In the Medical Spotlight: **Antibody-Drug Conjugates in Advanced HER2-Positive Gastric/Gastroesophageal Junction Cancer**

June 30, 2023

Barcelona, Spain

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Welcome and Introductions

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Disclosures

John L. Marshall, MD

Consulting Fees: AstraZeneca, Bayer Corporation, Caris, Merck & Co., Inc., Pfizer, Seagen, Taiho Oncology

Employee of an ineligible company: Indivumed

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Consulting Fees: Astellas, Bristol Myers Squibb, Merck, MSD, Roche

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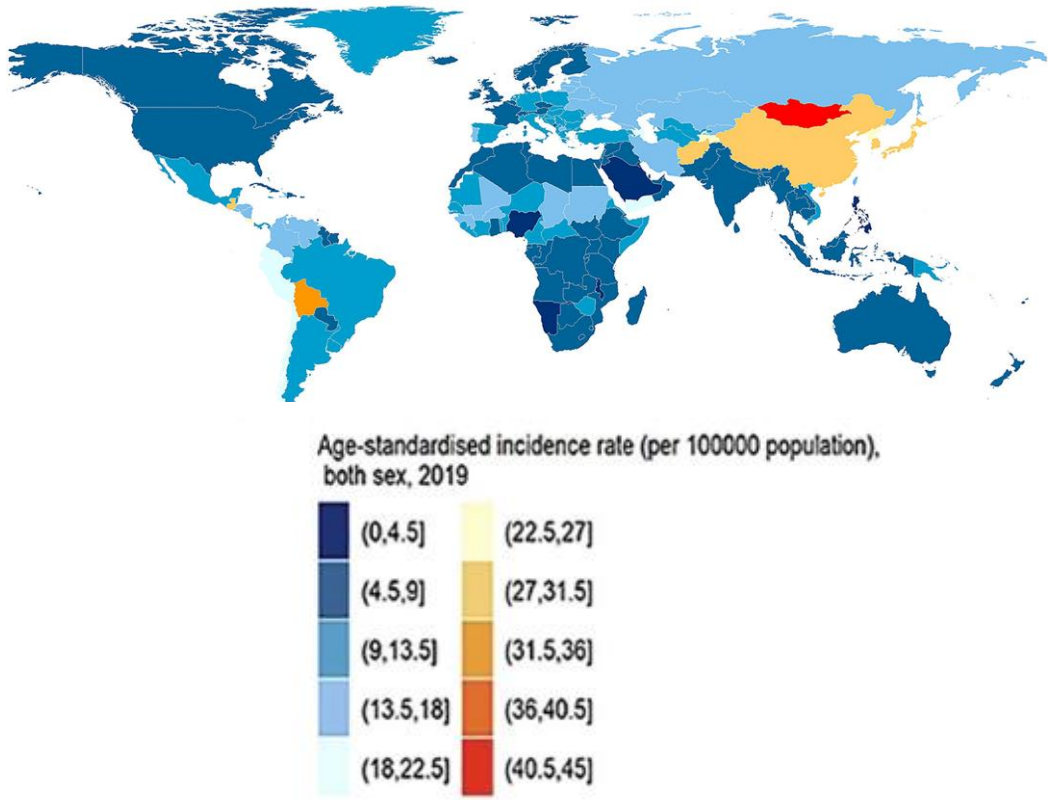
Elizabeth Smyth, MD

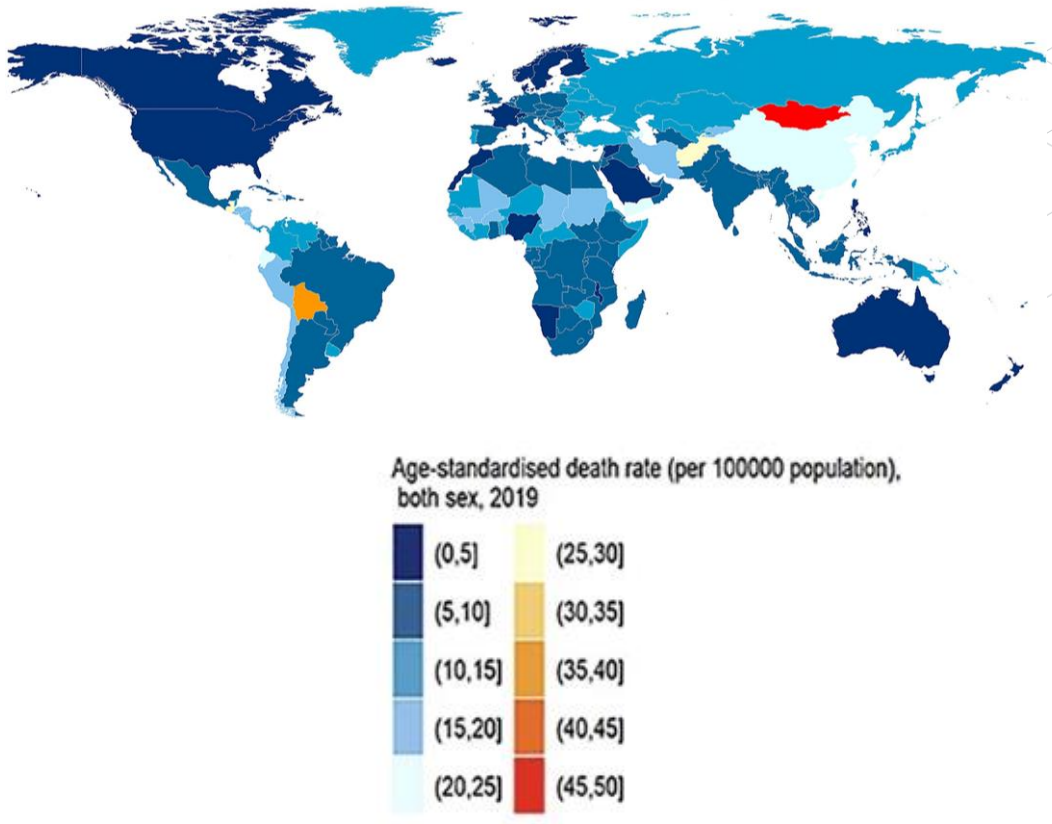
Consulting Fees: Amgen, Astellas, AstraZeneca, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Inc., Elsevier, Imdex, Merck, Novartis, Pfizer, SAI Med, Servier, touchONCOLOGY, Turning Point Therapeutics, Viracta, Zymeworks

Gastric Cancer: Global Challenges

Incidence



Death Rate



Song Y. et al. *Sci Rep*. 2022;12(1):11542.

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Unmet Needs in G/GEJ Cancers

- Third most common cause of cancer deaths globally
- ~80% of patients present with metastatic or unresectable disease
- 5-year relative survival in US: 33%
  - Distant disease: 6%
  - Regional: 33%
  - Localized: 72%
- Goal of current initial treatment for AGC
  - Prolong survival
  - Reduce cancer-related symptoms
  - Improve QoL
- Biomarkers: HER2, MSS/MMR status, PD-L1 expression
  - When to test? How do they guide treatment?

Li JJ, et al. *Biomolecules*. 2023;13(5):796.

A New World With Antibody-Drug Conjugates

HER2 Heterogeneity: Clinical Implications

Mar Iglesias, MD

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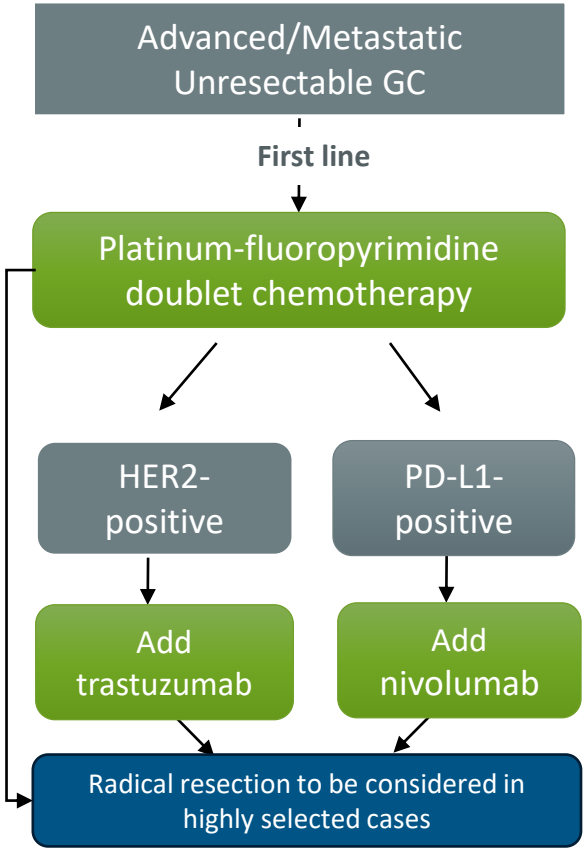
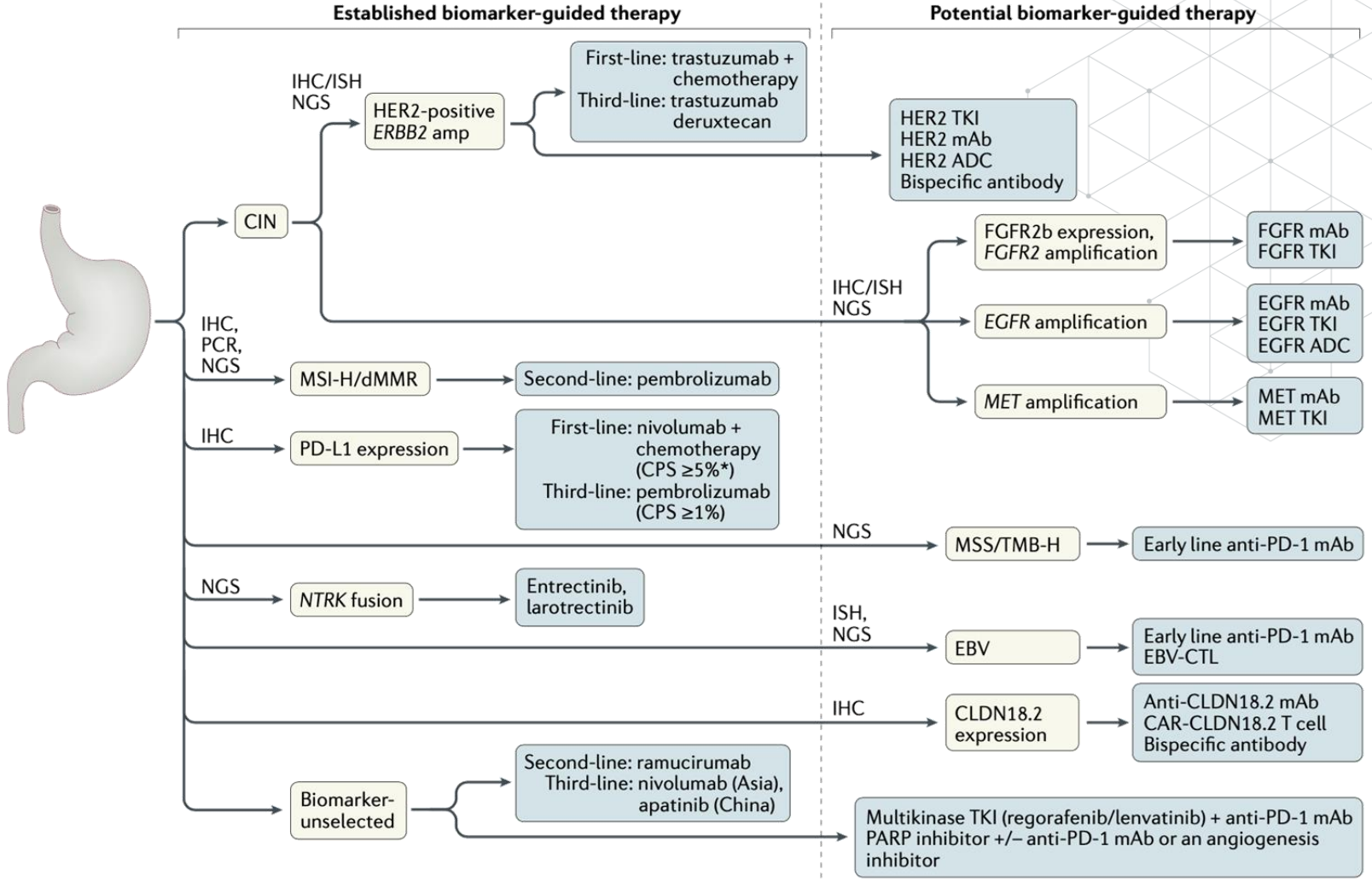
Index

- Gastric cancer and biomarkers
- EGFR Pathway and *HER2* alterations
- HER2 testing:
  - Determination
  - Samples
  - Report and heterogeneity
  - Methods

