate, Torque, Tizona, Janssen, Tolero, TD2 (Translational Drug Development), Amgen, Seattle Genetics, Moderna Therapeutics, Tanabe Research Laboratories, BeiGene, Continuum Clinical, Agios, Bicycle Therapeutics, Relay Therapeutics, Evelo, Pfizer, Piper Biotech, and Samsung Bioepios. **She reports the following food/beverage/travel paid to her institution**: Gilead, Genentech/Roche, BMS, Lilly, Merck, Med Immune, Celgene, Taiho, Novartis, OncoMed, Bl, ARMO, Ipsen, Oncogenex, and FORMA.

Dr. Ajani *has received research funding from Daiichi-Sankyo and consulting fees from AstraZeneca.*

Dr. Almhanna *has nothing to disclose.*

Dr. Bekaii-Saab *reports the following disclosures Research Funding (to institution): Boston Biomedical, Bayer, Amgen, Merck, Celgene, Lilly, Ipsen, Clovis, Seattle Genetics, Array Biopharma, Genentech, Abgenomics, Incyte, BMS. Consulting (to institution): Ipsen, Array Biopharma, Seattle Genetics, Bayer, Genentech, Incyte and Merck. Consulting (to self): Boehringer Ingelheim, TreosBio and Sobi. IDMC/DSMB (to self): Astra Zeneca, Exelixis, Lilly, PanCan and 1Globe. Scientific Advisory Board: Imugene, Immuneering and Sun Biopharma. Inventions/Patents: WO/2018/183488 and WO/2019/055687*

Dr. Cartwright serves on the speakers' bureau for Amgen and Taiho.

Dr. Dunne *has served as a consultant for Exelixes Inc.*

Dr. Gibson serves on the speakers' bureau for Bristol Myers Squibb, and as a Consultant for Merck & Co.

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

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Program Agenda

I. **Advanced Gastric Cancers – A Disease Primer**
   a. Profile of the patient with advanced disease
      i. Age does not affect either PFS or OS
   b. Characterization of disease
      i. HER2 expression versus amplification – test result use and interpretation of levels of expression
   c. Need for treatment in heavily treated patients
      i. Extending overall survival
   d. The multi-disciplinary team and required expertise to address complexity
      i. Surg onc, med onc, rad onc, gastroent, radiology, and pathology

II. **NCCN Guideline Evidence-Based Recommendations to Optimize Treatment for Advanced Gastric Cancer – After Progressing Through Trastuzumab**
   a. Targeting HER2 overexpression
      i. Prevalence of HER2 overexpression in gastric cancer
      ii. Evaluation and utility of HER2 testing
   b. Clinical trial data on trastuzumab – efficacy, safety
   c. Evaluation of the patient after progression through trastuzumab
   d. Lack of standard of care - second line options for HER2 disease

III. **Emerging Options in Heavily Treated, HER2-Positive Patients**
   a. Second-line regimens
      i. Treatment considerations
         1. Patient goals
         2. Response to prior therapy
         3. Performance status
         4. Comorbidities
      ii. Targeted agents and chemotherapy options
         1. Antibody-drug conjugate agents
      iii. Criteria for mono or combination therapy
      iv. Management of adverse events

IV. **Case Study**

V. **Conclusions**

VI. **Questions and Answers**

Going Beyond the Treatment Guidelines: Optimizing Therapy in Patients Progressing Through Trastuzumab With Advanced, HER2-Positive Gastric Cancer— A Whiteboard Animation View

Program Chair:
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Disclosures

- Please see Program Overview for specific speaker disclosure information.
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Learning Objectives

- Review HER2-status in advanced gastric cancers and associated biomarker interpretation and clinical application
- Discuss current clinical practice guideline recommendations for HER2-directed therapy for those patients with HER2-positive advanced gastric cancer
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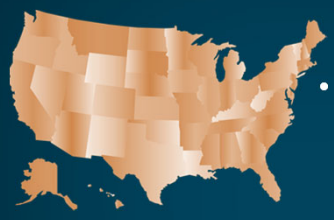
Advanced Gastric Cancer: An Overview

Gastric Cancer (GC)



United States[1]

- Estimates for 2020 are that 27,600 people will be diagnosed with GC and 11,010 will eventually die from the disease

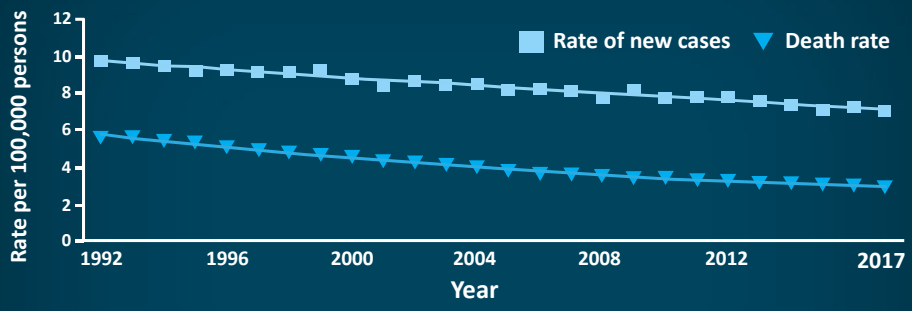
Worldwide (2017 data)[2]

- Gastric cancer is the **7th most common malignancy,** with *1.22 million incident cases worldwide*
- **GC is the 3rd most common cause of cancer mortality** (nearly 865,000 deaths)

1. American Cancer Society (ACS). Cancer Facts & Figures, 2020 (www.cancer.org/cancer/stomach-cancer/about/key-statistics.html). Accessed 7/12/2020. 2. GBD (Global Burden of Disease) 2017 Stomach Cancer Collaborators. *Lancet Gastroenterol Hepatol.* 2020;5:42-52.

Trends in Stomach Cancer Statistics

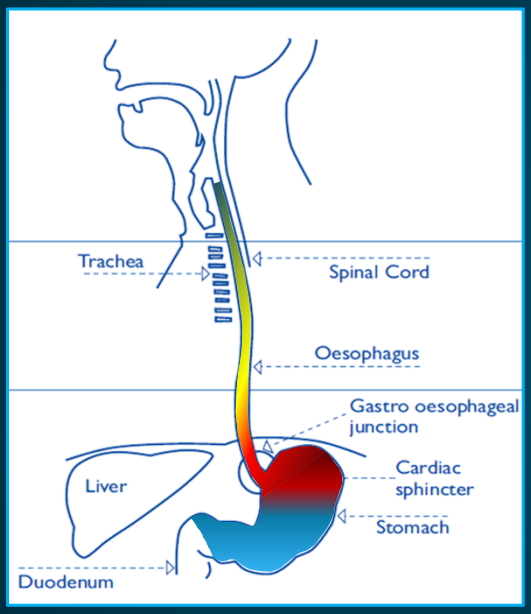
Incidence and mortality rates (1992–2012)



- 5-year relative rate survival varies by staging:
  - **localized = 69.5%, regional = 32.0%, distant = 5.5%,** and unknown = 23.4%
- Median age at diagnosis is 68 years
- New case incidence per 100,000 persons (of all races) is greater in males (9.9) compared with females (5.3).

National Cancer Institute (NCI). Stomach cancer stat facts. 2020 (https://seer.cancer.gov/statfacts/html/stomach.html). Accessed 7/10/2020.

Risk Factors for Gastroesophageal Cancer



Risk factors at different levels of the GI tract

- Diet, alcohol, hot drinks, tobacco smoking
- Acid reflux, obesity, smoking, diet
- *H. pylori*, atrophic gastritis

GI = gastrointestinal.

Slide courtesy of Manish A. Shah, MD

Barrett's Esophagus

- Principal risk factor: GERD[1,2]
- Cancer will develop in only <1% to 3% of patients[2,3]
- Assessed endoscopically, histologically[3]
  - Segment length
  - Dysplasia grade
    - ***Low grade:*** medical antireflux therapy, followed by endoscopic surveillance every 6–12 mo
    - ***High grade:*** medical antireflux therapy, followed by repeat endoscopic assessment and specialist review
      - Potential role for EMR, ablative therapy, surgery

GERD = gastroesophageal reflux disease; EMR = endoscopic mucosal resection; mo = month(s).

1. Jemal A, et al. *CA Cancer J Clin*. 2011;61:69-90. 2. Schnell TG, et al. *Gastroenterology*. 2001;120:1607-1619. 3. Spechler SJ, et al; American Gastroenterological Association (AGA). *Gastroenterology*. 2011;140:1084-1091.

Gastric Cancer: Risk Factors

- *H pylori* infection (*cagA* strain only)[1]
  - OR = 2.54, 95% CI 1.77–3.66[1]
    - ? Role of host (genetic polymorphisms)[2]
      - IL-1, IL-10, IL-4[3-5]
    - Bone marrow-derived stem cells[6]
- Tobacco use[1]
  - OR = 1.91, 95% CI 1.25–2.93[1]
- Family history of GC[1]
  - OR = 3.67, 95% CI 2.01–6.71[1]

OR = odds ratio; CI = confidence interval; IL = interleukin.

1. García-González MA, et al. *Am J Gastroenterol*. 2007;102:1878-1892. 2. Figueiredo C, et al. *J Natl Cancer Inst*. 2002;94:1680-1687. 3. El-Omar EM, et al. *Nature*. 2000;404:398-402. 4. He B, et al. *Am J Transl Res*. 2019;11:3698-3706. 5. Zali H, et al. *Gastroenterol Hepatol Bed Bench*. 2011; 4:175-185. 6. Houghton J, et al. *Science*. 2004;306:1568-1571.

Genetic Predisposition Syndromes
(10–15% of All Gastric Cancers)

- Hereditary diffuse gastric cancer (~3–5%)
- Lynch syndrome (~1–2%)
  - Germline mutations in MLH1, MSH2, MSH6, PMS1, or PMS2
  - Stomach cancers occur in ~11% of Lynch syndrome families
- Familial adenomatous polyposis (~1%)
  - Germline mutation in APC
  - Fundic gland polyps
- Li Fraumeni's syndrome (<1%)
  - p53 mutation
- Peutz-Jeghers syndrome (<1%)
  - Autosomal dominant, hamartomatous polyps of GI tract and mucocutaneous melanin deposits
  - Germline mutations in STK11

APC = adenomatous polyposis coli; STK11 = serine threonine kinase 11.

Lynch HT, et al. *J Surg Oncol*. 2005;90:114-133. Lott PC, Carvajal-Carmona LG. *Lancet Gatroenterol Hepatol*. 2018;3:874-883.

Criteria for Testing for E-cadherin Gene Mutation

2010 IGCLC Recommendations*

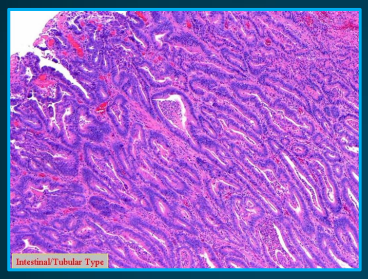
- ≥2 documented gastric cancer cases in first-degree relatives; at least 1 documented case diagnosed before 50 years of age
- ≥3 documented cases of diffuse gastric cancer in first- or second-degree relatives, independent of age at onset
- Diffuse gastric cancer before 40 years of age without family history
- Families with diagnoses of both diffuse gastric cancer and lobular breast cancer; 1 case before 50 years of age

*Consider genetic testing in cases where expert pathologists detect carcinoma *in situ* adjacent to diffuse-type gastric cancer.

IGCLC = International Gastric Cancer Linkage Consortium.