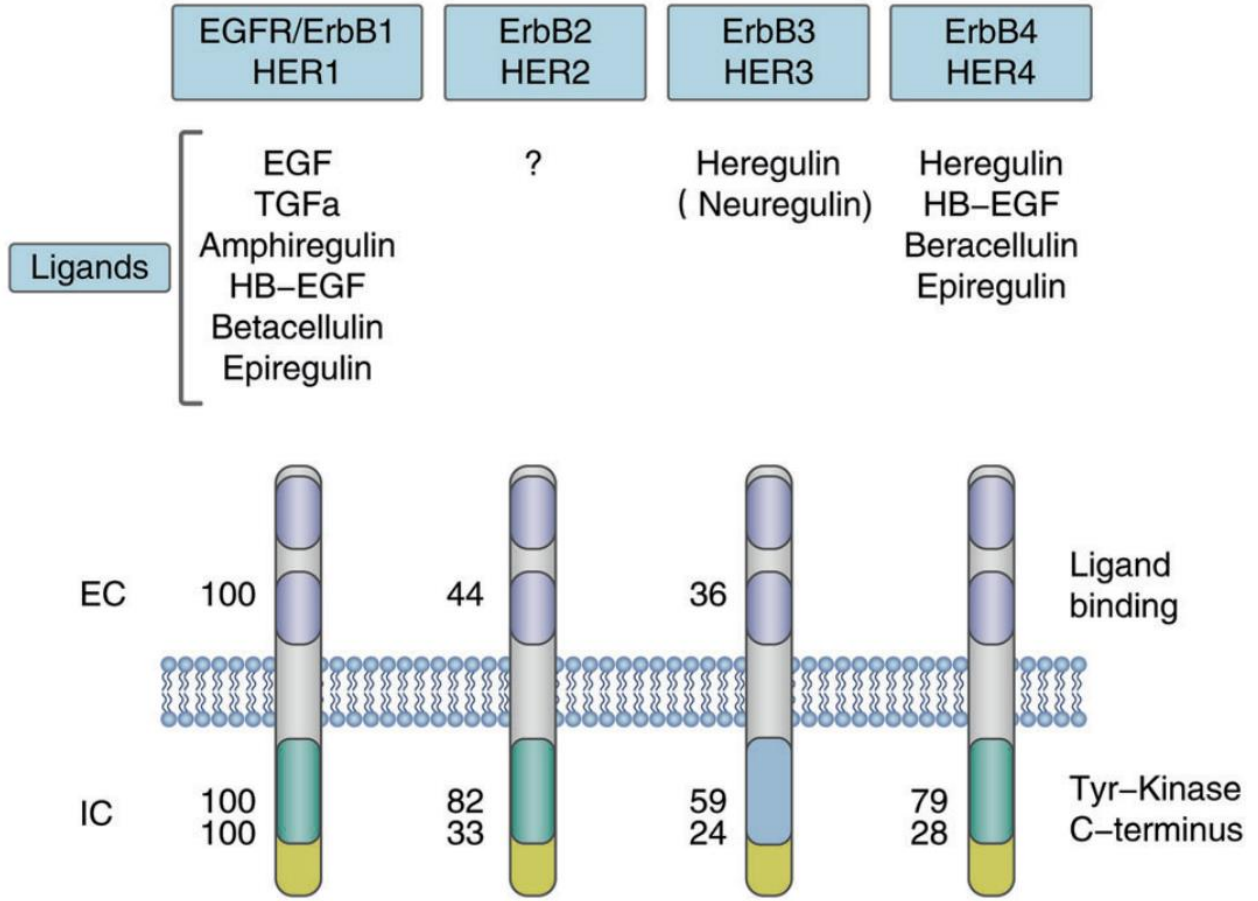
Gastric Cancer and Biomarkers





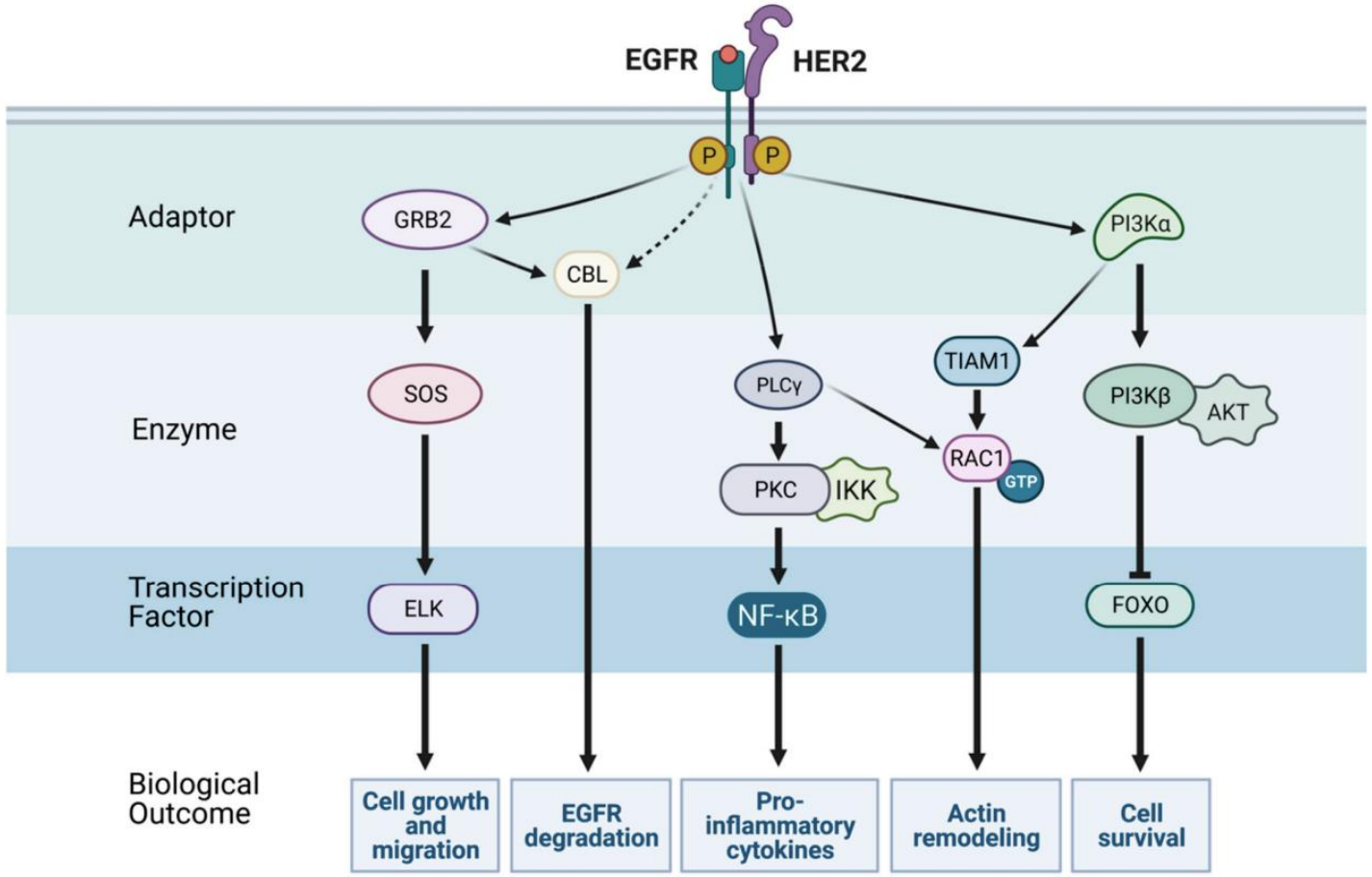
Lordick F, et al. *Ann Oncol*. 2022;33(10):1005-1020. Nakamura Y, et al. *Nat Rev Clin Oncol*. 2021;18(8):473-487.

EGFR Pathway and *HER2* Alterations



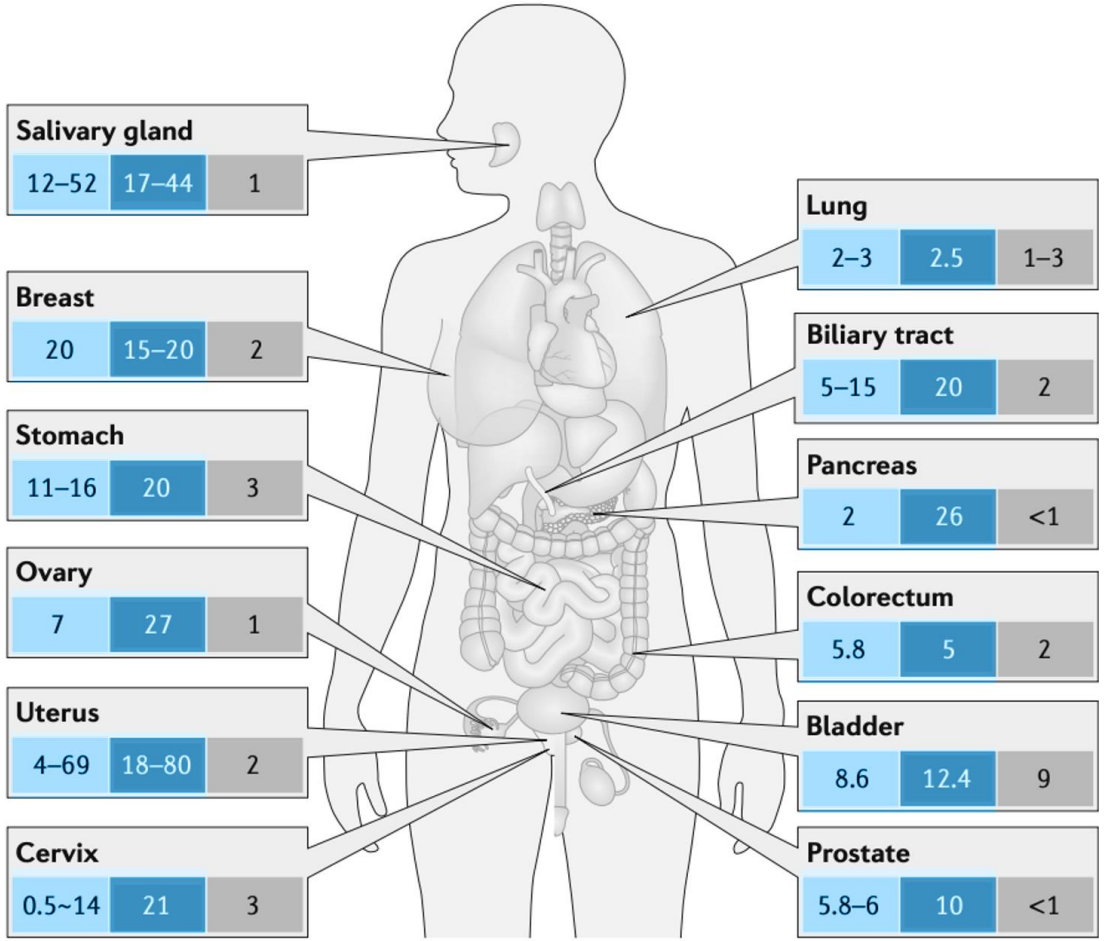
Wang J, et al. *Signal Transduct Target Ther*. 2019;4:34.

EGFR Pathway and *HER2* Alterations (cont)



Uribe ML, et al. *Cancers (Basel)*. 2021;13(11):2748.

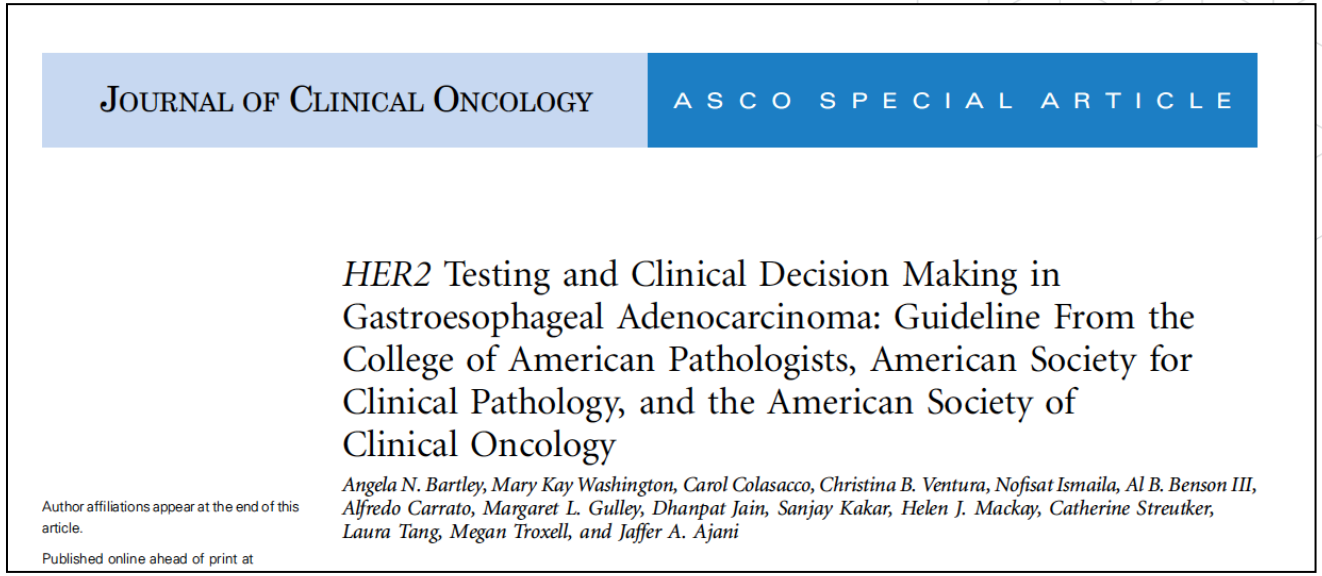
EGFR Pathway and *HER2* Alterations



Oh DY, Bang YJ. *Nat Rev Clin Oncol*. 2020;17(1):33-48.

HER2 Testing

- Principal aspects for HER2 testing:
  - Choice of **scoring criteria** – different from breast
  - Choice of **sample** with regards to cancer - heterogeneity
  - Choice of HER2 **evaluation methods** – IHC and ISH first



JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma: Guideline From the College of American Pathologists, American Society for Clinical Pathology, and the American Society of Clinical Oncology

Angela N. Bartley, Mary Kay Washington, Carol Colasacco, Christina B. Ventura, Nofisat Ismaila, Al B. Benson III, Alfredo Carrato, Margaret L. Gulley, Dhanpat Jain, Sanjay Kakar, Helen J. Mackay, Catherine Streutker, Laura Tang, Megan Troxell, and Jaffer A. Ajani

Author affiliations appear at the end of this article.

Published online ahead of print at

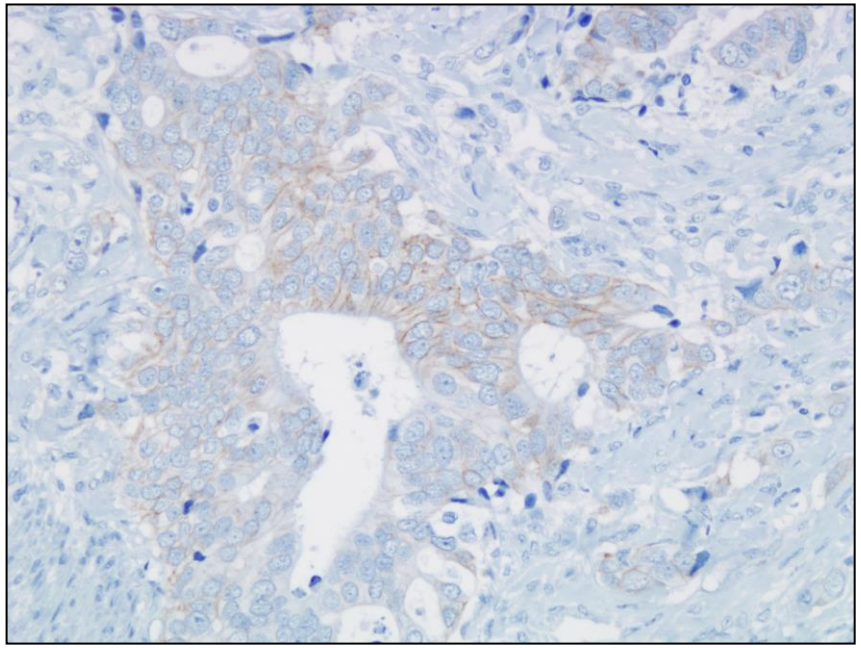
Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464. Grillo F, et al. *World J Gastroenterol*. 2016;22(26):5879-5887.

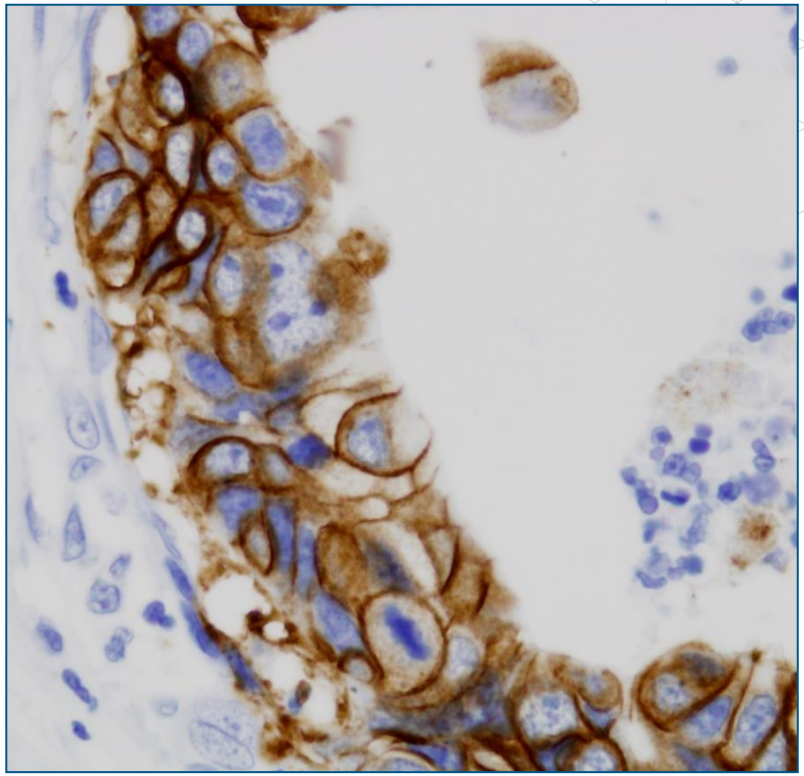
Scoring Criteria

Histopathology 2008, **52**, 797–805. DOI: 10.1111/j.1365-2559.2008.03028.x

Assessment of a HER2 scoring system for gastric cancer: results from a validation study

M Hofmann,[1] O Stoss,[2] D Shi,[3] R Büttner,[2,4] M van de Vijver,[5] W Kim,[6] A Ochiai,[7] J Rüschoff[1,2] & T Henkel[2]