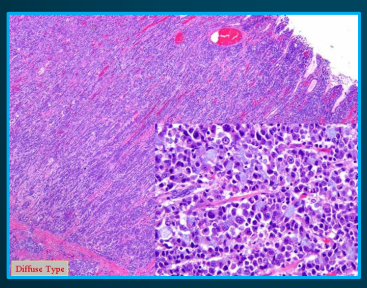
Fitzgerald RC, et al; International Gastric Cancer Linkage Consortium (IGCLC). *J Med Genet*. 2010;47:436-444.

Intestinal vs Diffuse Gastric Cancer



Intestinal gastric cancer

- Glandular appearance
- Spreads through wall as part of tumor mass
- "Epidemic-type" because more common to high-risk areas (ie, China, Japan)
- Possibly responsible for racial/ethnic disparity of disease
- Gastritis → metaplasia → dysplasia → malignancy



Diffuse gastric cancer

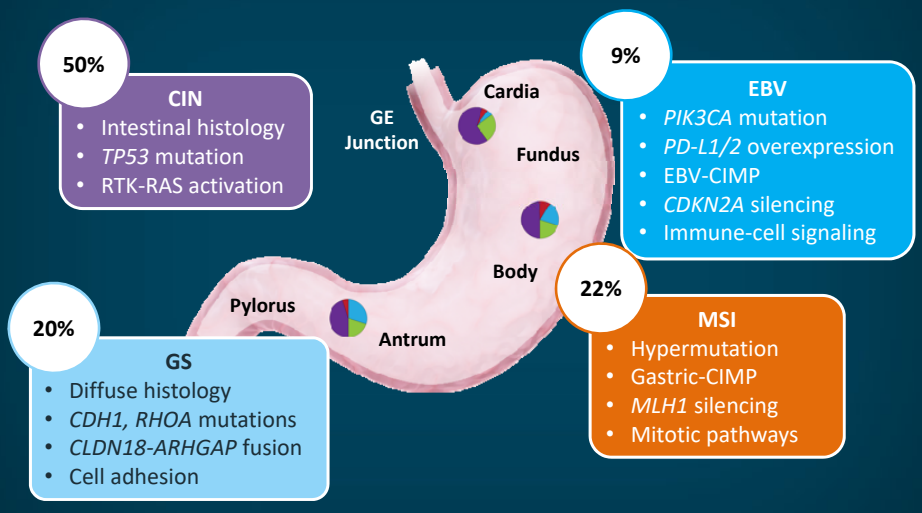
- Spreads as discohesive individual cells throughout stomach wall
- No regional variance
- Less common than intestinal type, though incidence rising (0.3 (cardia) – 1.7 (non-cardia)/100K)

Shah MA, Kelsen DP. *J Natl Compr Canc Netw*. 2010;8:437-447. Jácome AA, et al. *World J Gastroenterol*. 2016;22:1160-1171. Atlas of Pathology. 3rd Edition. 2004-2016 (http://www.pathologyatlas.ro/gastric-carcinoma-intestinal-type-gastrointestinal-pathology.php). Accessed July 24, 2020. Wu H, et al. *Cancer Epidemiol Biomarkers Prev*. 2009;18:1945-1952.

Whiteboard Presentation

Please scan the QR code below to view a brief depiction exploring gastric cancer pathophysiology

Comprehensive Molecular Characterization of Gastric Cancer: TCGA



TCGA = The Cancer Genome Atlas; CIN = chromosomal instability; EBV = Epstein–Barr virus; GE = gastroesophageal; GS = genomically stable; MSI = microsatellite instability.

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

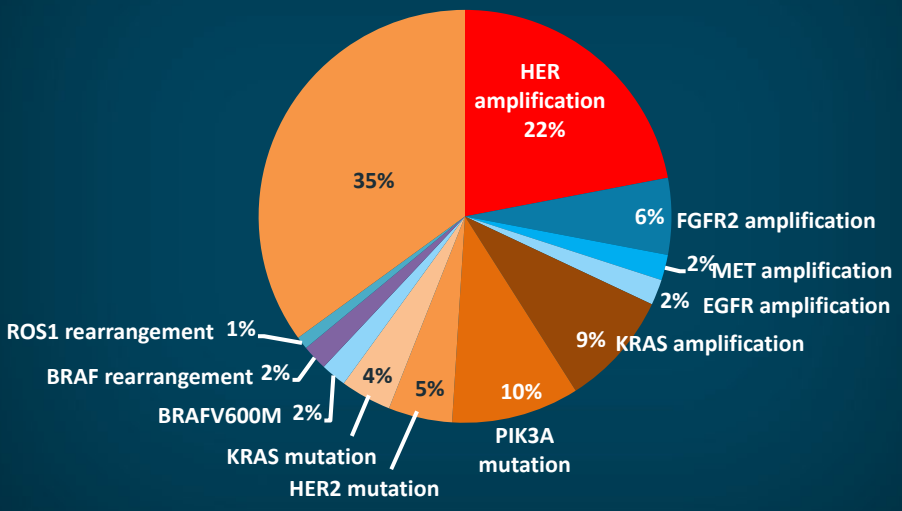
Role of HER2 in Gastric Cancer

- EGFR receptors are associated with tumor cell proliferation, apoptosis, adhesion, migration, and differentiation[1]
- HER2 amplified or overexpressed in an average of ~20% of GE junction and gastric adenocarcinomas[1]
- Prognostic significance of HER2 positivity remains controversial[2]

HER2 = human epidermal growth factor receptor 2; EGFR = epidermal growth factor receptor

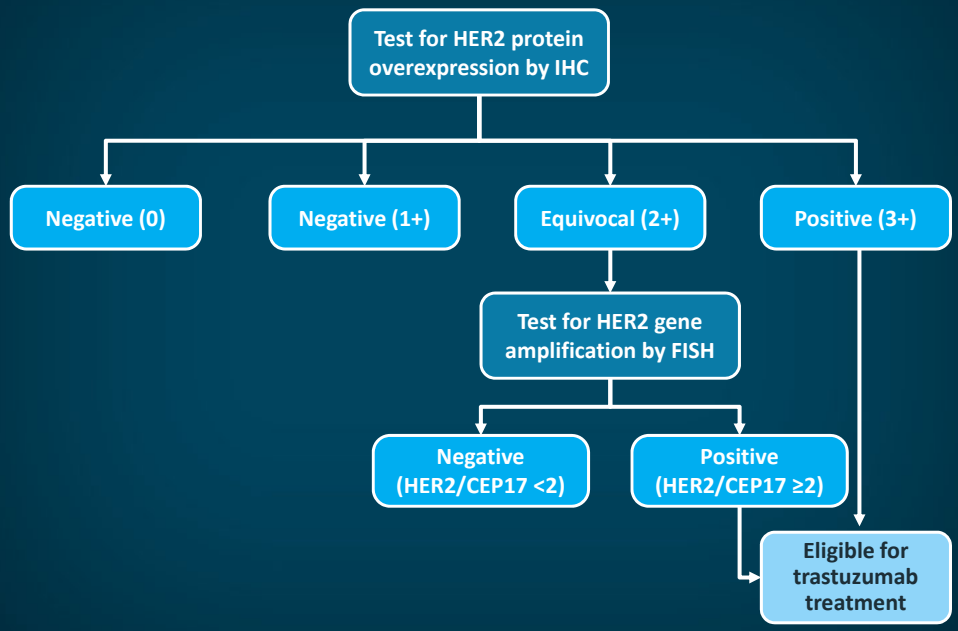
1. Bang YJ, et al. *Lancet*. 2010;376:687-697. 2. Namikawa T, et al. *Mol Clin Oncol*. 2013;1:249-252.

Prevalence of HER2 Amplification in Gastric Cancer



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

HER2 Testing in Gastric Cancer Algorithm



IHC = immunohistochemistry; FISH = fluorescent in situ hybridization; CEP17 = chromosome 17.

Abrahao-Machado LF, Scapulatempo-Neto C. *World J Gastroenterol*. 2016;22:4619-4625.

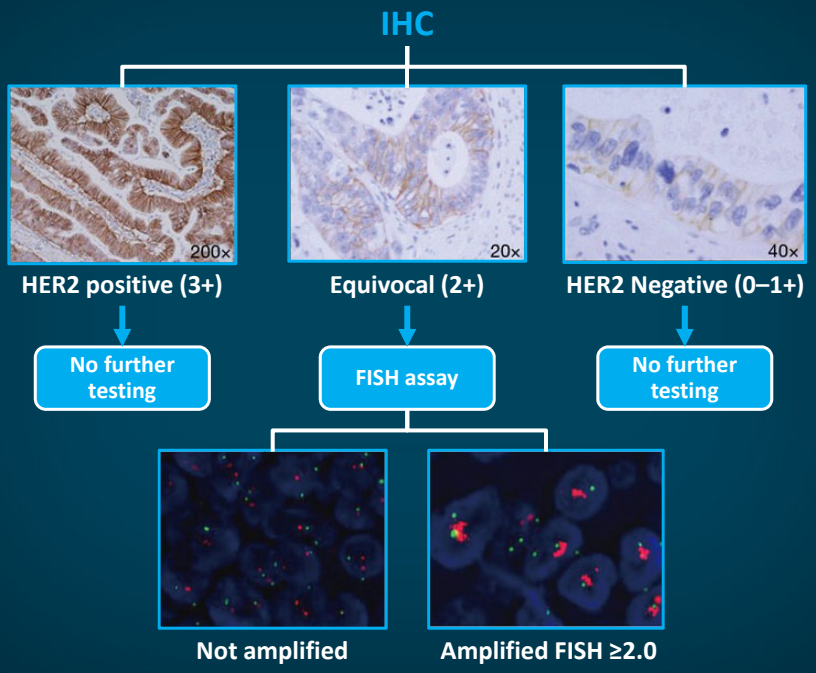
HER2 Testing in Gastric vs Breast Cancer

Analysis	Parameter	Gastric Cancer	Breast Cancer
Immunohistochemistry (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.

18

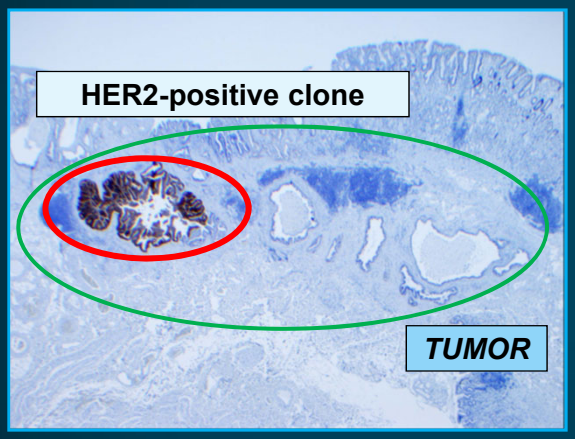
HER2 Expression vs Amplification



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

Intratumor HER2 Heterogeneity

Testing for HER2 on single section may miss HER2-positive clone



Mayo Clinic specimen

- ~20% of HER2-positive esophageal/GEJ adenocarcinomas have intertumor HER2 heterogeneity
- HER2+ GC patients respond differently according to concomitant genomic aberrations beyond ERBB2, high ERBB2 amplification by NGS or cfDNA can be a positive predictor for patient selection, and tumor genomic alterations change significantly during targeted agent therapy

GEJ = gastroesophageal junction; NGS = next-generation sequencing; DNA = deoxyribonucleic acid; cfDNA = cell-free DNA.

Kim ST, et al. *Ann Oncol*. 2018;29:1037-1048.

Courtesy of Axel Grothey.

Systemic Therapy for Gastric Cancer– 1st line

- **2-drug cytotoxic regimens** are preferred because of ***lower toxicity***

Preferred regimens

- **5-FU (or capecitabine) and cisplatin (or oxaliplatin)**
- **HER2+ disease: trastuzumab + cisplatin/5-FU (FOLFOX + trastuzumab is a commonly used regimen)**

Other recommended regimens

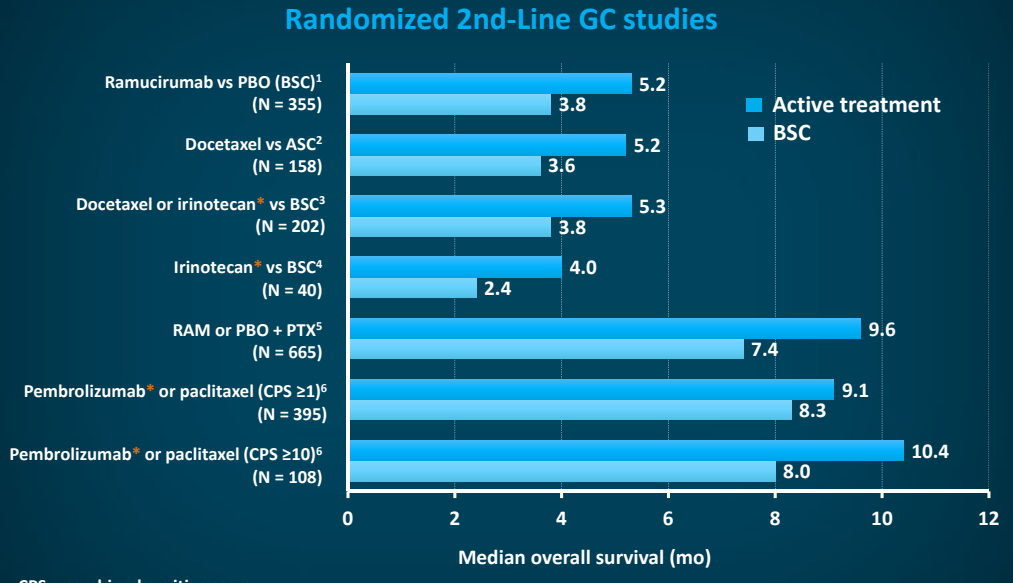
- Paclitaxel with cisplatin or carboplatin
- Docetaxel with cisplatin
- DCF modifications (docetaxel, cisplatin, 5-FU)
- ECF modifications (epirubicin, cisplatin, 5-FU)*
- 5-FU and irinotecan
- Single-agent fluoropyrimidine (5-FU or capecitabine) or taxane

- Regimens should be chosen in the context of performance status, comorbidities, toxicity profile, and biomarker status

Practical note: epirubicin is not commonly used due to CALGB 80403/E1206 clinical trial findings

National Comprehensive Cancer Network (NCCN). Guidelines for gastric Cancer, V2.2020

Randomized 2nd-Line GC Studies: Median OS



CPS = combined positive score;
BSC = best supportive care.

**Irinotecan and 1st-line pembrolizumab are not FDA-approved in gastric cancer.*

1. Fuchs CS et al. *Lancet.* 2014;383:31-39. 2. Ford H et al. *J Clin Oncol.* 2013;31(suppl 4): abstract 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;15:1224-35. 6. Fuchs C. *J Clin Oncol.* 38:15 2020 (15 suppl): abstract 4503.

Care of the Patient With Gastroesophageal Cancer Should Be Multidisciplinary

Adapted from Van Rossum PS, et al. *Nat Rev Gastroenterol Hepatol.* 2018;15:235-249.

Multidisciplinary Management

Relevant disciplines

- Surgical oncology
- Medical oncology
- Gastroenterology
- Radiation oncology
- Radiology
- Pathology
- Nutritional services
- Social workers
- Nursing
- Palliative care specialists
- Other supporting disciplines

Special considerations for GC patients

- Nutrition
- Gastric outlet obstruction
- Bleeding
- Nausea/vomiting
- Ascites
- Fatigue
- Pain management
- Physical therapy
- Psychosocial

NCCN guidelines recommend a multidisciplinary team approach to treatment decision-making in gastric cancer.
"The NCCN Panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of this group of patients."

NCCN. Guidelines for gastric cancer, V2.2020

NCCN Guidelines®:
Multidisciplinary Team Approach

PRINCIPLES OF MULTIDISCIPLINARY TEAM APPROACH FOR ESOPHAGOGASTRIC CANCERS

Category 1 evidence supports the notion that the combined modality therapy is effective for patients with localized esophagogastric cancer. The NCCN Panel believes in an infrastructure that encourages multidisciplinary treatment decision-making by members of all disciplines taking care of this group of patients.

The combined modality therapy for patients with localized esophagogastric cancer may be optimally delivered when the following elements are in place:

- The involved institution and individuals from relevant disciplines are committed to jointly reviewing the detailed data on patients on a regular basis. Frequent meetings (either once a week or once every two weeks) are encouraged.
- Optimally at each meeting, all relevant disciplines should be encouraged to participate and these may include: surgical oncology, medical oncology, gastroenterology, radiation oncology, radiology, and pathology. In addition, the presence of nutritional services, social workers, nursing, palliative care specialists, and other supporting disciplines are also desirable.
- All long-term therapeutic strategies are best developed after adequate staging procedures are completed, but ideally prior to any therapy that is rendered.
- Joint review of the actual medical data is more effective than reading reports for making sound therapy decisions.
- A brief documentation of the consensus recommendation(s) by the multidisciplinary team for an individual patient may prove useful.
- The recommendations made by the multidisciplinary team may be considered advisory to the primary group of treating physicians of the particular patient.
- Re-presentation of select patient outcomes after therapy is rendered may be an effective educational method for the entire multidisciplinary team.
- A periodic formal review of relevant literature during the course of the multidisciplinary meeting is highly encouraged.

NCCN. Guidelines for gastric cancer. V2.2020.

Nutrition Counseling

- The American Cancer Society (ACS) recognizes that “nutrition is an important thing to consider when…getting cancer treatment,” suggesting that patients “talk with your…dietitian if you have questions about certain foods or amounts.”
- In gastric cancer patients, early nutritional feeding and effective nutritional intervention with a proper nutritional screening tool are suggested to promote clinical outcomes and reduce complications
- Early identification of nutritional status in patients may prevent malnutrition and provide benefits in increasing their survival rates

ACS. Nutrition for people with cancer (www.cancer.org/content/dam/CRC/PDF/Public/6711.00.pdf). Accessed 7/16/2020. Shoi WJ, Kim J. *Clin Nutr Res.* 2016;5:65-78.

Clinical Trials in HER2-Positive Advanced Gastric Cancer

First-Line HER2-Directed Clinical Trials

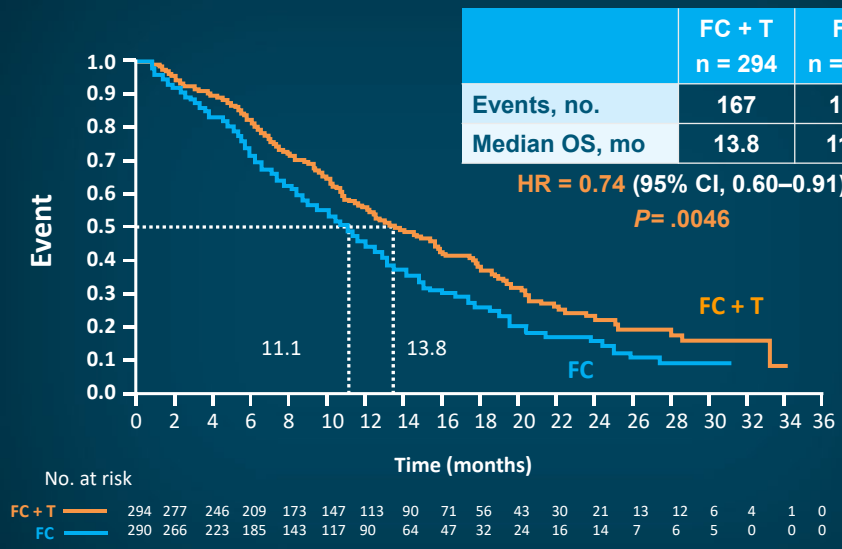
Clinical Trial	Regimen	Stratification
ToGA[1] **HER2-positive** **(n = 594)**	5-FU or capecitabine + cisplatin + trastuzumab	• Advanced vs metastatic • GC vs GEJ cancer • Measurable vs non-measurable • ECOG PS 0–1 vs 2 • Capecitabine vs 5-FU
	5-FU or capecitabine + cisplatin	
TRIO-013/LOGiC[2] **HER2-positive**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

**Lapatinib, pertuzumab not FDA-approved for use in gastric cancer.*

ECOG = Eastern Cooperative Oncology Group; PS = performance status; 5-FU = fluorouracil; ISH = in situ hybridization.

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, no.	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; T = trastuzumab; OS = overall survival; mo = month(s).

Bang YJ, et al. *Lancet.* 2010;376:687-697.

Moving Toward Evidence-Based Management of Advanced GC and GJC

NCCN guidelines for first-line therapy recommend:[1]

- HER2-positive disease
  - Trastuzumab with 5-FU (fluoropyrimidine) and cisplatin (category 1 evidence)[1,2]
- HER2-negative disease
  - Fluorouracil + leucovorin + oxaliplatin* has reduced toxicity compared with fluorouracil + leucovorin + cisplatin.[3]
  - Fluorouracil + leucovorin + irinotecan*[4]

GJC = gastroesophageal junction cancer.

*Not FDA-approved.

1. Ajani JA, et al. *J Natl Compr Canc Netw.* 2016;14:1286-1312. 2. Bang YJ, et al. *Lancet.* 2010;376:687-697. 3. Al-Batran SE, et al. *J Clin Oncol.* 2008;26:1435-1442. 4. Guimbaud R, et al. *J Clin Oncol.* 2014;32:3520-3526. NCCN Guidelines. Gastric Cancer. Version 2.2020.

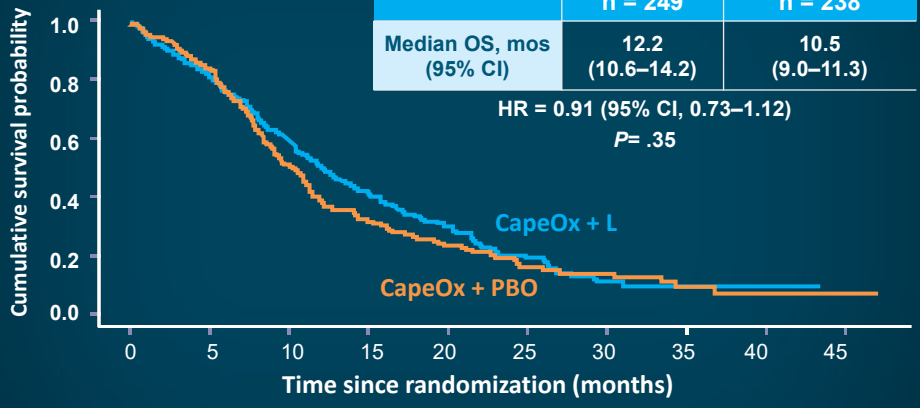
TRIO-013/LOGiC Trial

Primary Endpoint: OS in Primary Efficacy Population

	CapeOx + L n = 249	CapeOx + PBO n = 238
Median OS, mos (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.