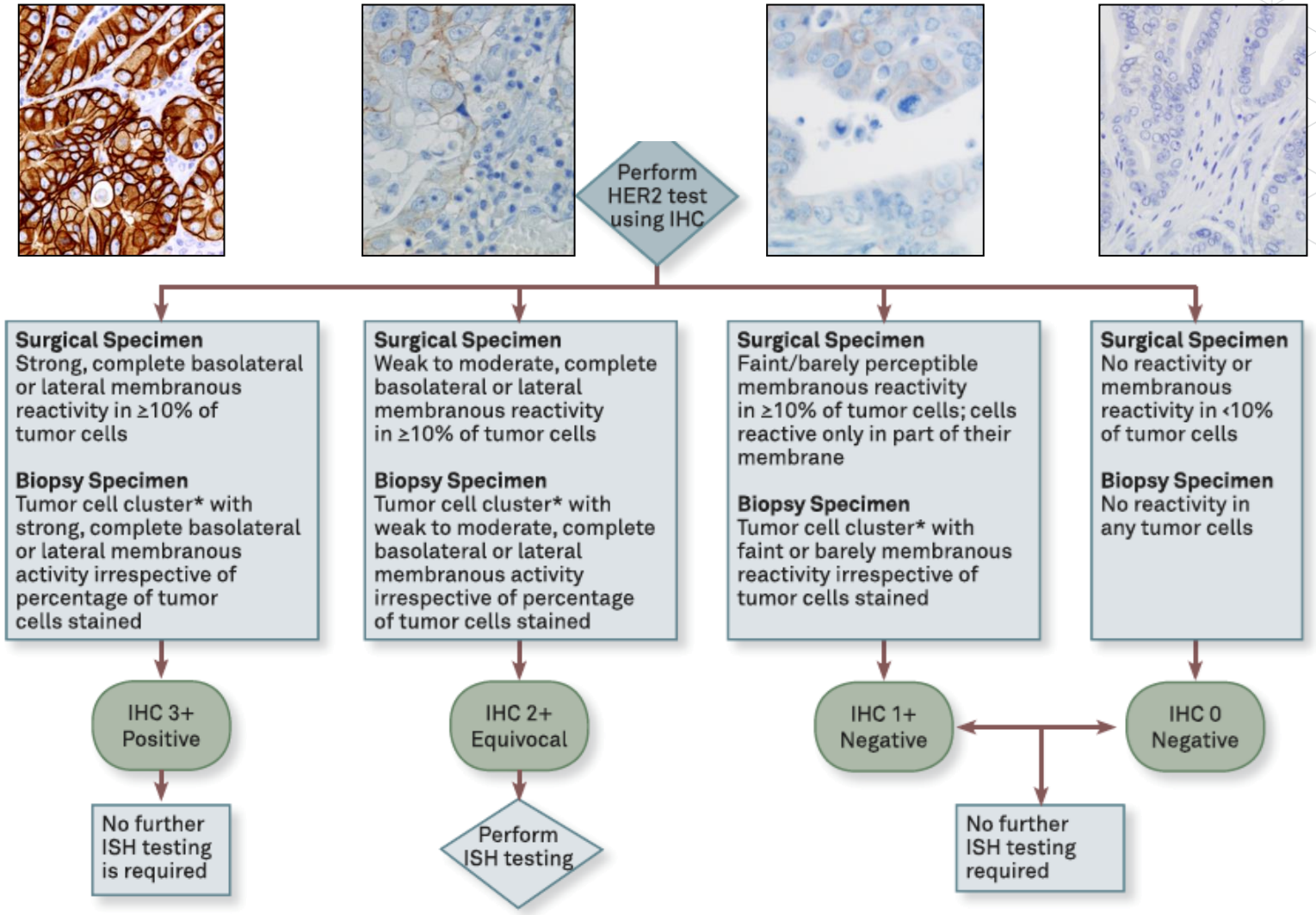




Basolateral positivity

Hofmann M, et al. *Histopathology*. 2008;52(7):797-805.

Scoring Criteria



Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464.

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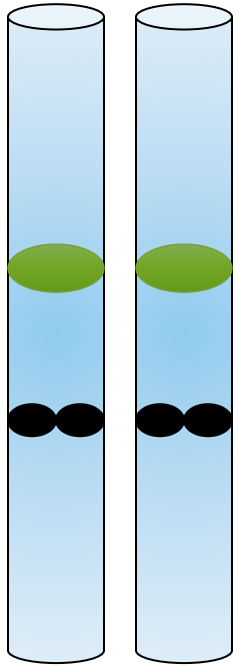
Scoring Criteria



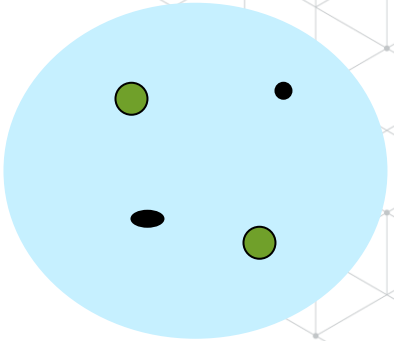
Centromere 17

Locus 17q21 (HER2)

Chromosome 17

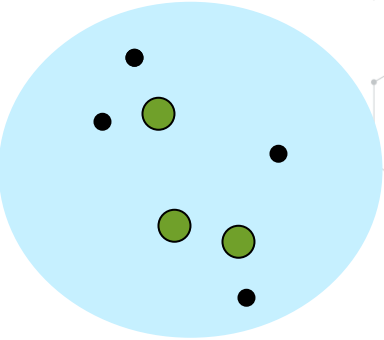
Ratio:
mean number of HER2 copies/
mean number of copies centromere

Normal cell



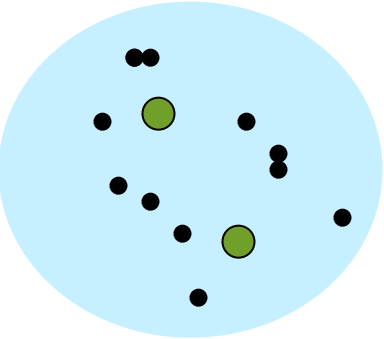
Ratio = 1

Polysomal cell



Ratio = 1.3

Amplified cell



Ratio = 5.5

Bartley AN, et al. J Clin Oncol. 2017;35(4):446-464.

Scoring Criteria

Count 20 Cells Grouped

If Ratio ≥ 2.0

If Ratio < 2 and
HER2 ≥ 4 and < 6

Count 20 extra cells

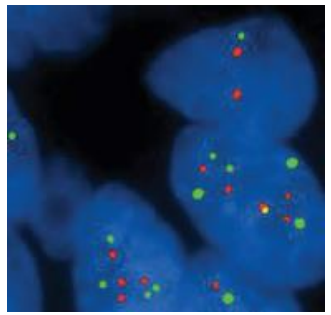
If Ratio < 2

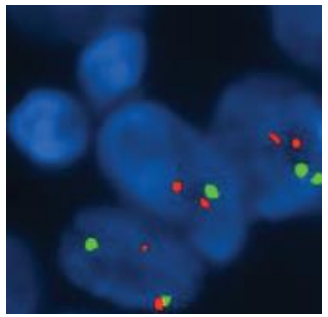
Perform counting in several zones (heterogeneity)

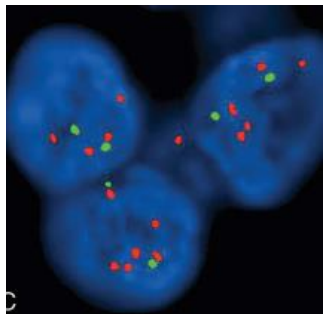
ISH Positive

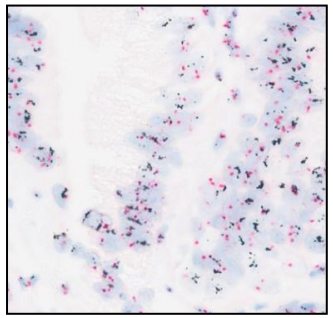
ISH Inconclusive

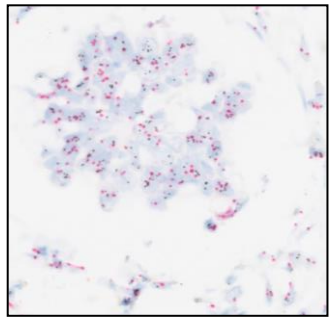
ISH Negative

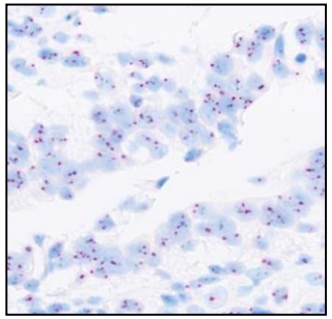












Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464.

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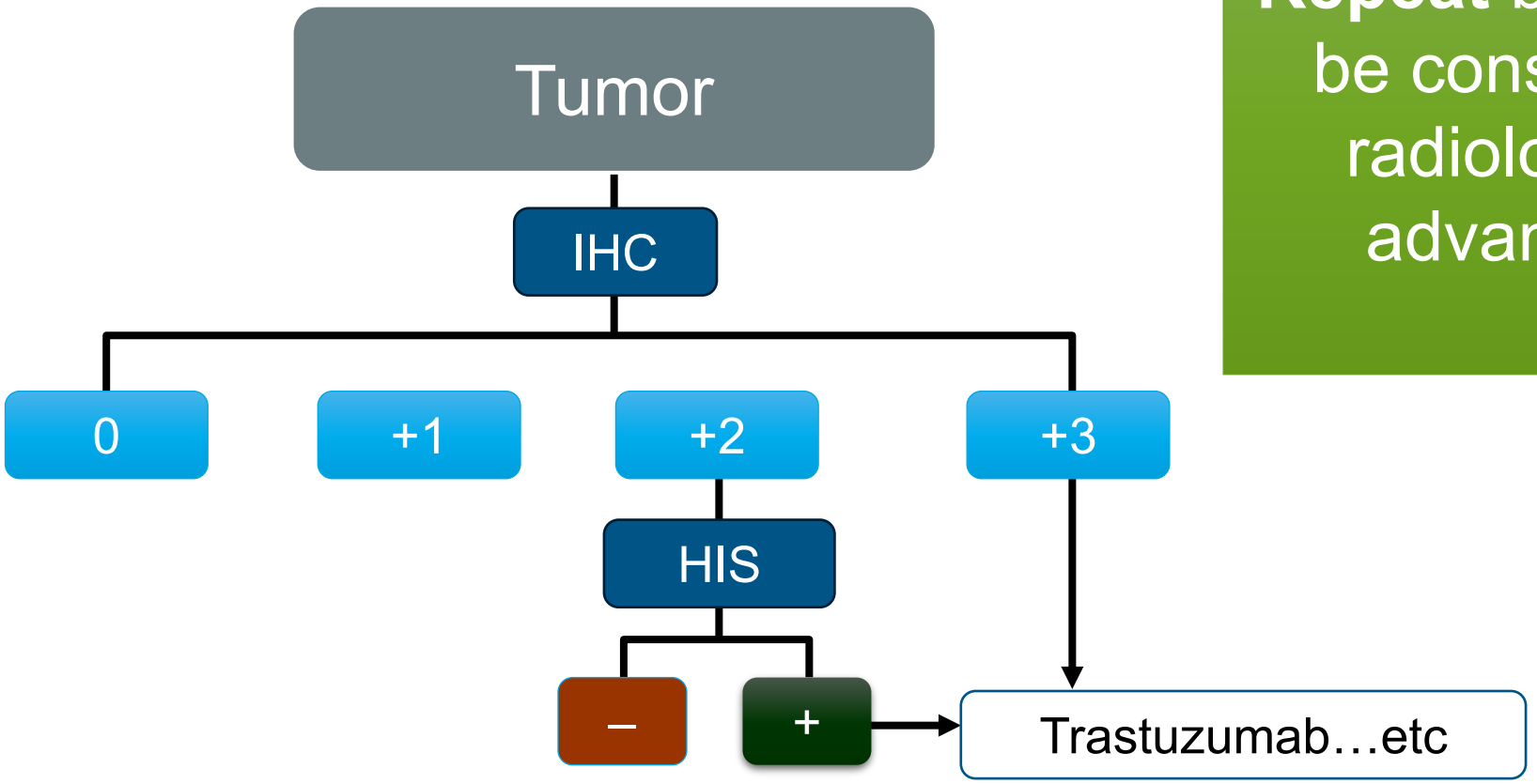
Scoring Criteria

- If HER2/CEP17 <2, but there are **more than 6 copies** of HER2 = Positive, **amplified** HIS
- If HER2/CEP17 <2, but there are **fewer than 4 copies** of HER2 = Negative, **not amplified**
- If HER2/CEP17 <2, and there are between **4 and 6 copies** of HER2 = **Inconclusive**; read 20 more cores, and if **inconclusive** again:
  - Select other areas
  - Use another test to analyze chromosome 17
  - Use genomics

Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464.

Scoring Criteria



Repeat biomarker testing may be considered at clinical or radiologic progression of advanced or metastatic disease

Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464. Viale G. HER2 in Gastric Cancer: ESMO Biomarker Factsheet. Accessed June1, 2023. https://oncologypro.esmo.org/education-library/factsheets-on-biomarkers/her2-in-gastric-cancer

Samples

- HER2-positive GC/GEJC are more frequently of i**ntestinal type or mixed**
- In mixed-type carcinomas, samples with a prevalence of intestinal-type areas should be selected when performing HER2 evaluation
- **Gastroesophageal carcinomas** tend to be more often HER2-positive (33%) compared to GC (21%) according to the ToGA trial and its post hoc exploratory analysis

Grillo F, et al. *World J Gastroenterol*. 2016;22(26):5879-5887.

Samples

- **Primary or metastases are valid**
- **High concordance between primary and metastases**
  - Discordance rate: 1-14%
- Possible explanations for discrepancies:
  - Genetic drift or clonal selection of *HER2* mutations during neoplastic progression
  - Intratumor heterogeneity of *HER2*
  - Repeat *HER2* assessment in recurrent sites may be recommended in patients whose initial evaluation was *HER2*-negative
    - > 5.7% *HER2-positive* on biopsy of metastases (GASTHER 1 study)

Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464. Grillo F, et al. *World J Gastroenterol*. 2016;22(26):5879-5887.

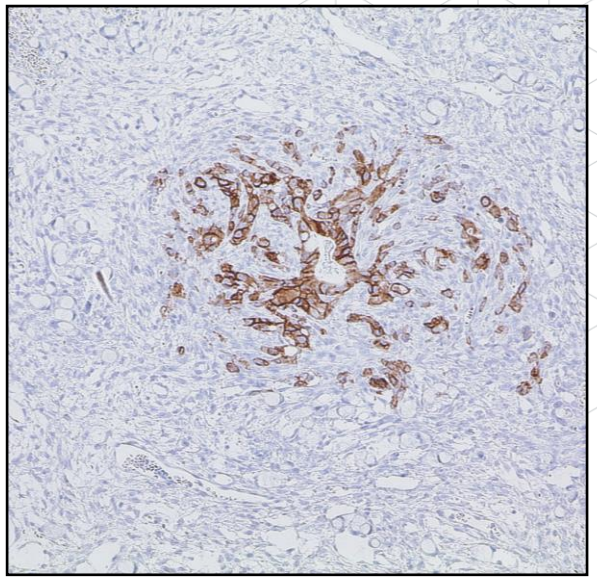
Samples

- **Biopsy or surgical specimen are valid:**
  - Concordance rates ranging from 45.5-94%
  - A probable explanation for false negative *HER2* status on biopsy is **heterogeneity**, whereas
  - *HER2* positivity on biopsy and not on surgical resections may be due to **prolonged cold ischemia and/or over- or under-fixation in larger specimens**

Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464. Grillo F, et al. *World J Gastroenterol*. 2016;22(26):5879-5887.

Samples

- If it is biopsy:
  - **Minimum 4 tumor fragments**
  - **Ideal between 6 and 8 fragments**
- **Multi-block analysis has shown to increase sensitivity** and accuracy
  - False negative rates for one-block analysis compared to multi-block analysis are between 7-10%
- Cytology cell block may be valid if you do not have a biopsy or surgical specimen



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HER2 Heterogeneity

Heterogeneity in HER2 determination

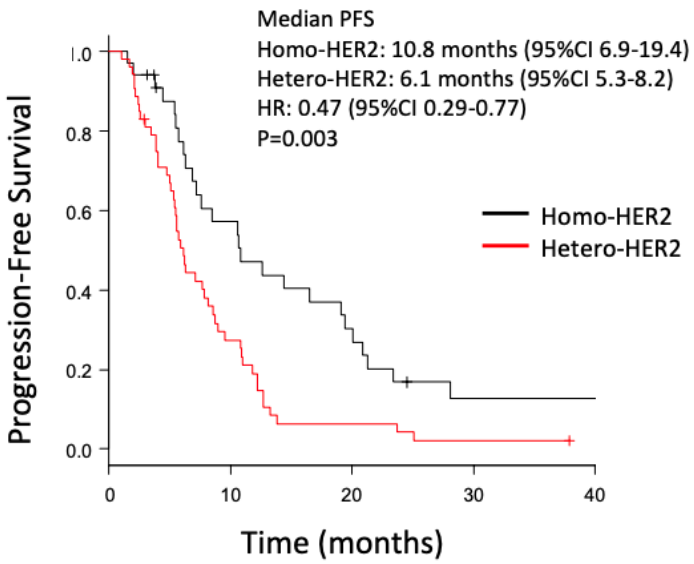
- HER2 heterogeneity by IHC range from 39.0-75.4%
- Up to 34.3% between surgical specimens and biopsy specimens ("intratumoral heterogeneity")
- Up to 11% between primary gastric cancers and metastatic tumors ("intertumoral heterogeneity")

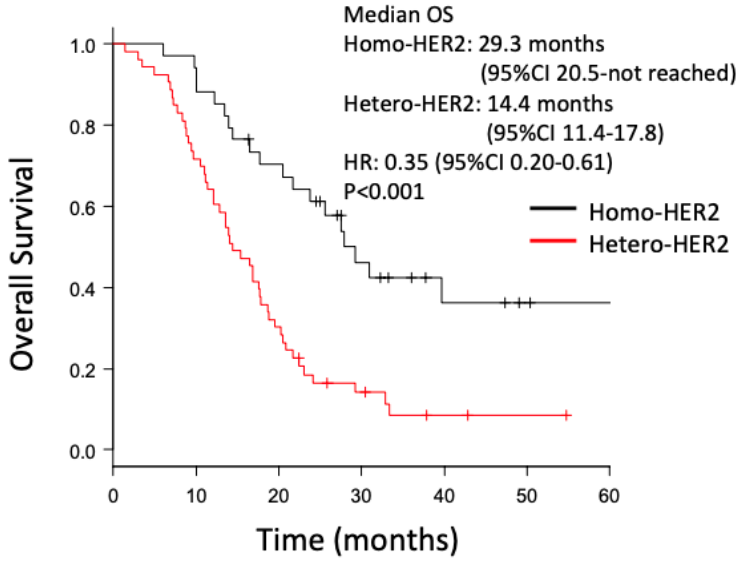
Ahn S, et al. *Oncotarget*. 2015;6(35):38372-38380. Yagi S, et al. *Gastric Cancer*. 2019;22(3):526.

HER2 Heterogeneity

Clinical significance of HER2 heterogeneity

- Higher response rate and a deeper response vs heterogeneous *HER2*-positive gastric cancer





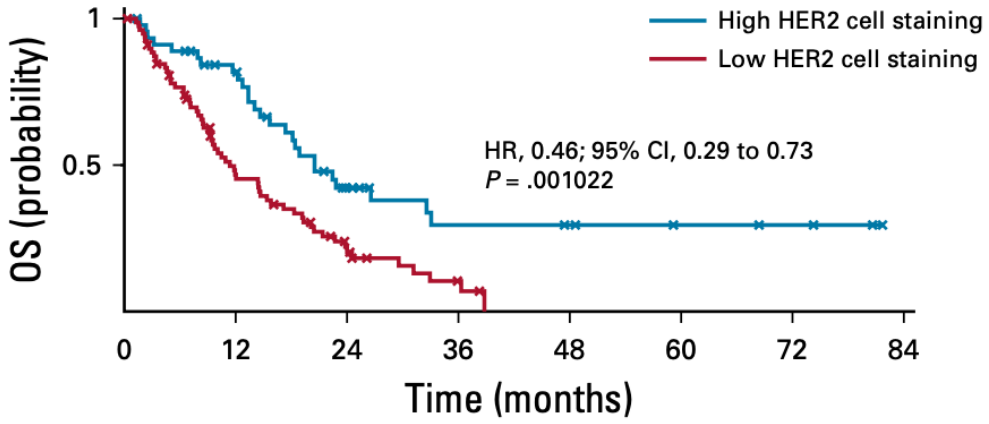
HER2 heterogeneity is a useful biomarker for predicting trastuzumab efficacy

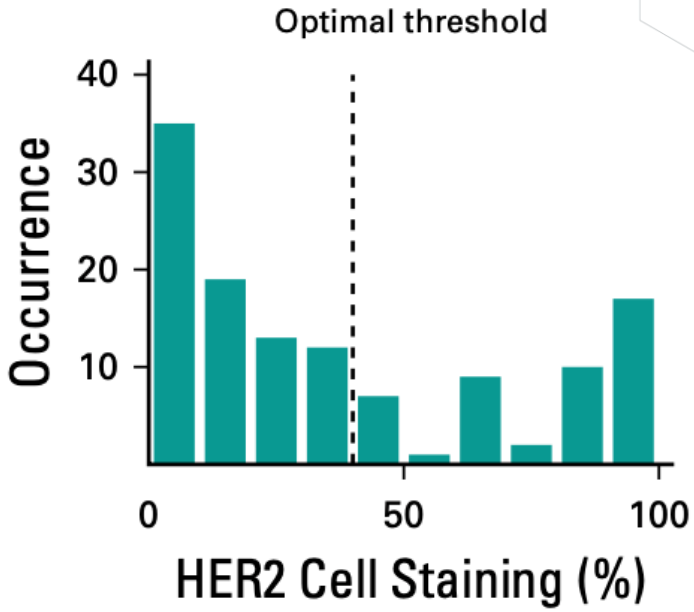
Significantly longer PFS and OS in the homogeneous *HER2*-positive group

Yagi S, et al. *Gastric Cancer*. 2019;22(3):526.

HER2 Heterogeneity

- A minimum of 40% HER2+ tumor cells and a HER2 amplification ratio of ≥3.0 were calculated as optimized thresholds for predicting benefit from trastuzumab





Haffner I, et al. *J Clin Oncol*. 2021;39(13):1468-1478.

Report

Key Reporting Elements
HER2 by immunohistochemistry result
___ Negative (score 0)
___ Negative (score 1+)
___ Equivocal (score 2+)
___ Positive (score 3+)
___ Indeterminate (explain): ____
HER2 (*ERBB2*) by ISH result
___ Negative (not amplified)
___ Positive (amplified)
___ Indeterminate (explain): ____
Number of cells counted: ____
___ Using dual-probe assay
HER2 (*ERBB2*) to CEP17 ratio: ____
Average number of *HER2* (*ERBB2*) signals per cell: ____
Range of number of *HER2* (*ERBB2*) signals per cell: ____
___ Using single-probe assay
Average number of *HER2* (*ERBB2*) signals per cell: ____
Range of number of *HER2* (*ERBB2*) signals per cell: ____
HER2 (*ERBB2*) genomic test (specify findings, eg, gene amplification, nucleotide sequence of specific mutation[s])
___ Negative
___ Positive
___ Indeterminate (explain): ____

Methods
HER2 protein expression by immunohistochemistry
___ FDA cleared (specify test/vendor): ____
___ Laboratory-developed test
Specify primary antibody
___ 4B5
___ HercepTest
___ A0485
___ SP3
___ CB11
___ Other (specify): ____
HER2 (*ERBB2*) gene amplification by ISH
___ FDA cleared (specify test/vendor): ____
___ Laboratory-developed test (specify FISH or ISH, probes, major instrument): ____
Number of observers: ____
HER2 (*ERBB2*) genomic test for amplification or mutation
Laboratory-developed test method: ____

No guidelines for HER2 heterogeneity assessment

The presence of heterogeneity (> 40% or ratio ≥ 3.0) **should be included in our report**

Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464.

Methods

- Recommended methodology for HER2 assessment:
  - IHC
  - ISH
  - NGS
  - Liquid biopsy

Grillo F, et al. *World J Gastroenterol*. 2016;22(26):5879-5887.

Methods

- **Problematic issues on the determination include:**
  - Pre-analytic variables with particular emphasis on **fixation**
- **Standardized tissue handling**
  - Time from biopsy/surgery to fixation (cold ischemia)
  - Type of fixation (10% neutral buffered formalin)
  - Time of fixation (minimum: 8h; maximum: 48h)
  - Freshly cut sections
- Quality assured laboratories with validated and standardized immunohistochemical testing kits

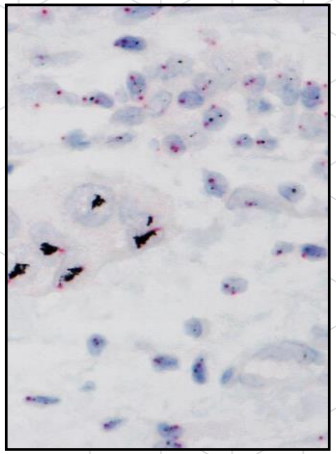
Grillo F, et al. *World J Gastroenterol*. 2016;22(26):5879-5887.

Method

- *HER2* testing in GC should be performed by **IHC as the first approach**
- High concordance rates between IHC protein overexpression and ISH amplification (87-98%)
- Concordance studies between FISH, CISH, and SISH showed high concordance rates (91-100%)
- **Bright field ISH techniques (CISH and SISH) may become the preferred assay** in the future
  - Enable parallel evaluation of the microscopic morphology

Grillo F, et al. *World J Gastroenterol*. 2016;22(26):5879-5887.

Methods: IHC and ISH



- Use **FDA-approved companion diagnostic** tests
- If using method not approved by the FDA, it must be **validated**
- Use appropriate **controls**
- Turnaround time should ideally not exceed 5 working days
- Centralized testing is recommended wherever possible
- All laboratories should be encouraged to participate in validated quality assurance programs

Bartley AN, et al. *J Clin Oncol*. 2017;35(4):446-464. Viale G. HER2 in Gastric Cancer: ESMO Biomarker Factsheet. Accessed June1, 2023. https://oncologypro.esmo.org/education-library/factsheets-on-biomarkers/her2-in-gastric-cancer

Methods: NGS

- **NCCN guidelines**
  - The use of IHC/ISH should be considered first, followed by additional NGS testing as appropriate
  - NGS offers the opportunity to **assess numerous mutations simultaneously**, along with other molecular abnormalities
  - Consider NGS **when limited diagnostic tissue is available**
  - Comprehensive genomic profiling via a **validated NGS assay** performed in a CLIA-approved laboratory may be used

NCCN Guidelines. Gastric Cancer. Version 1.2023.

Methods: Liquid Biopsy

- = identification of genomic alterations of solid cancers by evaluating circulating tumor DNA (ctDNA) in blood
- May be used in patients with **advanced disease**, particularly those who are unable to have a clinical biopsy, **for disease surveillance**
- The detection of mutations/alterations in DNA shed can identify targetable alterations or the **evolution** of clones with altered treatment response profiles
- Use of **validated NGS comprehensive genomic profiling** performed in a CLIA-approved laboratory

NCCN Guidelines. Gastric Cancer. Version 1.2023.

Key Takeaways

- We should test *HER2* in every metastatic/advanced unresectable gastric cancer
- We should follow the current guidelines to test *HER2*
- Inform about heterogeneity of the expression *HER2*
- Options of other methods
  - NGS in tumor samples
  - Liquid biopsy for surveillance

Unmet Needs in Second-Line HER2+ Gastric/Gastroesophageal Junction Cancer

Elizabeth Smyth, MD

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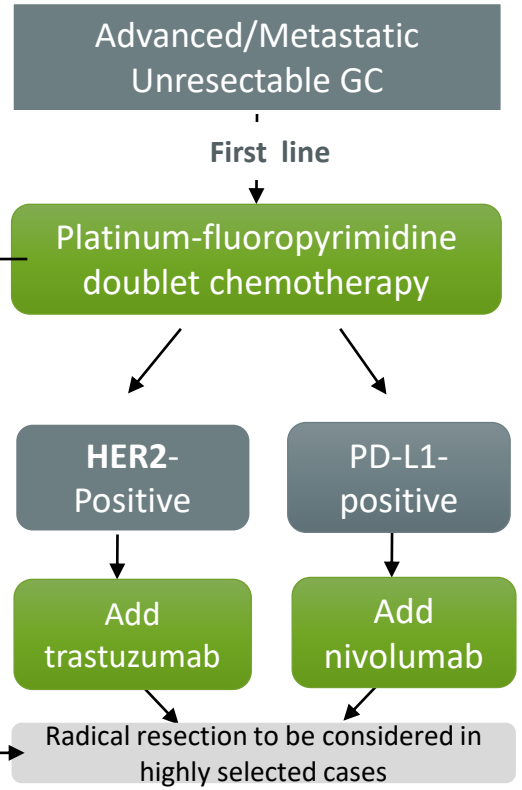
Anti-HER2 Therapy Is Global Standard for HER2-High AGC

ESMO Gastric Cancer Guidelines



Japanese Gastric Cancer Guidelines

First Line

HER2-Negative
- 5-FU + CDDP
- 5-FU/I-LV
- 5-FI/I-LV + PTX
- S-1
- S-1 + DTX

HER2-Positive
- 5-FU + CDDP + T-mAb
- FOLFOX + T-mAb

Second Line

HER2-Negative
- Weekly PTX
- Weekly nab-PTX
- DTX
- IRI
- RAM
- RAM + IRI
- Ram + nab-PTX

HER2-Positive
- Consider combo of T-mAb + chemo in the case o no prior T-mAb

NCCN Gastric Cancer Guidelines

Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease (where local therapy is not indicated)

First-Line Therapy

Oxaliplatin is preferred over cisplatin due to lower toxicity

HER2 overexpression-positive
- Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin and trastuzumab
- Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin and trastuzumab and pembrolizumab
- Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin and trastuzumab (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin and trastuzumab and pembrolizumab

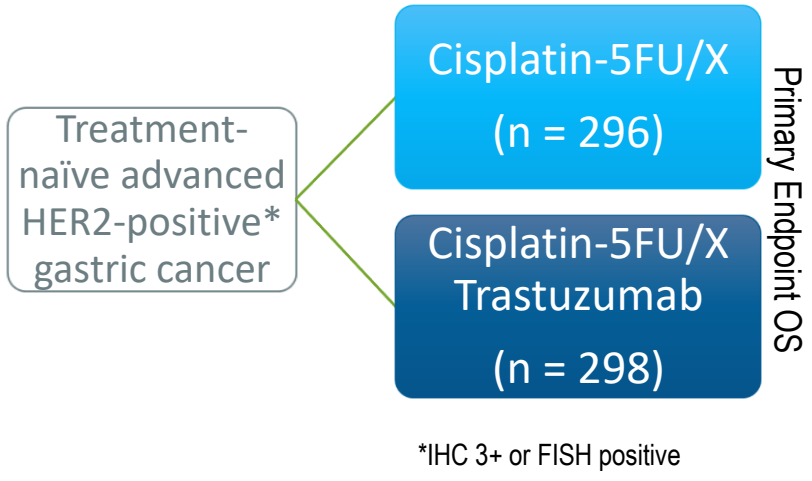
HER2 overexpression-negative
- Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)
- Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin
- Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin

Anti-HER2 therapy is recommended by all international gastric cancer guidelines

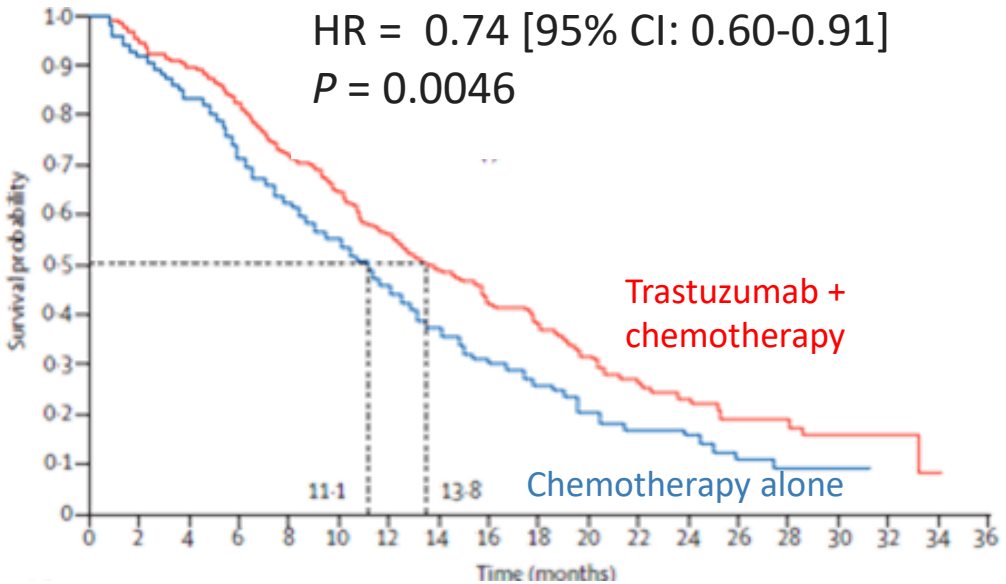
Anti-HER2 Therapy Is a Global Standard of Care for HER2-High Advanced Gastric Cancer