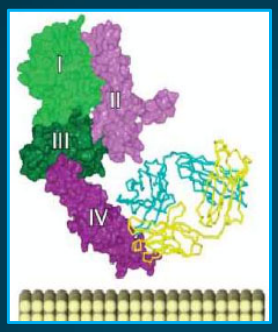
**Lapatinib not FDA-approved for use in gastric cancer.*

Whiteboard Presentation

Please scan the QR code below to view a brief depiction of the mechanism of action of antibody drug conjugates (ADCs)

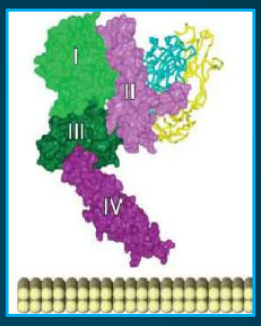
Binding Sites for HER2-Targeted Therapies

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]



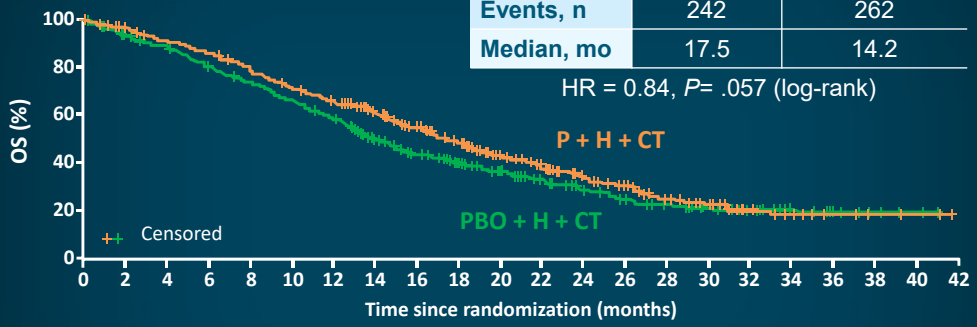
- Activates antibody-dependent cellular cytotoxicity[5]
- Prevents receptor dimerization[1]
- Potent inhibitor of HER-mediated signaling pathways[5]

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.

JACOB: Primary Endpoint—OS

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

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



Secondary Endpoints	P + H + CT (n = 388)	PBO + H + CT (n = 392)	HR (*P*-value)
mPFS, mos	8.5	7.0	0.73 (6.2–8.6)
ORR	56.7%	48.3%	—

ITT = intention-to-treat; P = pertuzumab; H = trastuzumab; CT = chemotherapy; mPFS = median progression-free survival; ORR = objective/overall response rate; NR = not reported.

Tabernero J, et al. *Lancet Oncol.* 2018;19:1372-2384.

**Pertuzumab not FDA-approved for use in gastric cancer.*

First-Line HER2-Directed Clinical Trials: OS

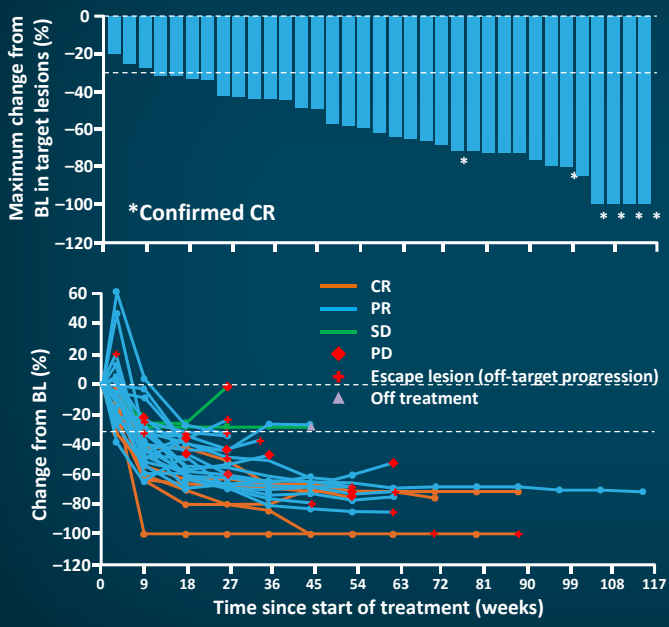
Clinical Trial	Regimen	mOS mo	HR (95% CI)	*P*-value
ToGA	5-FU or capecitabine + cisplatin + trastuzumab	13.8	0.74 (0.60–0.91)	.0046
	5-FU or capecitabine + cisplatin	11.1		
TRIO-013/ LOGiC	Capecitabine + oxaliplain + lapatinib	12.2	0.91 (0.73–1.12)	.3492
	Capecitabine + oxaliplain	10.5		
JACOB	Capecitabine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

**Lapatinib, pertuzumab not FDA-approved for use in gastric cancer.*

mOS = median overall survival.

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



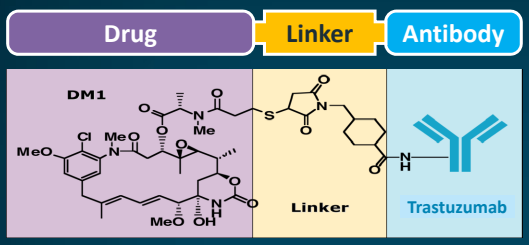
Best Response (N = 37)	Patients, n (%)
ORR, n (%)	32 (91%) 95% CI, 78–97
CR	6 (17)
PR	26 (74)
SD	3 (9)
PD	0
DCR	100%

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

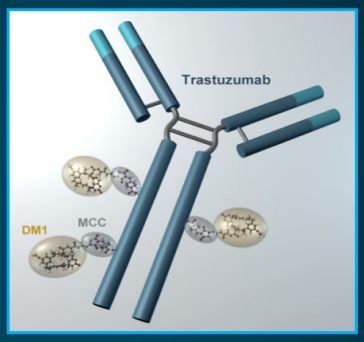
Janjigian YY, et al. *Lancet Oncol.* 2020;21:821-831.

**Pembrolizumab not FDA-approved for use 1st line use in gastric cancer.*

T-DM1 Structure



T-DM1 is a novel ADC



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

→ **T-DM1**

Average drug has an antibody ratio ≅ 3.5:1

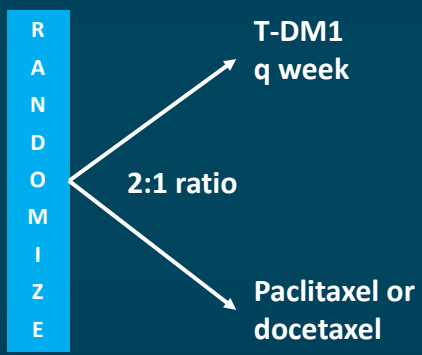
**TD-M1 not FDA-approved for use in gastric cancer.*

ADC = antibody-drug conjugate; T-DM1 = trastuzumab emtansine; MCC = N-maleimidomethyl]cyclohexane-1-carboxylate.

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-positive GC

345 HER2-positive patients following first-line therapy

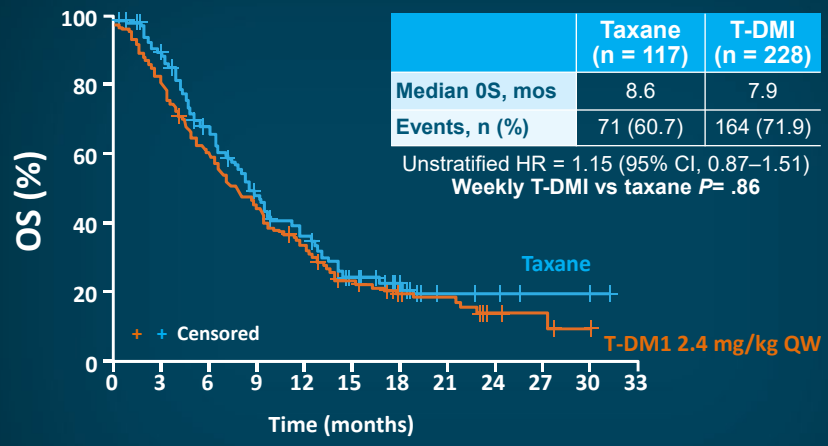


Primary endpoint: OS

**TD-M1 not FDA-approved for use in gastric cancer.*

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

GATSBY: Overall Survival



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

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

T-DMI	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

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

QW = each week.

**TD-M1 not FDA-approved for use in gastric cancer.*

Thuss-Patience PC, et al. *Lancet Oncol.* 2917;18:640-653. Kang Y-K et al. *J Clin Oncol.* 2016;34(4 suppl): abstract 5.

Paclitaxel (P) ± Trastuzumab (T) in HER2-positive GC and GEJ Cancers Refractory to T + 5-FU + Platinum
WJOG7112G (T-ACT)

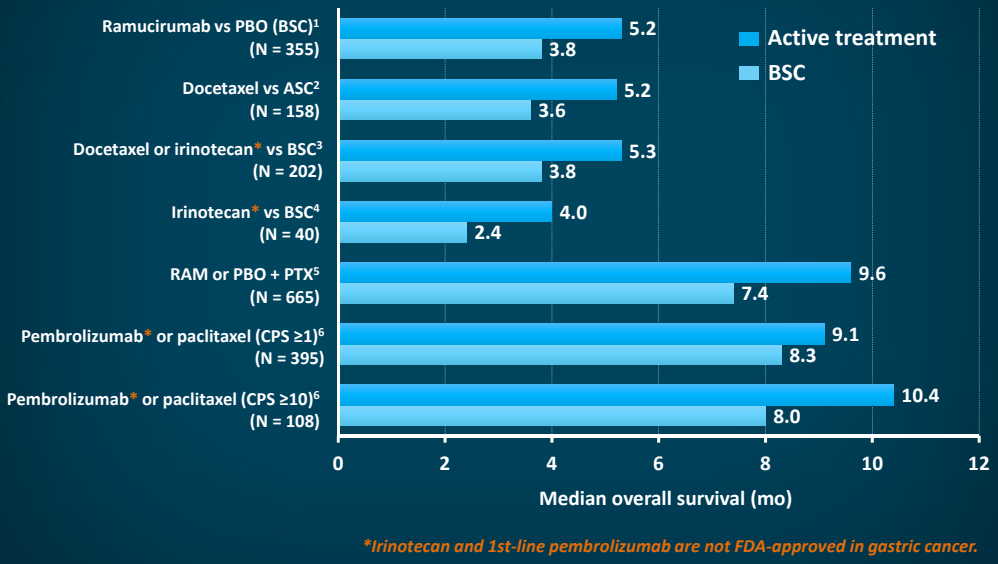
- Phase 2 (N = 91)
- Pts with HER2-positive advanced G/GEJ cancer progressing during first-line chemo with trastuzumab + 5-FU + platinum were randomized to receive either paclitaxel (P) (80 mg/m^2, day 1, 8, 15, Q4W) or P + trastuzumab (T) (initial T 8 mg/kg followed by 6 mg/kg, Q3W)
- Median PFS (primary endpoint) = 3.2 and 3.7 months in the P 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) were found to have lost their HER2+ status**

Q4W = every 4 weeks; Q3W = every 3 weeks; PFS = progression-free survival.

Makiyama A, et al. *J Clin Oncol.* 2018;36(suppl): abstract 4011.