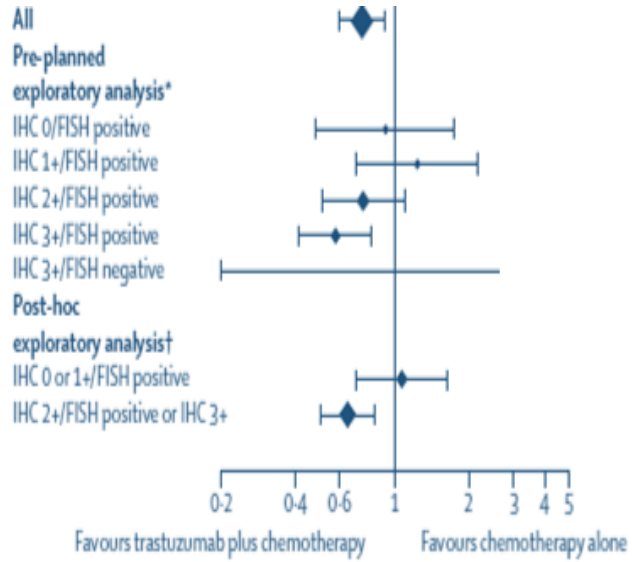
The TOGA trial established the longstanding standard of care

Trial Schema



*IHC 3+ or FISH positive



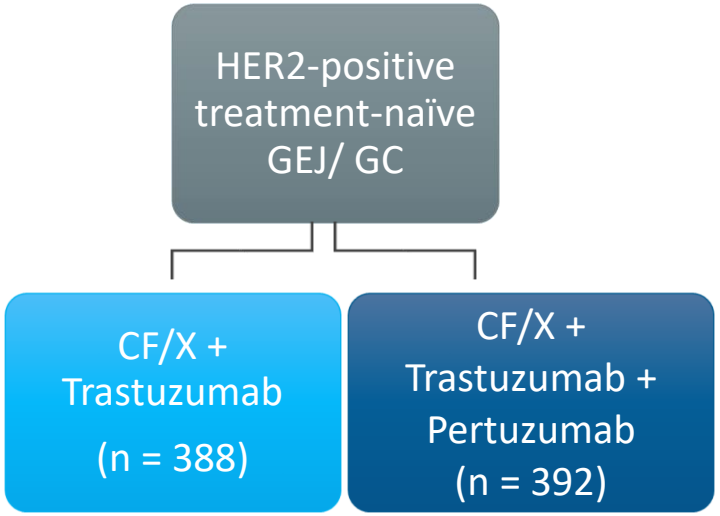


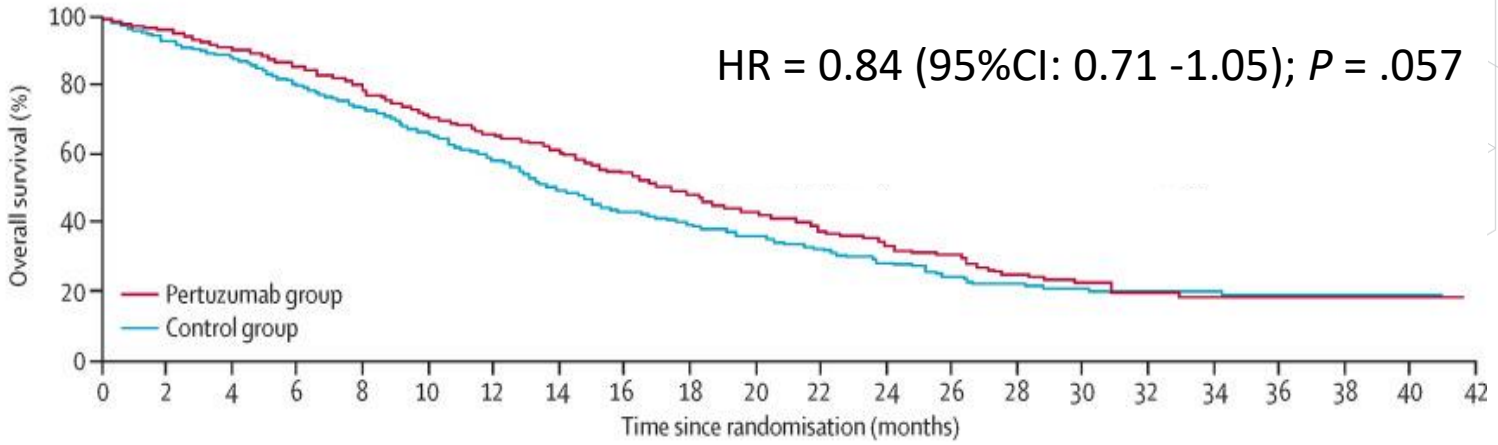
- Addition of trastuzumab to CF/X: ↑ response rate, PFS, and OS
- Trastuzumab is most effective in IHC 3+ or IHC 2+ FISH-positive disease

Bang YJ, et al. *Lancet*. 2010;376(9742):687-697.

JACOB: Trastuzumab + Pertuzumab in HER2-Positive AGC, First-Line Treatment, Initial Results

- JACOB: No significant improvement in OS for trastuzumab + pertuzumab vs trastuzumab alone



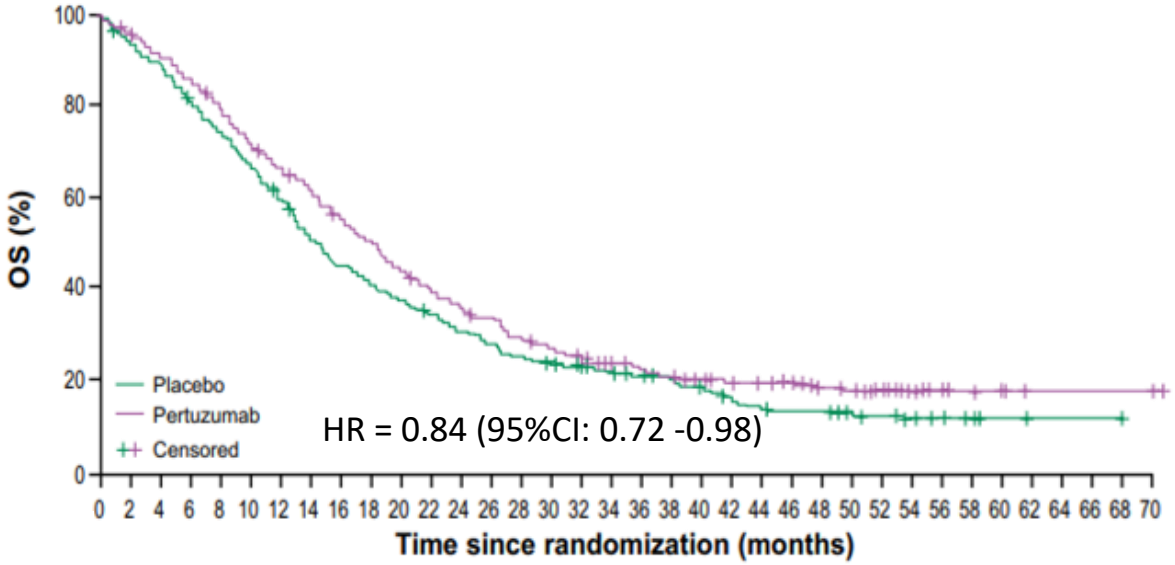


	CF/X + T	CF/X + T + P
ORR, %	56.7	48.3
DOR, mo	10.2	8.4
mPFS, mo	7.0	8.5
	HR = 0.73 (95%CI: 0.62 -0.86)	
mOS, mo	14.2	17.5

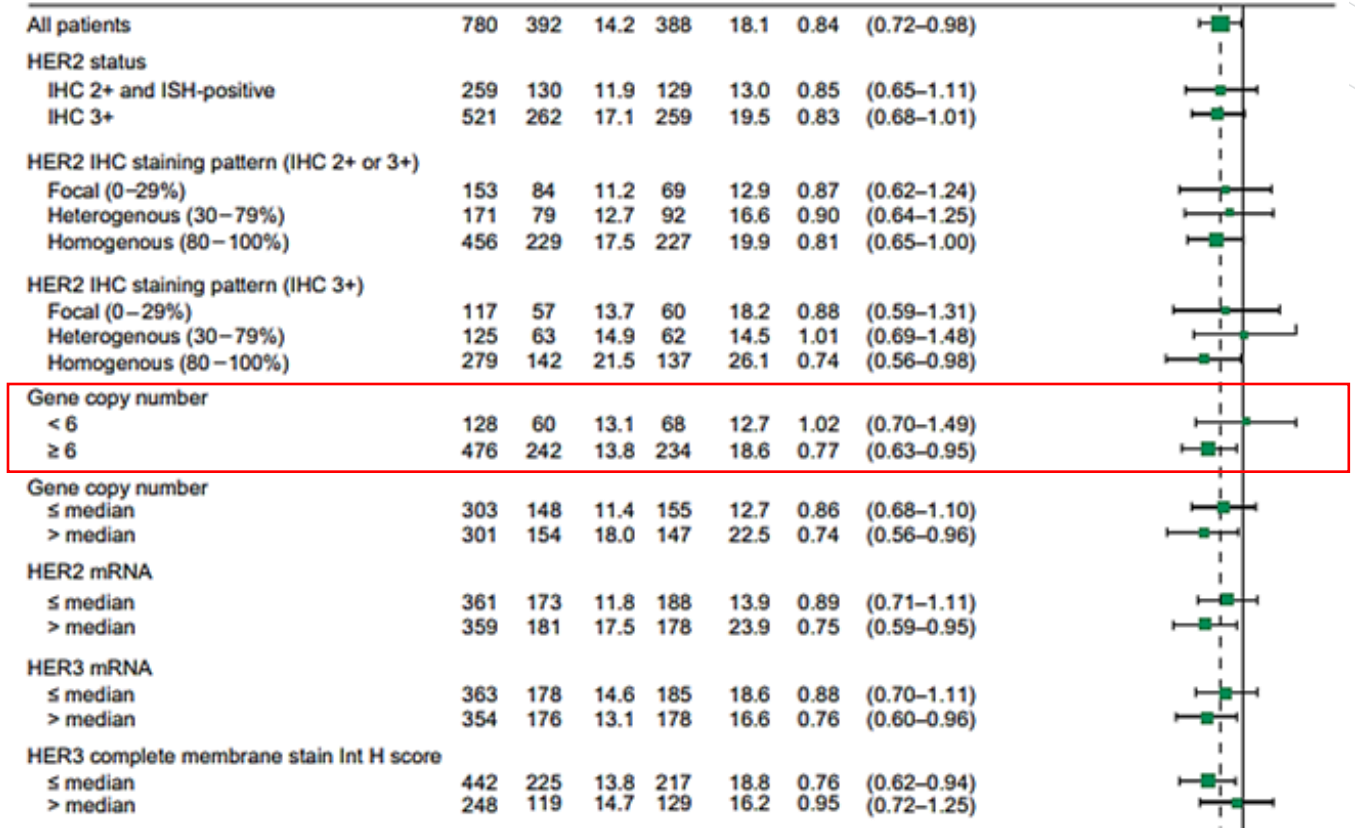
Tabernero J, *Lancet Oncol*.2018;19(10):1372-1384.

CF/X, cisplatin, 5-fluorouracil or capecitabine.

JACOB: Long-Term Follow-Up



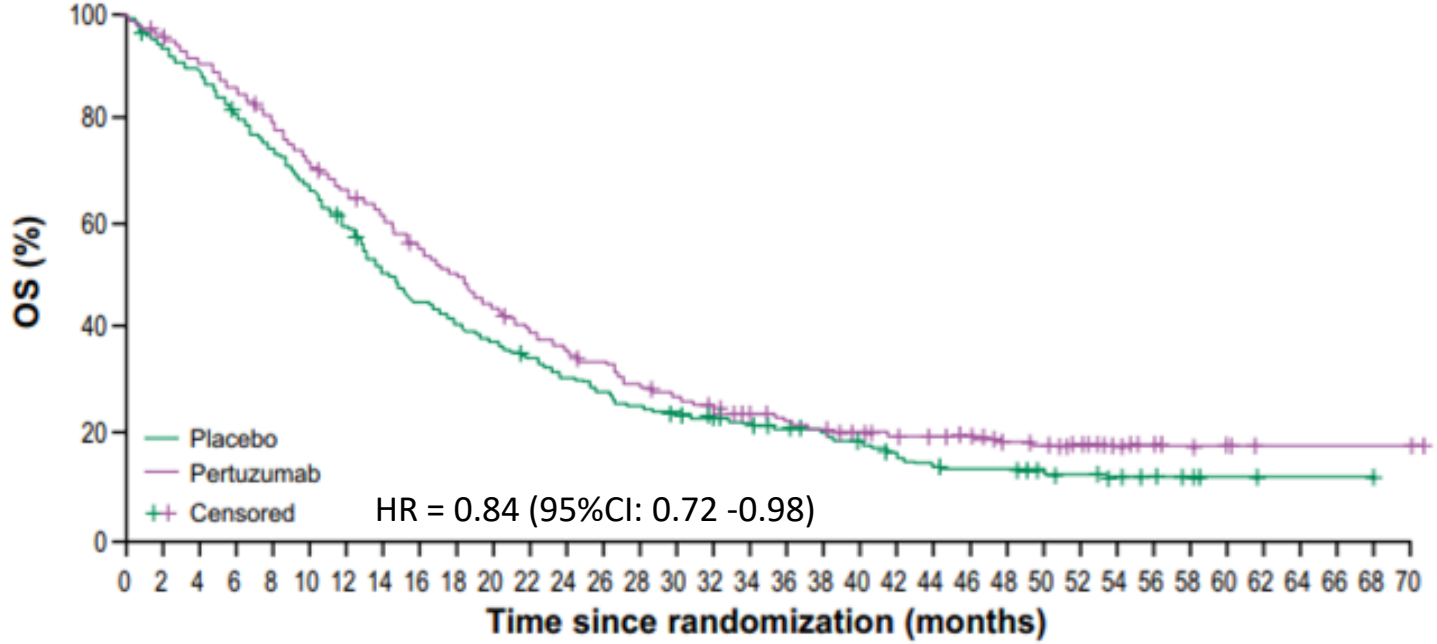
	Total N	Placebo (n = 392) Median n (months)		Pertuzumab (n = 388) Median n (months)		HR	95% Wald CI
All patients	780	392	14.2	388	18.1	0.84	(0.72–0.98)
HER2 status							
IHC 2+ and ISH-positive	259	130	11.9	129	13.0	0.85	(0.65–1.11)
IHC 3+	521	262	17.1	259	19.5	0.83	(0.68–1.01)
HER2 IHC staining pattern (IHC 2+ or 3+)							
Focal (0–29%)	153	84	11.2	69	12.9	0.87	(0.62–1.24)
Heterogenous (30–79%)	171	79	12.7	92	16.6	0.90	(0.64–1.25)
Homogenous (80–100%)	456	229	17.5	227	19.9	0.81	(0.65–1.00)
HER2 IHC staining pattern (IHC 3+)							
Focal (0–29%)	117	57	13.7	60	18.2	0.88	(0.59–1.31)
Heterogenous (30–79%)	125	63	14.9	62	14.5	1.01	(0.69–1.48)
Homogenous (80–100%)	279	142	21.5	137	26.1	0.74	(0.56–0.98)
Gene copy number							
< 6	128	60	13.1	68	12.7	1.02	(0.70–1.49)
≥ 6	476	242	13.8	234	18.6	0.77	(0.63–0.95)
Gene copy number							
≤ median	303	148	11.4	155	12.7	0.86	(0.68–1.10)
> median	301	154	18.0	147	22.5	0.74	(0.56–0.96)
HER2 mRNA							
≤ median	361	173	11.8	188	13.9	0.89	(0.71–1.11)
> median	359	181	17.5	178	23.9	0.75	(0.59–0.95)
HER3 mRNA							
≤ median	363	178	14.6	185	18.6	0.88	(0.70–1.11)
> median	354	176	13.1	178	16.6	0.76	(0.60–0.96)
HER3 complete membrane stain Int H score							
≤ median	442	225	13.8	217	18.8	0.76	(0.62–0.94)
> median	248	119	14.7	129	16.2	0.95	(0.72–1.25)

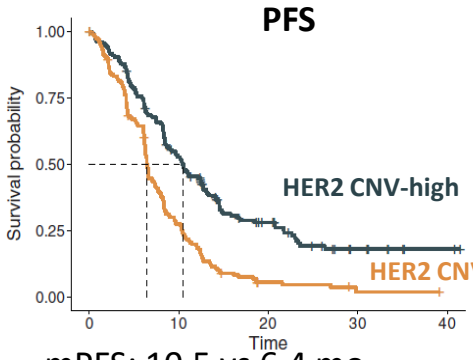


prova SM EDUCATION

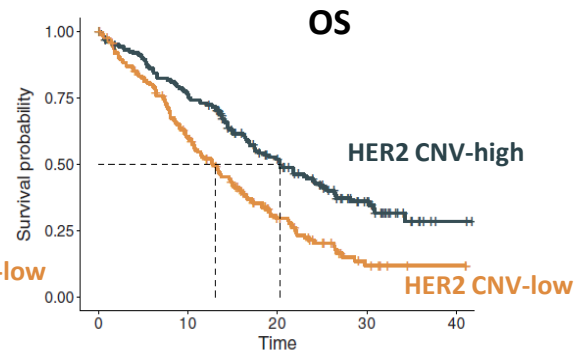
Tabernero J, et al. *Gastric Cancer*. 2023;26(1):123-131. Pietrantonio F, et al. *Clin Cancer Res*. 2023;29(3):571-580.