**Trastuzumab not FDA-approved for use in gastric cancer.*

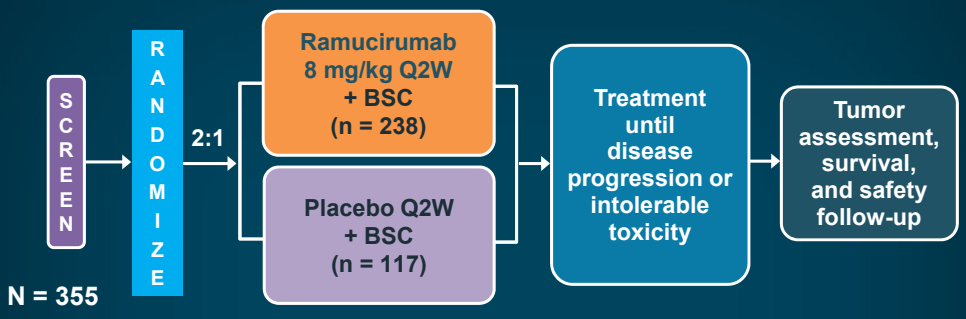
What Are Treatment Options After First-Line Progression for HER2+ Patients?



**Irinotecan and 1st-line pembrolizumab are not FDA-approved in gastric cancer.*

1. Fuchs CS et al. *Lancet.* 2014;383:31-39. 2. Ford H et al. *J Clin Oncol.* 2013;31(suppl 4): abstract 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;15:1224-35. 6. Fuchs C. *J Clin Oncol.* 38:15 2020 (15 suppl): abstract 4503.

REGARD: Study Design



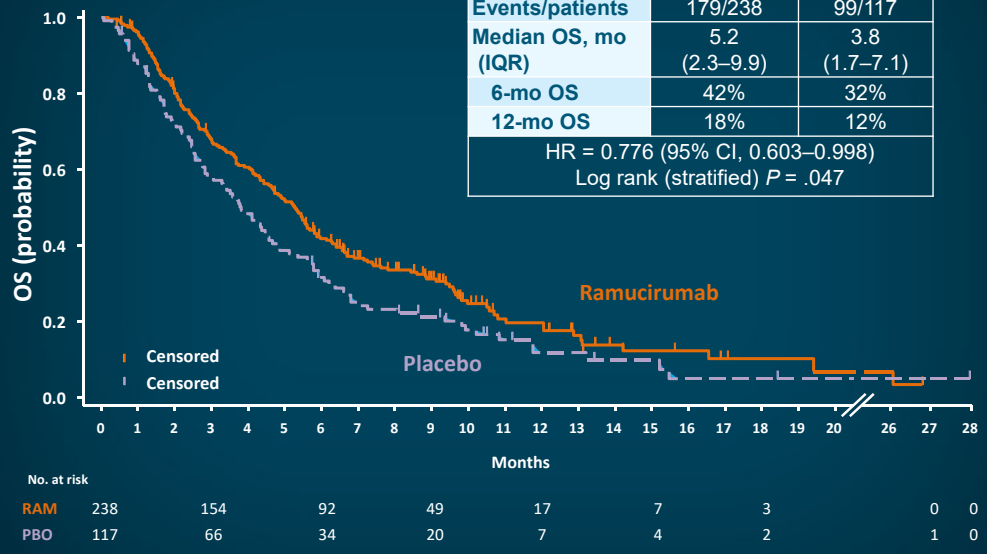
- Multicenter, randomized, double-blind, placebo-controlled, phase 3 trial
- Advanced gastric or GEJ adenocarcinoma and disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy
- Stratification factors: geographic region, weight loss (≥10% vs <10% over 3 mo), location of primary tumor (gastric vs GEJ)
- Global: 6 continents, 29 countries, 119 study centers

Q2W = every 2 weeks.

Fuchs CS, et al. *Lancet.* 2014;383:31-39. NCT00917384.

REGARD: Overall Survival

	RAM	PBO
Events/patients	179/238	99/117
Median OS, mo (IQR)	5.2 (2.3–9.9)	3.8 (1.7–7.1)
6-mo OS	42%	32%
12-mo OS	18%	12%
HR = 0.776 (95% CI, 0.603–0.998) Log rank (stratified) *P* = .047		



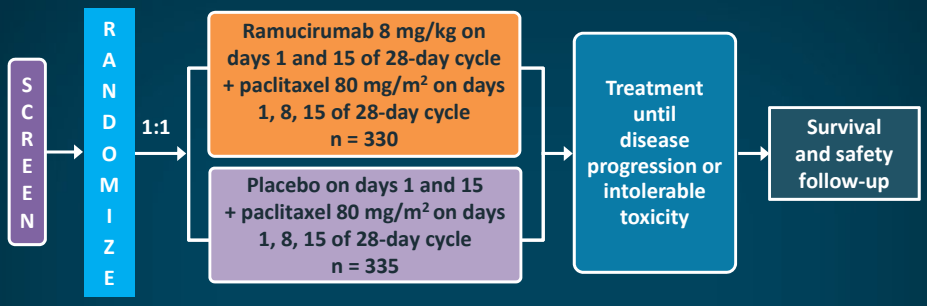
No. at risk

RAM	238	154	92	49	17	7	3	0	0
PBO	117	66	34	20	7	4	2	1	0

RAM = ramucirumab; IQR = interquartile range.

Fuchs CS, et al. *Lancet.* 2014;383:31-39.

RAINBOW: Study Design

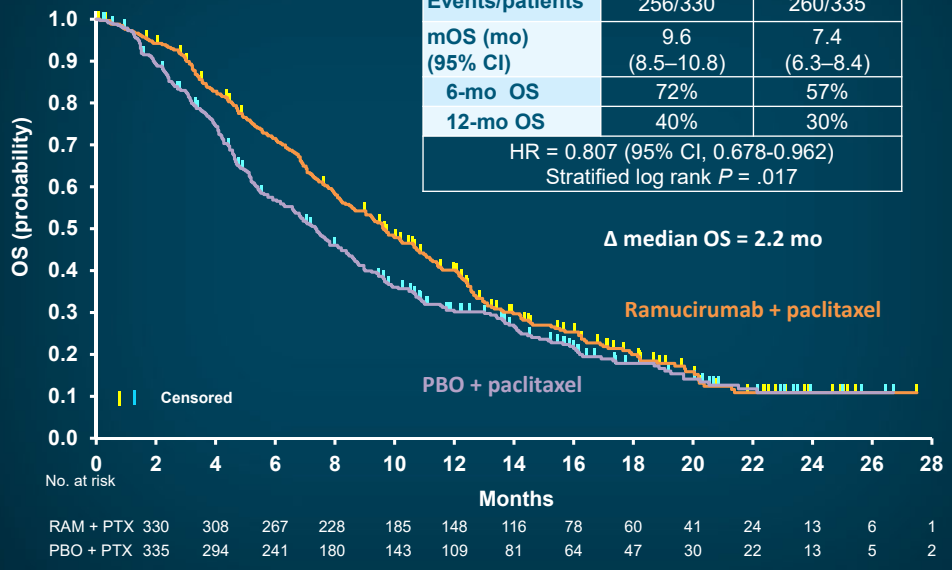


- Primary endpoint: overall survival
- Inclusion criteria
  - Metastatic or locally advanced unresectable gastric or GEJ adenocarcinoma
    - Progression after first-line platinum/fluoropyrimidine-based chemotherapy
  - Stratification factors
    - Geographic region
    - Measurable vs non-measurable disease
    - Time to progression on first-line therapy (<6 mo vs ≥6 mo)

Wilke H, et al. *Lancet Oncol.* 2014;15:1224-1235. NCT01170663.

RAINBOW: Overall Survival

	RAM + PTX	PBO + PTX
Events/patients	256/330	260/335
mOS (mo) (95% CI)	9.6 (8.5–10.8)	7.4 (6.3–8.4)
6-mo OS	72%	57%
12-mo OS	40%	30%
HR = 0.807 (95% CI, 0.678-0.962) Stratified log rank *P* = .017		



No. at risk

RAM + PTX	330	308	267	228	185	148	116	78	60	41	24	13	6	1	0
PBO + PTX	335	294	241	180	143	109	81	64	47	30	22	13	5	2	0

Wilke et al. *Lancet Oncol*. 2014;15:1224-1235.

KEYNOTE-061: Study Design (NCT02370498)

Key eligibility criteria

- Adenocarcinoma of stomach or GEJ that was metastatic or locally advanced but unresectable
- PD per RECIST v1.1 after first-line platinum- and fluoropyrimidine-containing therapy
- ECOG PS 0 or 1
- Provision of sample for PD-L1 assessment*
- First 489 patients: any PD-L1 CPS
- Final 103 patients: PD-L1 CPS ≥1†

Stratification factors

- Region (Europe/Israel/North America/Australia vs Asia vs rest of world)
- ECOG PS (0 vs 1)‡
- TTP on first-line therapy (<6 mo vs ≥6 mo)§
- PD-L1 CPS (<1 vs 21)§

R 1:1

N = 592

n = 296

Pembrolizumab 200 mg Q3W for 35 cycles or until confirmed PD, intolerable toxicity, patient withdrawal, or investigator decision

n = 296

Paclitaxel 80 mg/m² on days 1, 8, and 15 of 4-week cycles until confirmed PD, intolerable toxicity, patient withdrawal, or investigator decision

Endpoints

- **Primary**: OS and PFS in the CPS ≥1 population
- **Secondary**: ORR and DOR in CPS ≥1 population; safety in all treated patients

*PD-L1 was assessed using PD-L1 IHC 22C3 pharmDx assay (Agilent). Measured as CPS (number of PD-Li-positive cells (tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100. †At recommendation of independent external monitoring committee. ‡First 125 patients only. §Final 467 patients only.

TTP = time to progression.

**Pembrolizumab not FDA-approved for use 1st line use in gastric cancer.*

Shitara K, et al. *Lancet*. 2018;392:123-133. Fuchs C, et al. *J Clin Oncol*. 38:15 2020 (suppl): abstract 4503.

KEYNOTE-061: Overall Survival by CPS

CPS ≥1

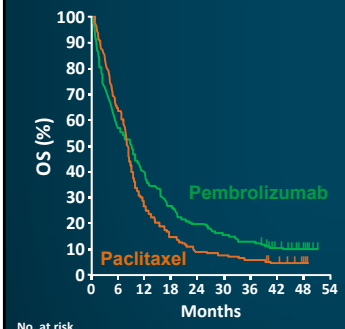
	Events/ Pts	mOS (95% CI)
Pembro	176/196	9.1 mo (6.2–10.7)
PTX	190/199	8.3 mo (7.6–9.0)
HR = 0.81 (95% CI, 0.66–1.00), *P*= .03		

CPS ≥5

	Events/ Pts	mOS (95% CI)
Pembro	84/95	10.4 mo (6.7–15.5)
PTX	86/91	8.3 mo (6.8–9.4)
HR = 0.72 (95% CI, 0.53–0.99), *P*= .02		

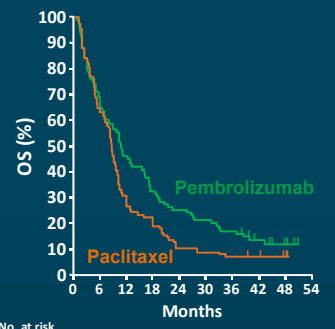
CPS ≥10

	Events/ Pts	mOS (95% CI)
Pembro	44/53	10.4 mo (5.9–18.3)
PTX	51/55	8.0 mo (5.1–9.9)
HR = 0.69 (95% CI, 0.46–1.05), *P*= .04		



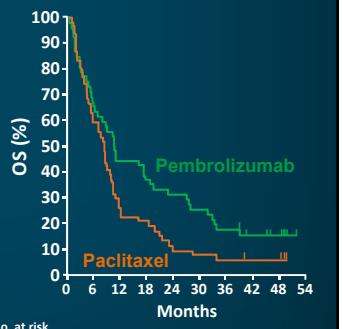
No. at risk

Pembro	196	114	78	52	39	30	25	16	9	0
Paclitaxel	199	130	54	30	17	15	11	7	2	0



No. at risk

Pembro	95	61	43	30	23	19	15	9	6	0
Paclitaxel	91	57	23	16	8	7	5	4	2	0



No. at risk

Pembro	53	34	24	20	17	14	10	7	5	0
Paclitaxel	55	33	13	11	6	5	4	3	2	0

Data cutoff date: Oct. 7, 2019.