JACOB: Long-Term Follow-Up

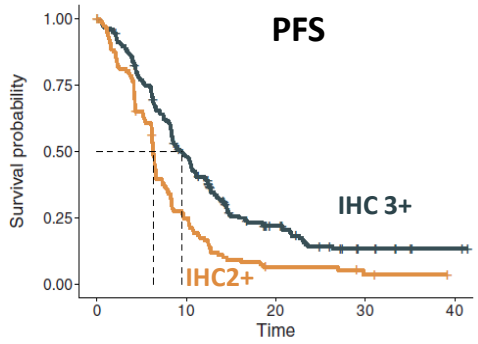




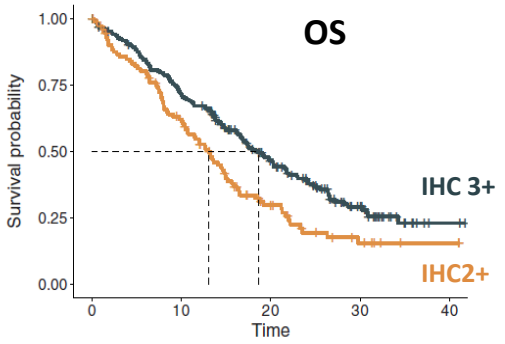
mPFS: 10.5 vs 6.4 mo
HR = 0.48; *P* < 0.001



mOS: 20.3 vs 13.0 mo
HR = 0.54; *P* < 0.001



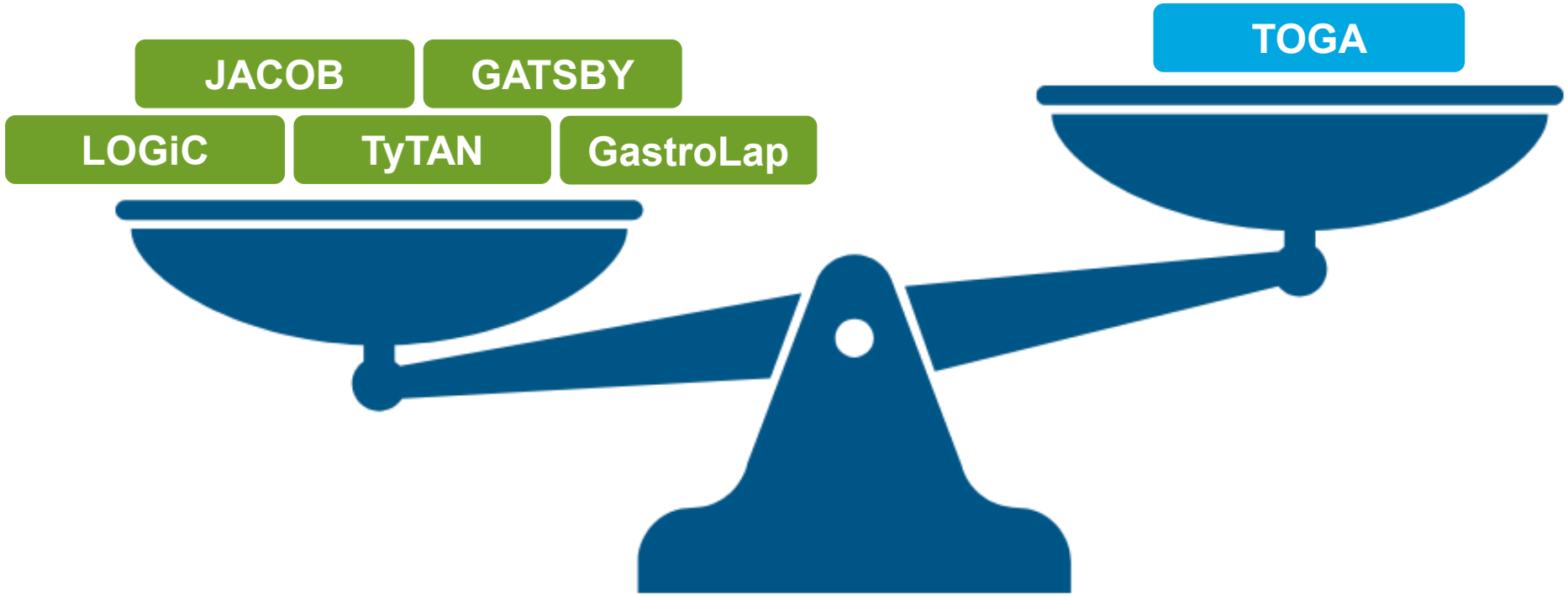
mPFS: 9.5 vs 6.3 mo
HR = 0.55; *P* < 0.001



mOS: 18.6 vs 13.0 mo
HR = 0.64; *P* = 0.002)

Tabernero J, et al. *Gastric Cancer*. 2023;26(1):123-131. Pietrantonio F, et al. *Clin Cancer Res*. 2023;29(3):571-580.

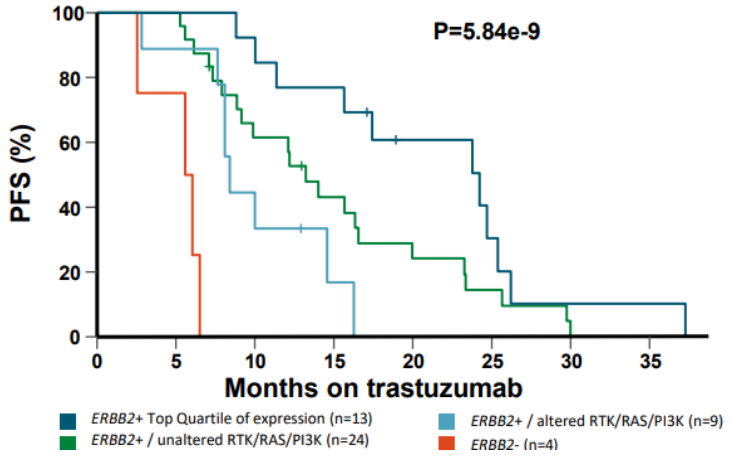
HER2+ AGC Treatment: Why Were So Many Trials Negative?

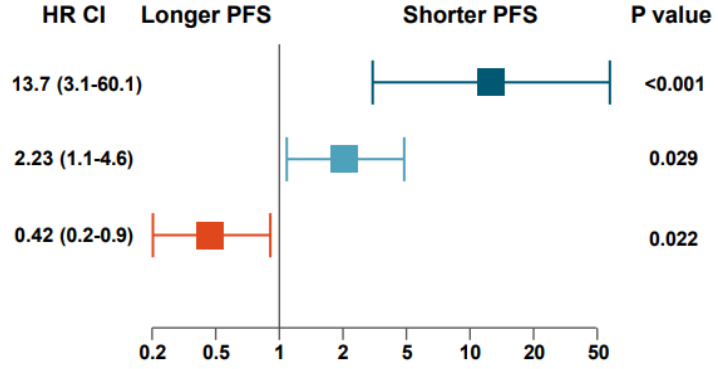


Lorenzen S, et al. Eur J Cancer. 2015;51(5):569-576. Satoh T, et al. J Clin Oncol. 2014;32(19):2039-2049. Hecht JR, et al. J Clin Oncol. 2016;34(5):443-451.

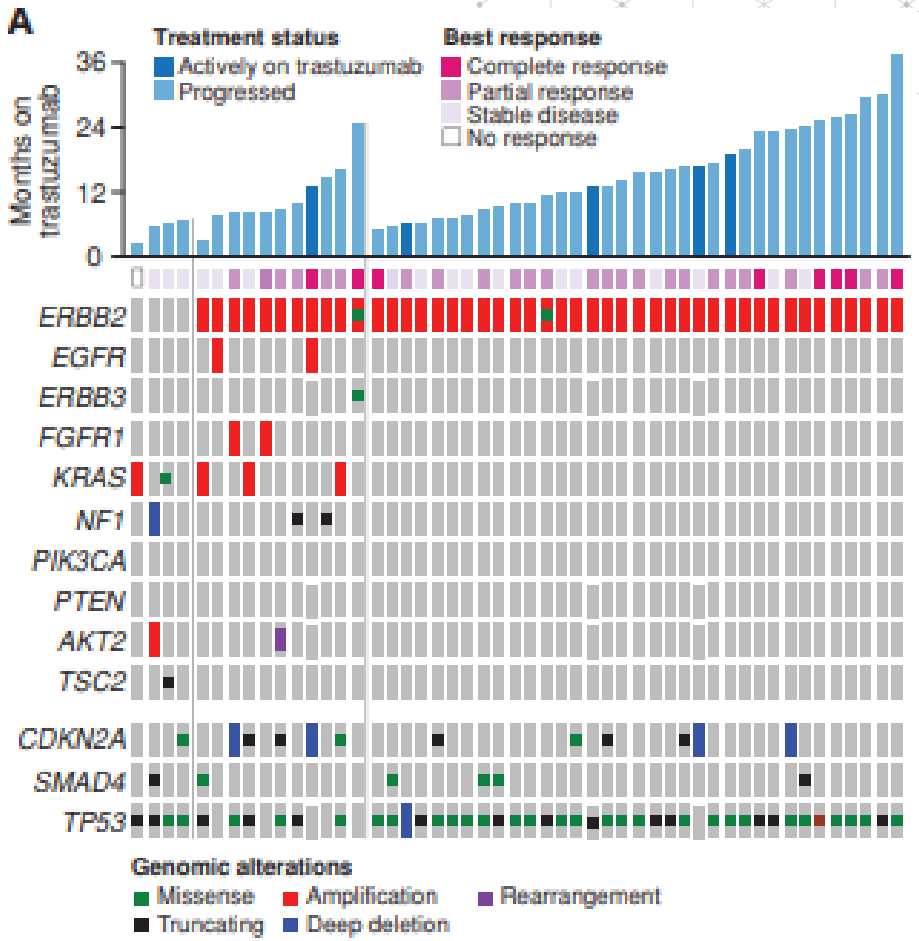
Genomic Predictors of Resistance to Trastuzumab

- Retrospective analysis of MSKCC cohort
  - Predominantly stage IV gastroesophageal cancer (N = 295)
- 30% of HER2+ tumors lacked ERBB2 amplification or had co-mutations of the RTK/RAS/PI3K pathway
  - These patients had rapid progression on trastuzumab





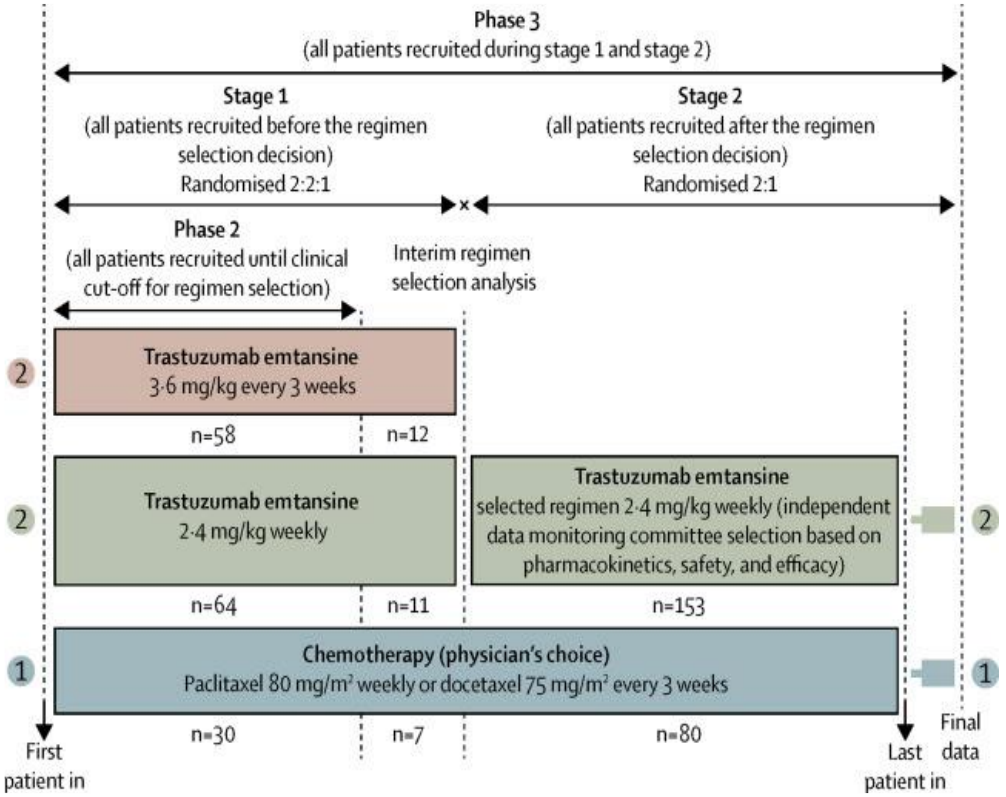
Genomic Biomarkers in Esophagogastric Adenocarcinoma



Janjigian YY, et al. *Cancer Discov*. 2018;8(1):49-58.