**Pembrolizumab not FDA-approved for use 1st line use in gastric cancer.*

Shitara K, et al. *Lancet.* 2018;392:123-133. Fuchs C, et al. *J Clin Oncol.* 2020;38(suppl): abstract 4503.

Current Treatment Options for Second-Line Therapy in HER2+ patients

- Continuing trastuzumab past first-line progression has not shown significant improvement in outcomes
- Treatment options in line with HER2– disease options
- Treatment choices based on PD-L1 status and patient/ provider decision
  - Toxicity profile of regimen
  - Patient performance status
  - Patient goals
  - Patient co-morbidities
- More options are clearly needed

Trifluridine/Tipiracil* vs Placebo in Metastatic GC Refractory to Standard Therapies (TAGS, Phase 3)

NCT02500043 Study Design

Patients with mGC
(including GEJ cancer)
- ≥2 prior regimens including fluoropyrimidine; platinum; taxane and/or irinotecan; HER2 inhibitor, if available, for HER2+ disease
  - Refractory to/intolerant of last prior therapy
- ECOG PS of 0 or 1
- Age ≥18 y (≥20 y in Japan)

Target sample size = 500

R 2:1

FTD/TPI (TAS-102) + BSC (n = 337)
35 mg/m² BID orally on days 1–5 and 8–12 of each 28-day cycle

Placebo + BSC (n = 170)
BID orally on days 1–5 and 8–12 of each 28-day cycle

Endpoints
- Primary
  - OS
- Key secondary
  - PFS, safety
- Other secondary
  - ORR
  - DCR
  - QoL
  - Time to ECOG PS ≥2

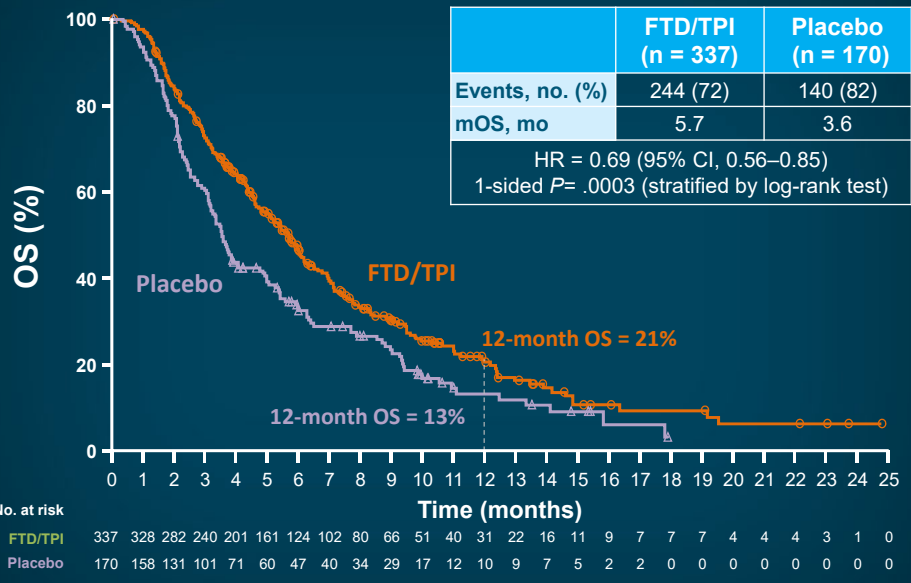
- Treatment until progression, intolerable toxicity, or patient withdrawal
- Multicenter, randomized, double-blind, placebo-controlled, phase 3 study
- Trifluridine/tipiracil (FTD/TPI; TAS-102) is novel oral thymidine analog consisting of thymidine-based nucleoside analogue (FTD) and thymidine phosphorylase inhibitor (TPI).
- FDA approved for metastatic GEJ adenocarcinoma with at least 2 prior lines of CT

Data cutoff date: March 31, 2018

mGC = metastatic GC; BID = twice daily; QoL = quality of life; RoW = rest of world.

Shitara K, et al. *Lancet Oncol.* 2018;19:1437-1448. Tabernero J, et al. 2018 World Congress on Gastrointestinal Cancer (WCGC): abstract LBA-002. Press Release. Trifluridine/tipiracil (Lonsurf®), 2019 (https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-lonsurf-recurrent-metastatic-gastric-and-gastroesophageal-junction-adenocarcinoma).

TAGS Primary Endpoint—OS

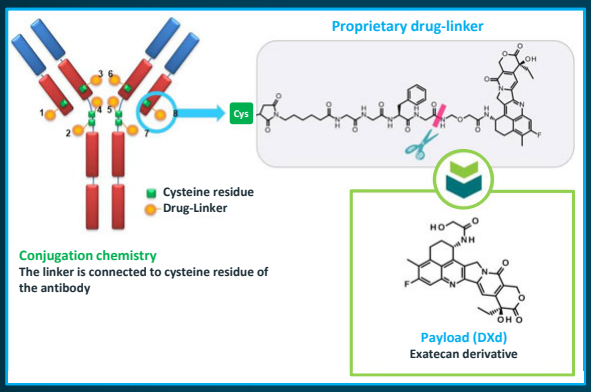


	FTD/TPI (n = 337)	Placebo (n = 170)
Events, no. (%)	244 (72)	140 (82)
mOS, mo	5.7	3.6
HR = 0.69 (95% CI, 0.56–0.85) 1-sided *P*= .0003 (stratified by log-rank test)		

ITT population.

Shitara K, et al. *Lancet Oncol.* 2018;19:1437-1448. Tabernero J, et al. 2018 WCGC): abstract LBA-002.

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

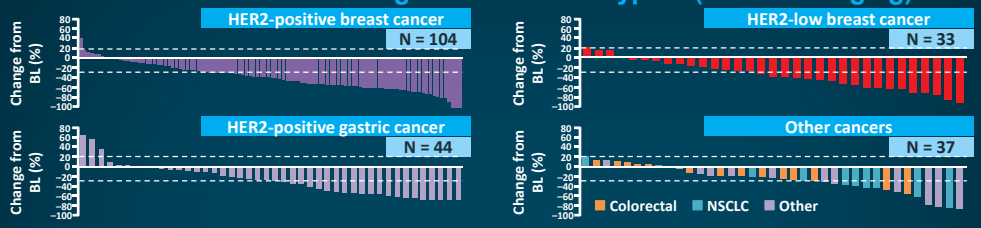
DS-8201a was designed with goal of improving critical attributes of an ADC

**DS-8201a not FDA-approved for use in gastric cancer.*

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

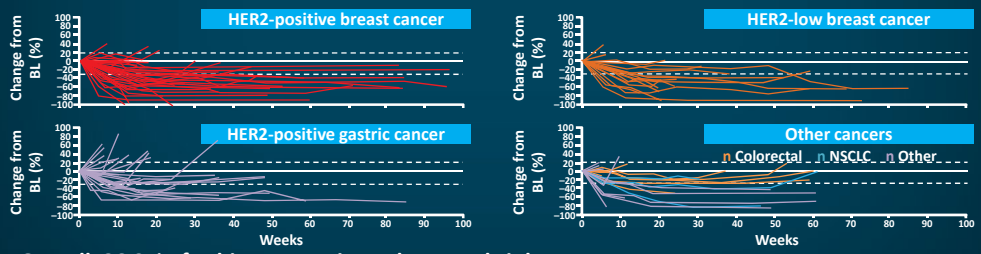
Anti-Tumor Activity of DS-8201a

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.

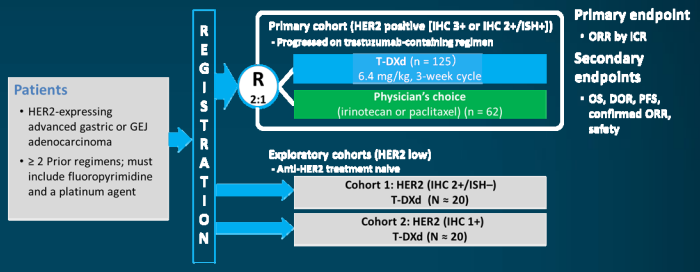
**DS-8201a not FDA-approved for use in gastric cancer.*

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

DESTINY-Gastric01

An open-label, multicenter, randomized phase 2 study

- T-DXd is an antibody-drug conjugate 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 mPFS of 5.6 months in 44 patients with HER2-positive gastric or GEJ cancer previously treated with trastuzumab (NCT02564900)
- Shown is the schema for for 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

T-DXd = trastuzumab deruxtecan.

DS-8201a not FDA-approved for use in gastric cancer.

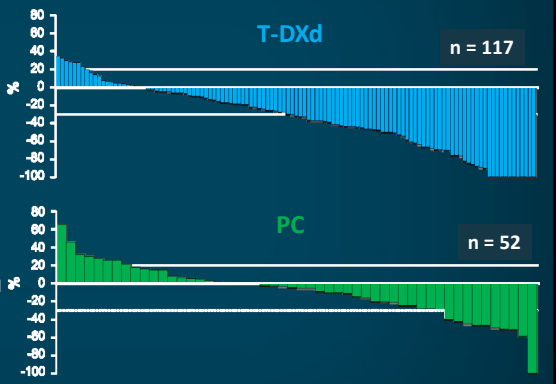
Shitara K, et al. *N Engl J Med*. 2020;381:2419-2430. NCT03329690.

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 independent central review at baseline.

Best % change from baseline in tumor size



Line at 20% indicates progressive disease; line at –30% indicates partial response. Includes patients who had both baseline and postbaseline target lesion assessments by independent central review in both treatment arms.

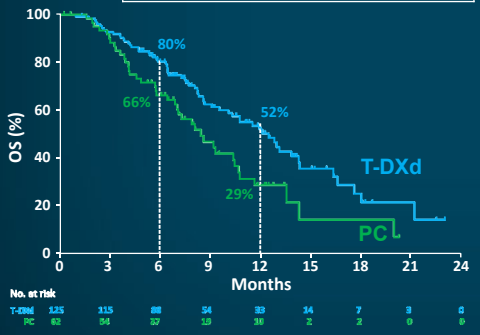
Shitara K, et al. *N Engl J Med*. 2020;381:2419-2430.

DS-8201a not FDA-approved for use in gastric cancer.

DESTINY-Gastric01:
Overall Survival and Progression-Free Survival

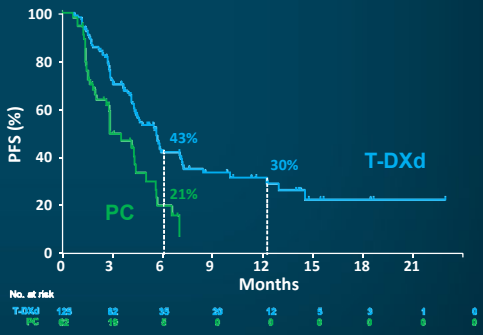
Overall Survival

	Events/n	Median OS
T-DXd	62/125	12.5 months (95% CI, 9.6–14.3)
Physician's choice	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)
Physician's choice	36/62	3.5 months (95% CI, 2.0–4.3)
HR = 0.47 (95% CI, 0.31–0.71)		

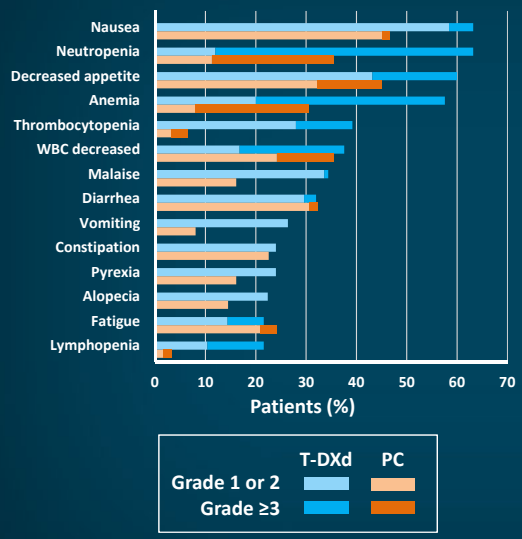


PC = physician's choice (of chemotherapy).

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

**DS-8201a not FDA-approved for use in gastric cancer.*

DESTINY-Gastric01: Safety Summary



TEAEs 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)

WBC = white blood count; ILD = interstitial lung disease.

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

**DS-8201a not FDA-approved for use in gastric cancer.*

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+
Partial response	5/19	2/21
Stable disease	12/19	
Confirmed ORR (95% CI)	26.3% (5/19)	9.5% (2/21)
DCR (95% CI)	89.5%	71.4%
Median PFS (95% CI)	4.4 mo (2.7–7.1)	2.8 mo (1.5–4.3)
Median OS (95% CI)	7.8 mo (4.7–NE)	8.5 mo (4.3–10.9)
12-mo OS rate	40%	25.7%

Yamaguchi K, et al. *Ann Oncol.* 2020;31(suppl 4): abstract 1422MO.

Case Study

- A 64-year-old woman with no significant medical history and initial presentation of dysphagia and weight loss of 15 pounds
- A barium swallow revealed a mass at the gastroesophageal junction, which was biopsied via esophagogastroduodenoscopy
- Tumor pathology was notable for moderately differentiated adenocarcinoma, with molecular profile of HER2 IHC 3+, FISH positive, MSI-stable, and PD-L1 CPS <1
- CT scan of the chest, abdomen, and pelvis was significant for multiple enlarged periaortic lymph nodes, the largest of which was 3 cm
- Nutritional services were consulted to assist her with dietary issues

CT = computed tomography; MSS = microsatellite stable.

Case Study: Question 1

Based on the findings of conducted diagnostic studies and tumor pathology, what treatment strategy would be most appropriate for this patient?

a) FOLFOX
b) FOLFOX + bevacizumab
c) FOLFOX + trastuzumab
d) FOLFOX + palliative radiotherapy

FOLFOX, = leucovorin, 5-fluorouracil, and oxaliplatin.

Case Study: Question 1

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FOLFOX, = leucovorin, 5-fluorouracil, and oxaliplatin.

Case Study: Question 2

- She was started on FOLFOX-trastuzumab with good response; this regimen was continued for 6 months, at which time neuropathy developed and therapy was switched to capecitabine-trastuzumab
- Ten months later she had disease progression; residual neuropathy effects have been minimal
- Which treatment strategy should be considered for this patient?

a) FOLFIRI
b) Paclitaxel + ramucirumab
c) Sorafenib

Case Study: Question 2

- She was started on FOLFOX-trastuzumab with good response; this regimen was continued for 6 months, at which time neuropathy developed and therapy was switched to capecitabine-trastuzumab
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- Which treatment strategy should be considered for this patient?

a) FOLFIRI
b) Paclitaxel + ramucirumab
c) Sorafenib

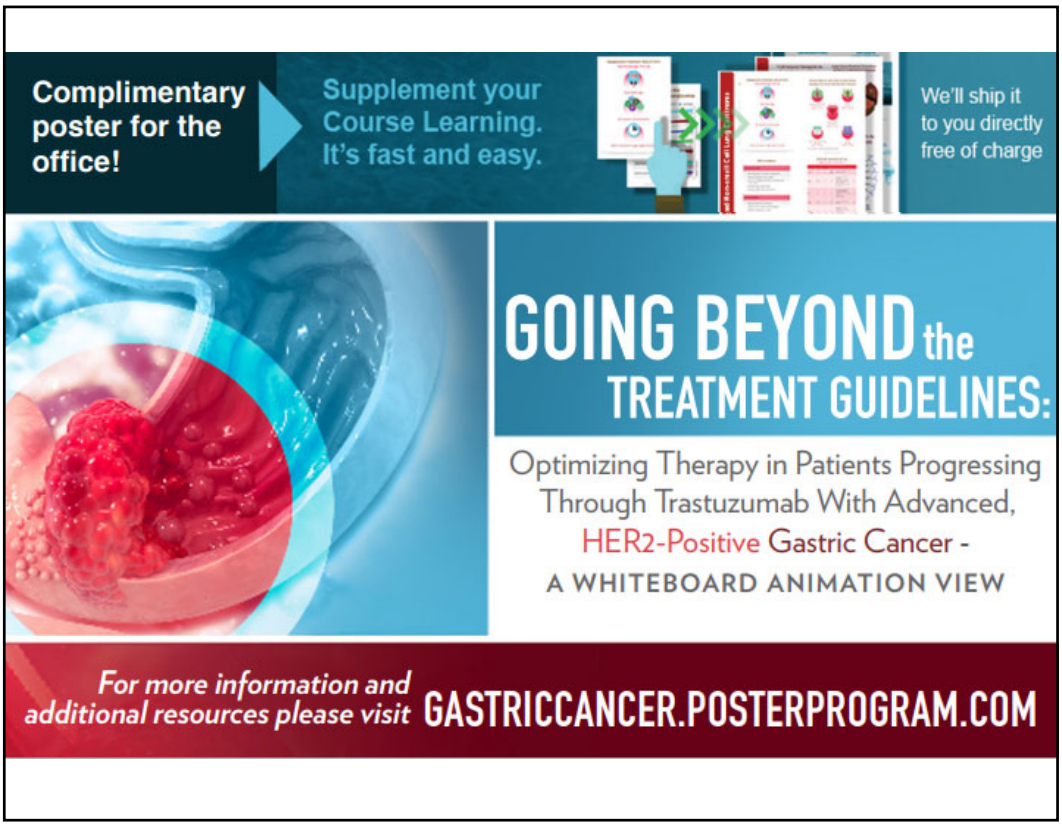
Case Study 2

- A 70-year-old male diagnosed with locally advanced gastric carcinoma (HER2 IHC2+/ ISH–) was found to have metastatic progression during neoadjuvant treatment with cisplatin + 5-FU. Additionally, he experienced multiple adverse events with systemic therapy including persistent neuropathy. When he presents for evaluation for his next line of therapy, he asks if there is a way to minimize potential adverse effects of treatment since his current symptoms significantly impact his quality of life and activities of daily living.
- What treatment strategy would you consider for this patient?

a) Paclitaxel + carboplatin
b) 5-FU + irinotecan
c) Trastuzumab monotherapy
d) Clinical trial with T-DXd

Conclusions

- It should be standard practice to test patients with gastric cancer for HER2 status at initial diagnosis of advanced disease
- The requirements for HER2 positivity are different for gastric and breast cancers
- Eligible patients who are HER2-positive should receive trastuzumab in combination with chemotherapy in the first line setting
- As opposed to breast cancer, once patients with gastric cancer have progressed on first-line trastuzumab-based therapy, further anti-HER2 therapies have not shown success until recently
- There are promising new data of anti-HER2 ADC T-DXd in the refractory setting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Thank you!

Gastric Cancer Overview

Citation	Address
American Cancer Society. Key Statistics About Stomach Cancer. Published December 1, 2017. Revised December 14,2017.	https://www.cancer.org/content/dam/CRC/PDF/Public/8838.00.pdf
American Gastroenterological Association, Spechler SJ, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology*. 2011;140(3):1084-1091.	https://pubmed.ncbi.nlm.nih.gov/21376940/
GBD 2017 Stomach Cancer Collaborators. The global, regional, and national burden of stomach cancer in 195 countries, 1990-2017: A systematic analysis for the Global Burden of Disease study 2017. *Lancet Gastroenterol Hepatol*. 2020;5(1):42-54.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7033564/
Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin*. 2011;61(2):69-90.	https://pubmed.ncbi.nlm.nih.gov/21296855/
National Cancer Institute. Cancer of the Stomach - Cancer Stat Facts. Published 2020.	https://seer.cancer.gov/statfacts/html/stomach.html.
Schnell TG, Sontag SJ, Chejfec G, et al. Long-term nonsurgical management of Barrett's esophagus with high-grade dysplasia. *Gastroenterology*. 2001;120(7):1607-1619.	https://pubmed.ncbi.nlm.nih.gov/11375943/

Risk Factors and Predispositions

Citation	Address
El-Omar EM, Carrington M, Chow WH, et al. Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature*. 2000;404(6776):398-402.	https://pubmed.ncbi.nlm.nih.gov/10746728/
Figueiredo C, Machado JC, Pharoah P, et al. Helicobacter pylori and interleukin 1 genotyping: An opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst.* 2002;94(22):1680-1687.	https://pubmed.ncbi.nlm.nih.gov/12441323/
Fitzgerald RC, Hardwick R, Huntsman D, et al. Hereditary diffuse gastric cancer: Updated consensus guidelines for clinical management and directions for future research. *J Med Genet*. 2010;47(7):436-444.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2991043/
García-González MA, Lanas A, Quintero E, et al. Gastric cancer susceptibility is not linked to pro-and anti-inflammatory cytokine gene polymorphisms in whites: A Nationwide Multicenter Study in Spain. Am *J Gastroenterol*. 2007;102(9):1878-1892.	https://pubmed.ncbi.nlm.nih.gov/17640324/
He B, Pan B, Pan Y, et al. *IL-4/IL-4R* and *IL-6/IL-6R* genetic variations and gastric cancer risk in the Chinese population. *Am J Transl Res*. 2019;11(6):3698-3706.	https://pubmed.ncbi.nlm.nih.gov/31312381/
Houghton J, Stoicov C, Nomura S, et al. Gastric cancer originating from bone marrow-derived cells. *Science.* 2004;306(5701):1568-1571.	https://pubmed.ncbi.nlm.nih.gov/15567866/
Lott PC, Carvajal-Carmona LG. Resolving gastric cancer aetiology: An update in genetic predisposition. *Lancet Gastroenterol Hepatol*. 2018;3(12):874-883.	https://pubmed.ncbi.nlm.nih.gov/30507471/
Lynch HT, Grady W, Suriano G, Huntsman D. Gastric cancer: New genetic developments. *J Surg Oncol.* 2005;90(3):114-133.	https://pubmed.ncbi.nlm.nih.gov/15895459/

Zali H, Rezaei-Tavirani M, Azodi M. Gastric cancer: Prevention, risk factors and treatment. *Gastroenterol Hepatol Bed Bench.* 2011;4(4):175-185.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4017429/

Characterization of Gastric Cancer

Citation	Address
Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*. 2014;513(7517):202-209.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170219/
Gastric carcinoma, intestinal type. Atlas of Pathology, 3rd Edition. January 2009.	http://www.pathologyatlas.ro/gastric-carcinoma-intestinal-type-gastrointestinal-pathology.php
Jácome AA, Coutinho AK, Lima EM, Andrade AC, Dos Santos JS. Personalized medicine in gastric cancer: Where are we and where are we going?. *World J Gastroenterol*. 2016;22(3):1160-1171.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4716027/
Kang Y-K et al. A randomized, open-label, multicenter, adaptive phase 2/3 study of trastuzumab emtansine (T-DM1) versus a taxane (TAX) in patients (pts) with previously treated HER2-positive locally advanced or metastatic gastric/gastroesophageal junction adenocarcinoma (LA/MGC/GEJC). *J Clin Oncol.* 2016;34(suppl 4):5.	https://ascopubs.org/doi/abs/10.1200/jco.2016.34.4_suppl.5
Shah MA, Kang YK, Thuss-Patience PC, et al. Biomarker analysis of the GATSBY study of trastuzumab emtansine versus a taxane in previously treated HER2-positive advanced gastric/gastroesophageal junction cancer. *Gastric Cancer*. 2019;22(4):803-816.	https://pubmed.ncbi.nlm.nih.gov/30706247/

Shah MA, Kelsen DP. Gastric cancer: A primer on the epidemiology and biology of the disease and an overview of the medical management of advanced disease. *J Natl Compr Canc Netw*. 2010;8(4):437-447.	https://pubmed.ncbi.nlm.nih.gov/20410336/
Wu H, Rusiecki JA, Zhu K, Potter J, Devesa SS. Stomach carcinoma incidence patterns in the United States by histologic type and anatomic site. *Cancer Epidemiol Biomarkers Prev*. 2009;18(7):1945-1952.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2786772/

Role of HER2 in Gastric Cancer

Citation	Address
Abrahao-Machado LF, Scapulatempo-Neto C. HER2 testing in gastric cancer: An update. *World J Gastroenterol*. 2016;22(19):4619-4625.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4870069/
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. *Lancet.* 2010;376(9742):687-697.	https://pubmed.ncbi.nlm.nih.gov/20728210/
Kelly CM, Janjigian YY. The genomics and therapeutics of HER2-positive gastric cancer-from trastuzumab and beyond. *J Gastrointest Oncol.* 2016;7(5):750-762.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5056254/
Kim ST, Banks KC, Pectasides E, et al. Impact of genomic alterations on lapatinib treatment outcome and cell-free genomic landscape during HER2 therapy in HER2+ gastric cancer patients. *Ann Oncol.* 2018;29(4):1037-1048.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5913644/

Lee J, Ou SH. Towards the goal of personalized medicine in gastric cancer—time to move beyond HER2 inhibition. Part I: Targeting receptor tyrosine kinase gene amplification. *Discov Med.* 2013;15(85):333-341.	https://www.discoverymedicine.com/Jeeyun-Lee/2013/06/25/towards-the-goal-of-personalized-medicine-in-gastric-cancer-time-to-move-beyond-her2-inhibition-part-i-targeting-receptor-tyrosine-kinase-gene-amplification/
Namikawa T, Shiga M, Ichikawa K, Kitagawa H, Kobayashi M, Hanazaki K. Metachronous liver and bone metastasis from small early gastric carcinoma without lymph node involvement: A case report. *Mol Clin Oncol*. 2013;1(2):249-252.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3956265/
Rüschoff J, Dietel M, Baretton G, et al. HER2 diagnostics in gastric cancer-guideline validation and development of standardized immunohistochemical testing. *Virchows Arch.* 2010;457(3):299-307.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2933810/

First-line Gastric Cancer Therapy

Citation	Address
American Cancer Society. Nutrition for People with Cancer. Published July 15, 2015. Revised June 9, 2020.	https://www.cancer.org/content/dam/CRC/PDF/Public/6711.00.pdf
Choi WJ, Kim J. Nutritional Care of Gastric Cancer Patients with Clinical Outcomes and Complications: A Review. *Clin Nutr Res.* 2016;5(2):65-78.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4855043/
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. *J Clin Oncol.* 2013;31(Suppl 4):LBA4.	https://ascopubs.org/doi/abs/10.1200/jco.2013.31.4_suppl.lba4
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. *Lancet.* 2014;383(9911):31-39.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61719-5/fulltext

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. *J Clin Oncol*. 2012;30(13):1513-1518.	https://ascopubs.org/doi/pdf/10.1200/JCO.2011.39.4585
National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Gastric Cancer, Version 2. 2020.	https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO*). Eur J Cancer*. 2011;47(15):2306-2314.	https://pubmed.ncbi.nlm.nih.gov/21742485/
van Rossum PSN, Mohammad NH, Vleggaar FP, van Hillegersberg R. Treatment for unresectable or metastatic oesophageal cancer: Current evidence and trends. *Nat Rev Gastroenterol Hepatol*. 2018;15(4):235-249.	https://pubmed.ncbi.nlm.nih.gov/29235549/
Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial*. Lancet* Oncol. 2014;15(11):1224-1235.	https://pubmed.ncbi.nlm.nih.gov/25240821/

HER2+ Directed Studies and Trials

Citation	Address
Ajani JA, D'Amico TA, Almhanna K, et al. Gastric Cancer, Version 3.2016, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2016;14(10):1286-1312.	https://jnccn.org/view/journals/jnccn/14/10/article-p1286.xml

Al-Batran SE, Hartmann JT, Probst S, et al. Phase III trial in metastatic gastroesophageal adenocarcinoma with fluorouracil, leucovorin plus either oxaliplatin or cisplatin: A study of the Arbeitsgemeinschaft Internistische Onkologie. *J Clin Oncol*. 2008;26(9):1435-1442.	https://pubmed.ncbi.nlm.nih.gov/18349393/
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. *Lancet.* 2010;376(9742):687-697.	https://pubmed.ncbi.nlm.nih.gov/20728210/
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. *J Clin Oncol.* 2013;31(suppl 4): abstract LBA4.	https://ascopubs.org/doi/abs/10.1200/jco.2013.31.4_suppl.lba4
Fuchs C, 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. *J Clin Oncol*. 2020;38:15 (suppl 15):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. *Lancet.* 2014;383(9911):31-39.	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(13)61719-5/fulltext
Guimbaud R, Louvet C, Ries P, et al. Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: A French intergroup	https://pubmed.ncbi.nlm.nih.gov/25287828/

(Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) study. *J Clin Oncol.* 2014;32(31):3520-3526.	
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. *J Clin Oncol*. 2016;34(5):443-451.	https://ascopubs.org/doi/10.1200/JCO.2015.62.6598
Hubbard SR. EGF receptor inhibition: Attacks on multiple fronts. *Cancer Cell.* 2005;7(4):287-288.	https://www.cell.com/cancer-cell/fulltext/S1535-6108(05)00100-5
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. *Lancet Oncol.* 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. *J Clin Oncol.* 2012;30(13):1513-1518.	https://ascopubs.org/doi/10.1200/JCO.2011.39.4585
Krop IE, Beeram M, Modi S, et al. Phase I study of trastuzumab-DM1, an HER2 antibody-drug conjugate, given every 3 weeks to patients with HER2-positive metastatic breast cancer. *J Clin Oncol*. 2010;28(16):2698-2704.	https://pubmed.ncbi.nlm.nih.gov/20421541/
Mahato R, Tai W, Cheng K. Prodrugs for improving tumor targetability and efficiency. *Adv Drug Deliv Rev*. 2011;63(8):659-670.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3132824/

Makiyama A, et al. A randomized phase II study of weekly paclitaxel ± trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT). *J Clin Oncol.* 2018;36(suppl 15):4011	https://ascopubs.org/doi/abs/10.1200/JCO.2018.36.15_suppl.4011
Molina MA, Codony-Servat J, Albanell J, Rojo F, Arribas J, Baselga J. Trastuzumab (herceptin), a humanized anti-Her2 receptor monoclonal antibody, inhibits basal and activated Her2 ectodomain cleavage in breast cancer cells. *Cancer Res.* 2001;61(12):4744-4749.	https://pubmed.ncbi.nlm.nih.gov/11406546/
Fuchs C, et al. Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): An international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet.* 2014;383(9911):31-39.	https://pubmed.ncbi.nlm.nih.gov/24094768/
Petit AM, Rak J, Hung MC, et al. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells in vitro and in vivo: Angiogenic implications for signal transduction therapy of solid tumors. *Am J Pathol.* 1997;151(6):1523-1530.	https://pubmed.ncbi.nlm.nih.gov/9403702/
Scheuer W, Friess T, Burtscher H, Bossenmaier B, Endl J, Hasmann M. Strongly enhanced antitumor activity of trastuzumab and pertuzumab combination treatment on HER2-positive human xenograft tumor models. *Cancer Res.* 2009;69(24):9330-9336.	https://pubmed.ncbi.nlm.nih.gov/19934333/

Shitara K, Özgüroğlu M, Bang YJ, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): A randomised, open-label, controlled, phase 3 trial. *Lancet*. 2018;392(10142):123-133.	https://pubmed.ncbi.nlm.nih.gov/29880231/
Tabernero J, Hoff PM, Shen L, et al. Pertuzumab plus trastuzumab and chemotherapy for HER2-positive metastatic gastric or gastro-oesophageal junction cancer (JACOB): Final analysis of a double-blind, randomised, placebo-controlled phase 3 study. *Lancet Oncol.* 2018;19(10):1372-1384.	https://pubmed.ncbi.nlm.nih.gov/30217672/
Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer*. 2011;47(15):2306-2314.	https://pubmed.ncbi.nlm.nih.gov/21742485/
Thuss-Patience PC, Shah MA, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): An international randomised, open-label, adaptive, phase 2/3 study. *Lancet Oncol.* 2017;18(5):640-653.	https://pubmed.ncbi.nlm.nih.gov/28343975/
Wilke H, Muro K, Van Cutsem E, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): A double-blind, randomised phase 3 trial. *Lancet Oncol*. 2014;15(11):1224-1235.	https://pubmed.ncbi.nlm.nih.gov/25240821/

zum Büschenfelde CM, Hermann C, Schmidt B, Peschel C, Bernhard H. Antihuman epidermal growth factor receptor 2 (HER2) monoclonal antibody trastuzumab enhances cytolytic activity of class I-restricted HER2-specific T lymphocytes against HER2-overexpressing tumor cells. *Cancer Res*. 2002;62(8):2244-2247.	https://pubmed.ncbi.nlm.nih.gov/11956077/

2nd Line Therapies in HER2+ Gastric Cancer

Citation	Address
Shitara K, Bang YJ, Iwasa S, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. *N Engl J Med*. 2020;382(25):2419-2430.	https://pubmed.ncbi.nlm.nih.gov/32469182/
Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): A randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2018;19(11):1437-1448.	https://pubmed.ncbi.nlm.nih.gov/30355453/
Shitara K, Tabernero J, Dvorkin M et al. Overall survival results from a phase III trial of trifluridine/tipiracil versus placebo in patients with metastatic gastric cancer refractory to standard therapies (TAGS). *Annal Oncol.* 2018;29(suppl 9):IX55.	https://www.annalsofoncology.org/article/S0923-7534(19)43142-6/fulltext
U.S. Food and Drug Administration. FDA approves Lonsurf for recurrent, metastatic gastric and gastroesophageal junction adenocarcinoma. February 2019.	https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-lonsurf-recurrent-metastatic-gastric-and-gastroesophageal-junction-adenocarcinoma