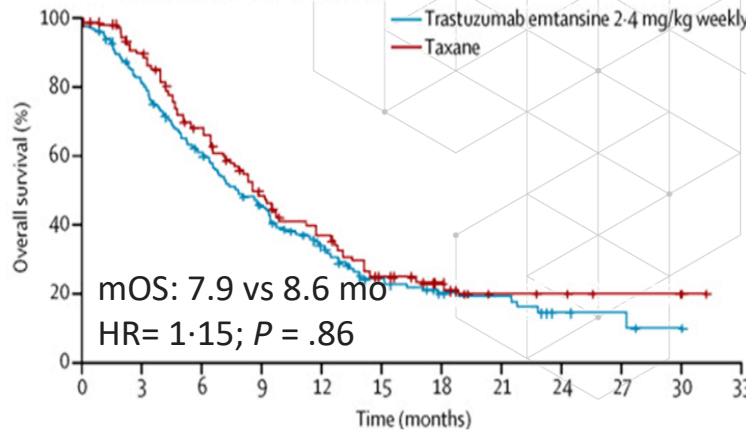
T-DM1 vs Taxane in HER2+ AGC: GATSBY

- GATSBY: **No significant improvement in OS** for trastuzumab emtansine vs taxane alone

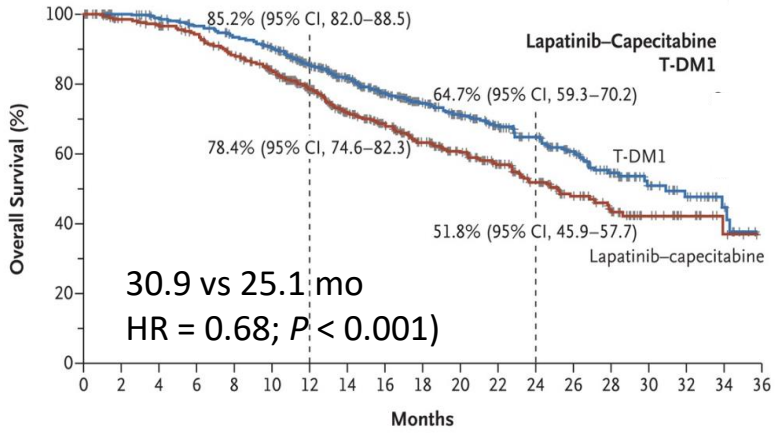


	Taxane	T-DM1
ORR, %	19.6	20.6
mDOR, mo	3.7	4.3
mPFS, mo	2.0	2.7
mOS, mo	8.6	7.9

GATSBY: AGC

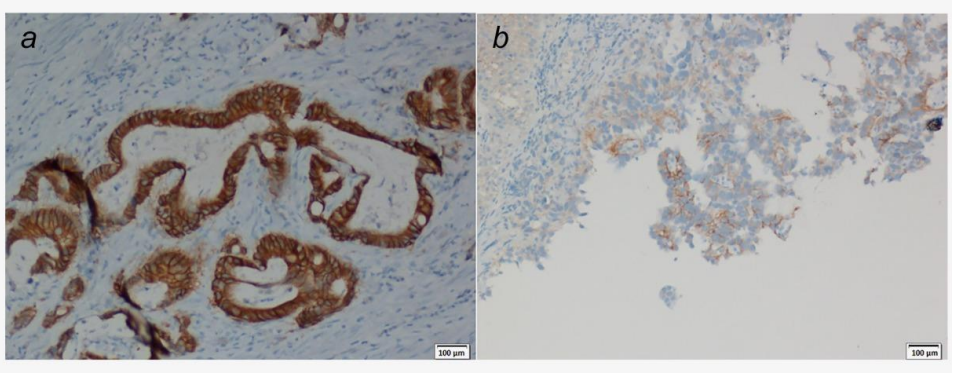


EMILIA: Breast Cancer



Thuss-Patience PC, et al. *Lancet Oncol*. 2017;18(5):640-653; Verma S, et al. *N Engl J Med*. 2012; 367:1783-1791.

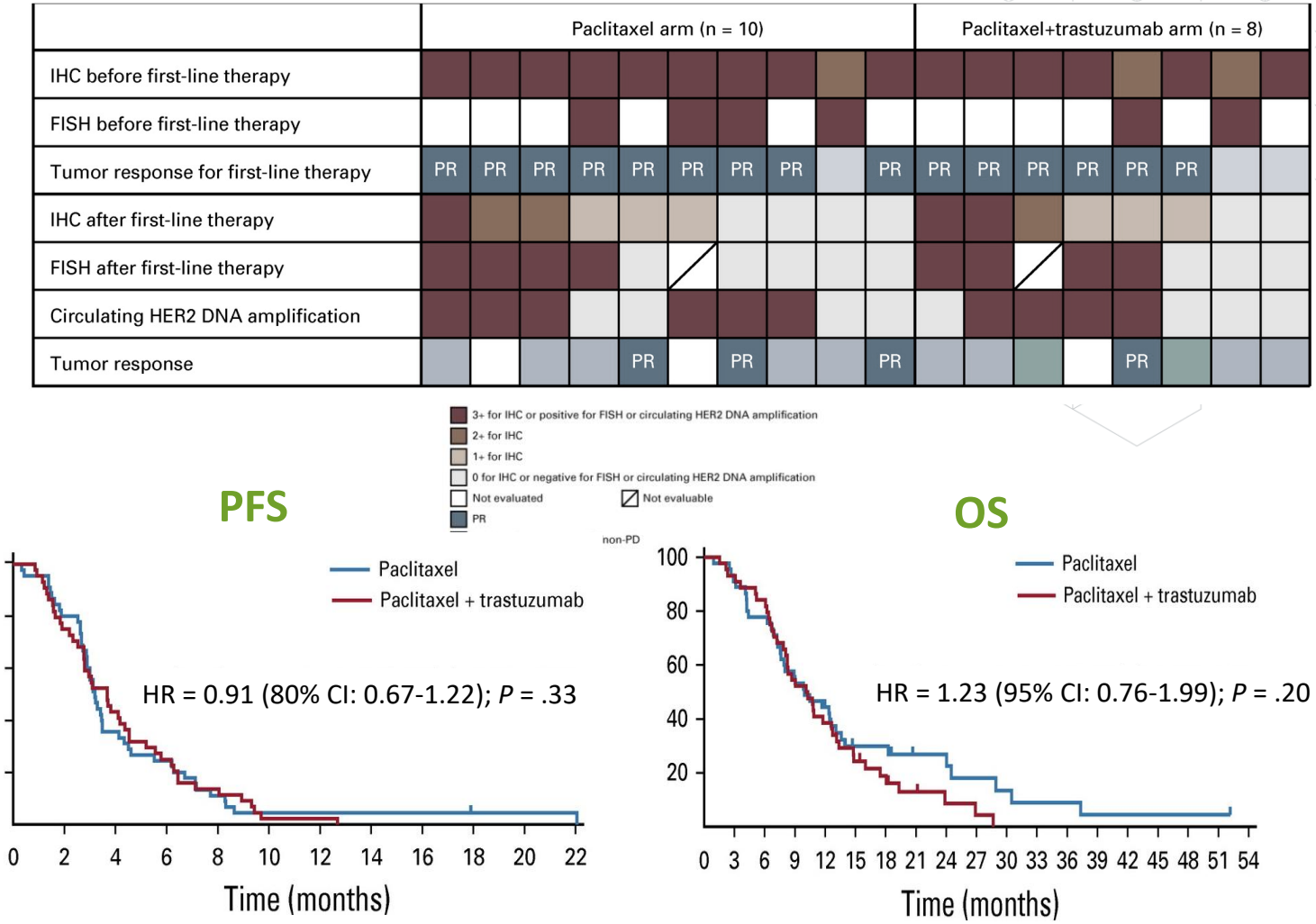
HER2+ AGC Treatment: Dynamic Changes in HER2 Affect Efficacy of 2L Treatment



Pre and post trastuzumab biopsy

- A significant proportion of patients do not express HER2 in the tumor after trastuzumab treatment
  - Demonstrated retrospectively and prospectively
- The addition of paclitaxel to trastuzumab in a biomarker unselected population is not helpful

T-ACT Trial

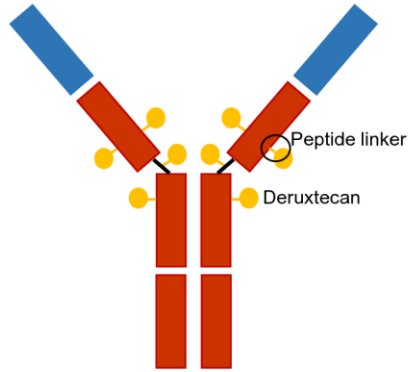


PFS

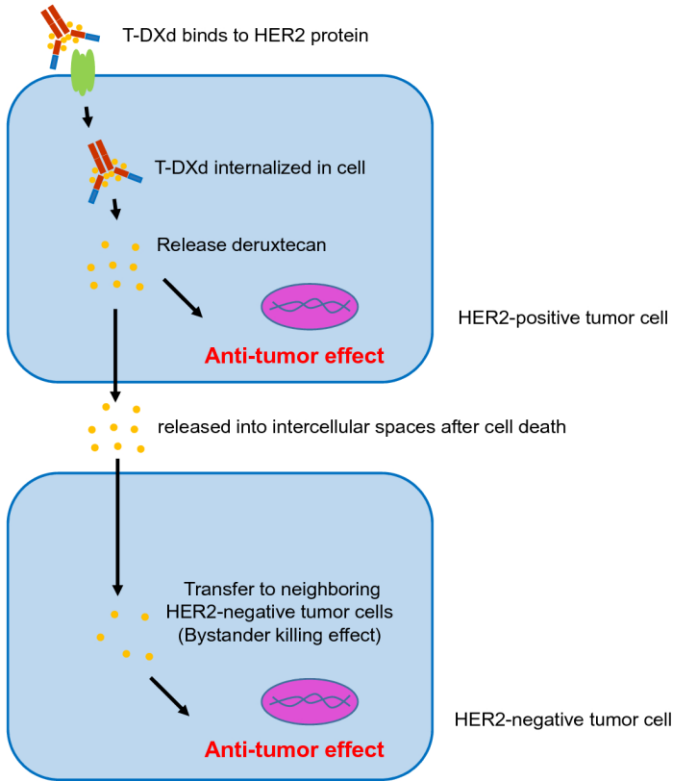
OS

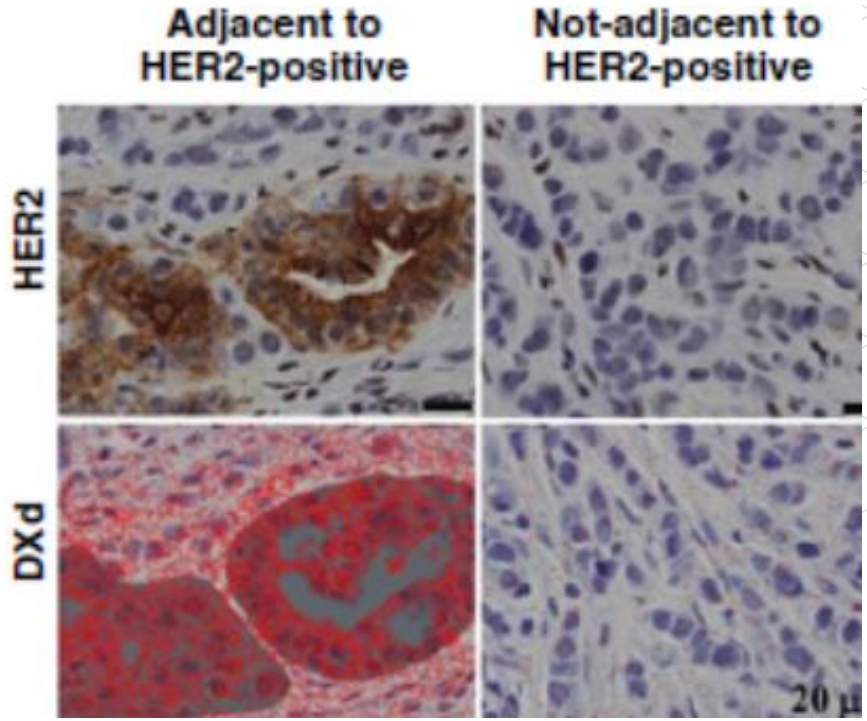
Pietrantonio F, et al. *Int J Cancer*. 2016;139(12):2859-2864. Makayman, et al. *J Clin Oncol*. 2020;38:17:1919-1927.

Trastuzumab Deruxtecan



Trastuzumab deruxtecan (T-DXd)

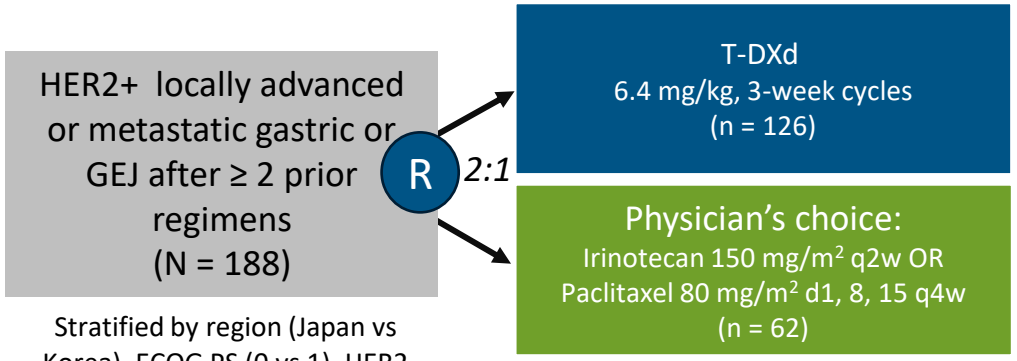




- High drug:antibody ratio ~8
- High potency payload with short systemic half-life
- Pronounced bystander killing effect

Suzuki M, et al. *Clin Cancer Res*. 2021;27(14):3970–3979. Aoki M, et al. *Gastric Cancer*. 2021;24(3):567-576.

DESTINY-Gastric01



Stratified by region (Japan vs Korea), ECOG PS (0 vs 1), HER2 status (IHC 3+ vs IHC 2+/ISH+)

HER2+ based on IHC 3+ or IHC 2+/ISH+ according to ASCO/CAP guidelines.

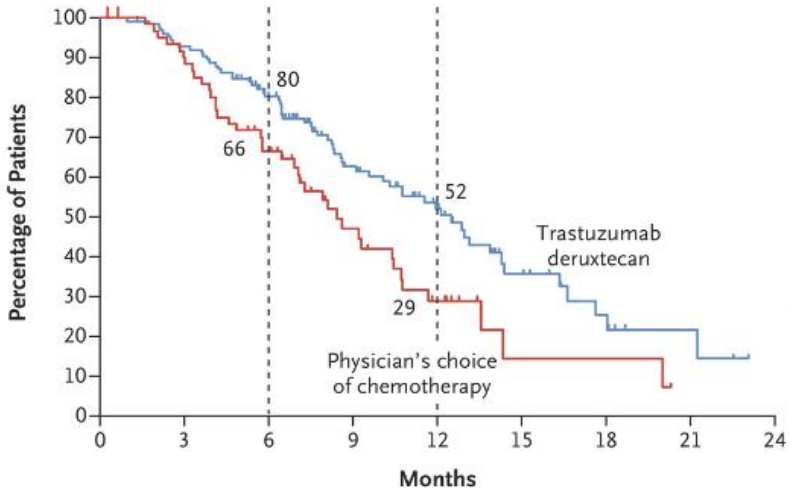
Until PD, unacceptable AEs, or pt withdrawal

	T-DXd (n = 125)	PC (n = 62)
Median age, y (range)	65 (34-82)	66 (28-82)
Female, %	24	24
ECOG PS 0 / 1, %	50 / 50	48 / 52
Primary site, % ▪ Stomach ▪ GEJ	 86 14	 89 11
Region, % ▪ Japan ▪ Korea	 79 21	 81 19
HER2 expression IHC 3+/IHC 2+, ISH+, %	77 / 23	76 / 24
Intestinal/ diffuse / other histological subtype	71 / 22 / 6	61 / 29 / 10
Prior systemic therapies ▪ 2 / 3 ▪ ≥ 4	 53 / 27 20	 61 / 29 10
Prior treatment ▪ Trastuzumab ▪ Taxane ▪ Ramucirumab ▪ Irinotecan or other topoisomerase inhibitor ▪ Immune checkpoint inhibitor	 100 84 75 6 35	 100 89 66 8 27

Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430.

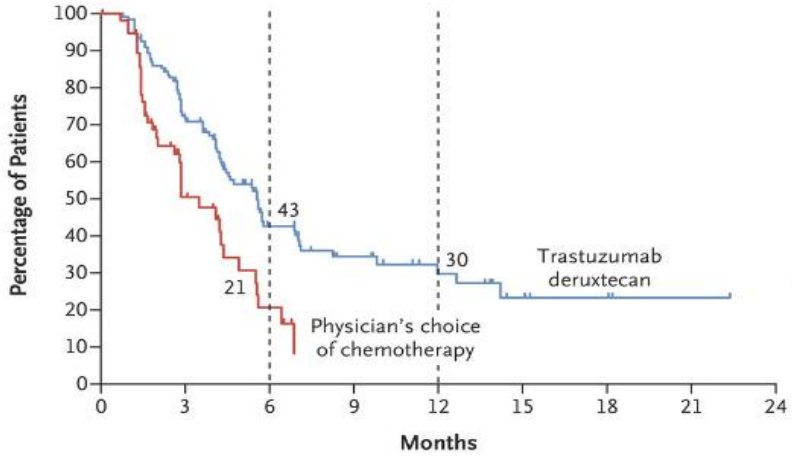
DESTINY-Gastric01

Overall Survival



mOS: 12.5 vs 8.4 mo
HR = 0.59; *P* = 0.01

Progression-Free Survival



mOS: 5.6 vs 3.5 mo
HR = 0.47

Response	T-DXd, (n = 119)	PC, (n = 56)
ORR, %	51	14

Jan 15, 2021
T-DXd FDA-approved for pts with locally advanced or metastatic HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen.

Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430.

DESTINY-Gastric02

Unresectable or metastatic gastric or GEJ cancer; HER2+* **on biopsy after progression** on first-line trastuzumab-containing regimen
ECOG PS 0/1
(N = 79)

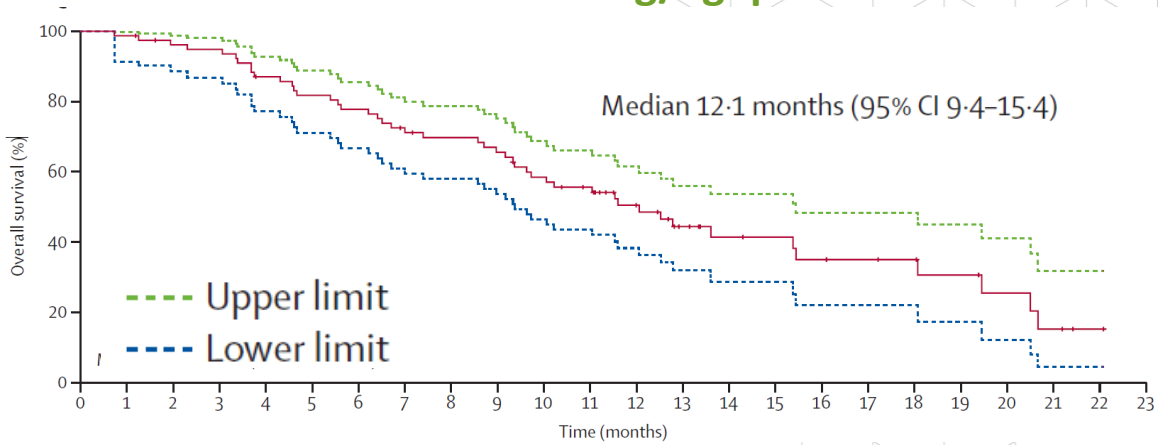
→ **T-DXd**
6.4 mg/kg Q3W

*Defined as IHC 3+ or IHC 2+/ISH+

Primary EP: confirmed ORR by ICR

DG-02	Data Cutoff April 9, 2021 (N = 79)	Data Cutoff Nov 8, 2021 (N= 79)
ORR, %	38	42
CR, %	4	5
PR, %	34	37
SD, %	43	39
PD, %	16	16
Confirmed DCR, %	81	81
Median DOR, mo	8.1	8.1
Median TTR, mo	1.4	1.4

OS: T-DXd at 6.4 mg/kg q 3w



Dec. 19. 2022
Approved in the EU as a monotherapy for the treatment of adult patients with advanced HER2-positive gastric or GEJ adenocarcinoma who have received a prior trastuzumab-based regimen.

DESTINY-Gastric04: T-DXd vs ramucirumab + paclitaxel in HER2+ G/GEJ cancer after progression on a trastuzumab-containing regimen

Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04704934

Van Cutsem E, et al. *Lancet Oncol.* 2023:S1470-2045(23)00215-2.

Treatment-Related Adverse Events with T-DXd

DG-01: TRAEs, %	T-DXd, n = 125 Any Grade/Grade 3/4, %	PC, n = 62 Any Grade/Grade 3/4, %
Nausea	**63** / 5	47 / 2
↓ neutrophil count	63 / **51**	35 / 24
↓ appetite	60 / 17	45 / 13
Anemia	58 / 38	31 / 23
↓ platelet count	39 / 12	6 / 4
↓ white cell count	38 / 21	35 / 11
Malaise	34 / 1	32 / 2
Diarrhea	**32** / 2	32 / 4
Vomiting	**26** / 0	8 / 0
Constipation	24 / 0	23 / 0
Pyrexia	24 / 0	16 / 0
Alopecia	22 / 0	15 / 0
Fatigue	22 / 7	24 / 3
↓ lymphocyte count	22 / 11	3 / 2

DG-02: TRAEs, %	T-DXd (N = 79), %			
	Gr 1/2	Gr 3	Gr 4	Gr 5
Nausea	**59**	8	0	0
Fatigue	38	4	0	0
Vomiting	42	30	0	0
Diarrhea	**35**	1	0	0
↓ weight	28	4	0	0
Constipation	29	0	0	0
↓ appetite	28	5	0	0
Alopecia	24	0	0	0
Anemia	24	14	0	0
↓ platelet count	15	3	0	0
↓neutrophil count	9	**3**	**5**	**0**

Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430; Van Cutsem E, et al. *Lancet Oncol.* 2023:S1470-2045(23)00215-2.

Interstitial Lung Disease in DESTINY-Gastric-02

DG-02, N = 79	Any TEAE, %	Drug-Related
Any	79	75
Grade ≥ 3	44	24
Serious TEAE	33	10
Discontinuation Associated with TEAE	15	10
Dose reduction associated with TEAE	17	14
Death associated with TEAE	11	2

- Drug-related ILD/pneumonitis
  - 8 patients (10%)
    - Grade 1: 2 patients (3%)
    - Grade 2: 4 (5%)
    - Grade 5: 2 (2%)
- Median time to onset: 80.5 days
- Median duration: 36 days
- 2 fatal cases
  - 171 days
  - 353 days

Ku G, et al. *Ann Oncol*. 2022;33(suppl_7):S555-S580. Van Cutsem E, et al. *Lancet Oncol.* 2023:S1470-2045(23)00215-2.

Management of ILD

Suspected ADC-related ILD

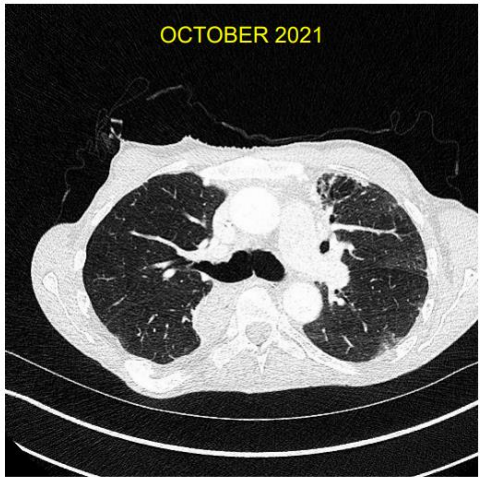
Discontinue; start corticosteroids according to grade

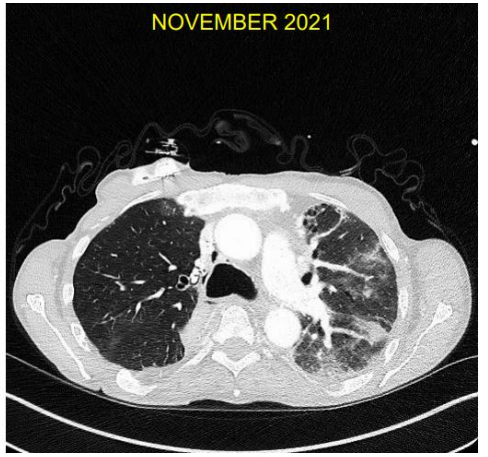
History and physical exam
Laboratory tests
HRCT scan of the chest
Pulmonary consultation with pulmonary function testing
Bronchoscopy and bronchoalveolar lavage ± transbronchial lung biopsy

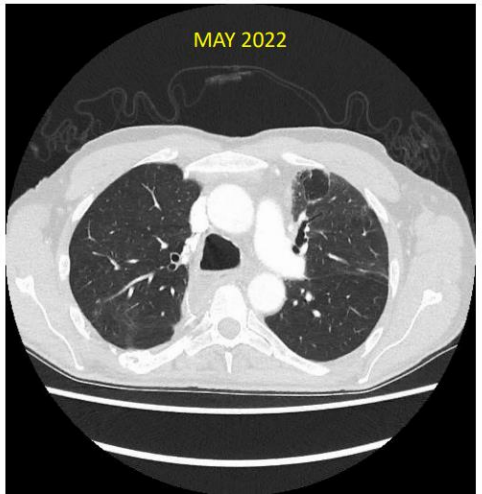
Differential diagnosis: Exclude cancer progression, infective source, ILD related to other drugs, RT-induced pneumonitis, or other causes

	Corticosteroid Management
Grade 1	Oral prednisolone, 0.5 mg/kg/d
Grade 2	Oral prednisolone, 1 mg/kg/d, Increase to 2 mg/kg/d if no improvement
Grade 3 & grade 4	Hospitalization, IV methylprednisolone, 0.5-1 g/d followed by oral prednisolone after 3d • Oxygen supplementation for hypoxia • Supportive treatment for prolonged corticosteroid use • If corticosteroid-refractory, consider infliximab, MMF, IVIG, or other immunosuppressant

	Severity	Treatment modification
ILD/Pneumonitis	Asymptomatic (grade 1)	Interrupt until resolved to grade 0, then: • If resolved in ≤ 28 d of onset, maintain dose • If resolved > 28 d of onset, reduce dose 1 level • Consider corticosteroid treatment as soon as ILD/pneumonitis is suspected
	Symptomatic (≥ grade 2)	• Permanently discontinue • Promptly initiate corticosteroid treatment as soon as ILD/pneumonitis is expected







Management of Toxicities

Neutropenia

- Grade 3
  - Interrupt until resolved to grade 2 or less; maintain dose
- Grade 4
  - Interrupt until resolved to grade 2; reduce dose by one level

Febrile neutropenia

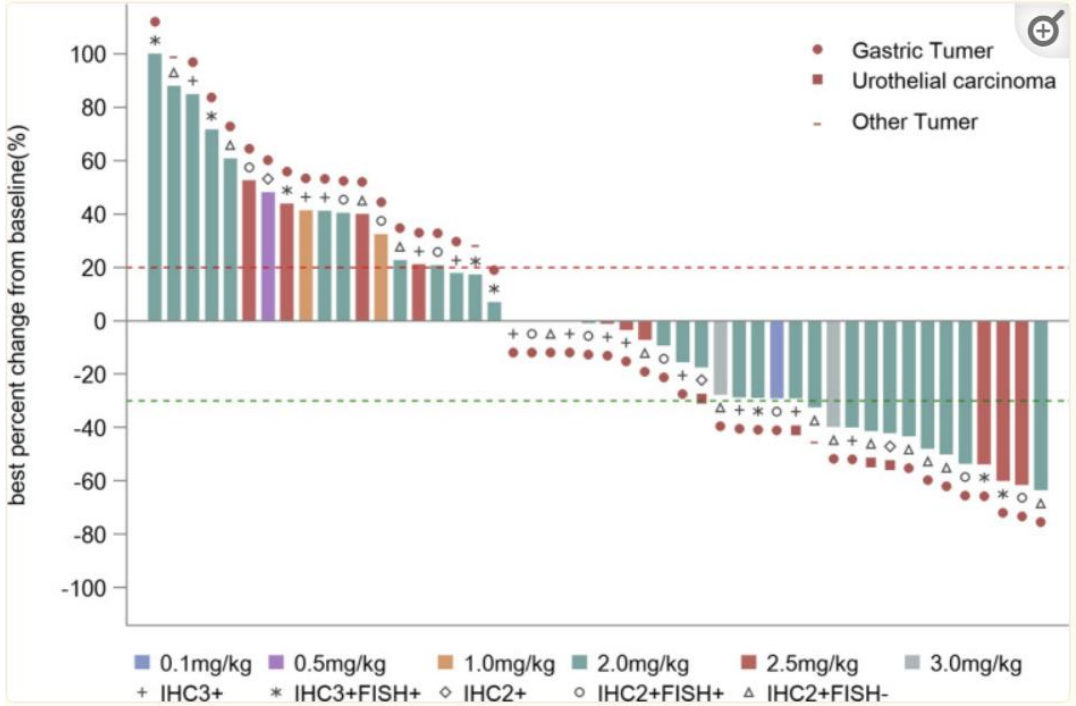
- ANC < 1.0 x 10^9/L and temperature > 38.3°C or a sustained temperature Of ≥ 38°C for > 1h
  - Interrupt until resolves; reduce dose by one level

Left Ventricular Dysfunction

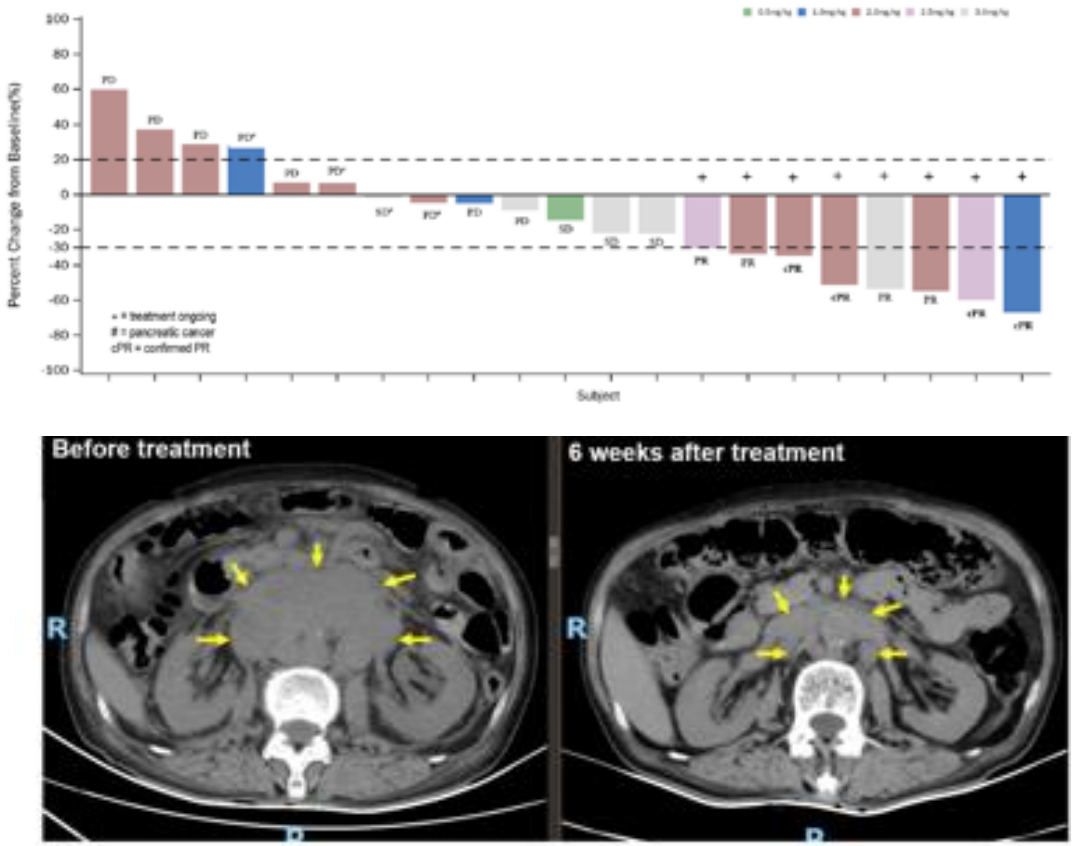
- **<u>LVEF > 45% and absolute decrease from baseline is 10% to 20%</u>**
  - **<u>Continue treatment</u>**
- LVEF 40%-45%
  - + ANC decrease > 10%: continue treatment; repeat LVEF assessment within 3 wks
  - + ANC decrease 10%-20%: Interrupt treatment; repeat LVEF assessment within 3 wks; if LVEF has not recovered to within 10% from baseline: permanently discontinue
  - Symptomatic CHF
- **<u>LVEF <40% or ANC decrease from baseline >20%</u>**
  - Interrupt treatment; repeat LVEF assessment within 3 wks; If LVEF of <40% or ANC decrease from baseline of >20% is confirmed: permanently discontinue
- Symptomatic CHF
  - Permanently discontinue

Emerging ADCs

Disitamab Vedotin (RC48): HER2-Directed ACC



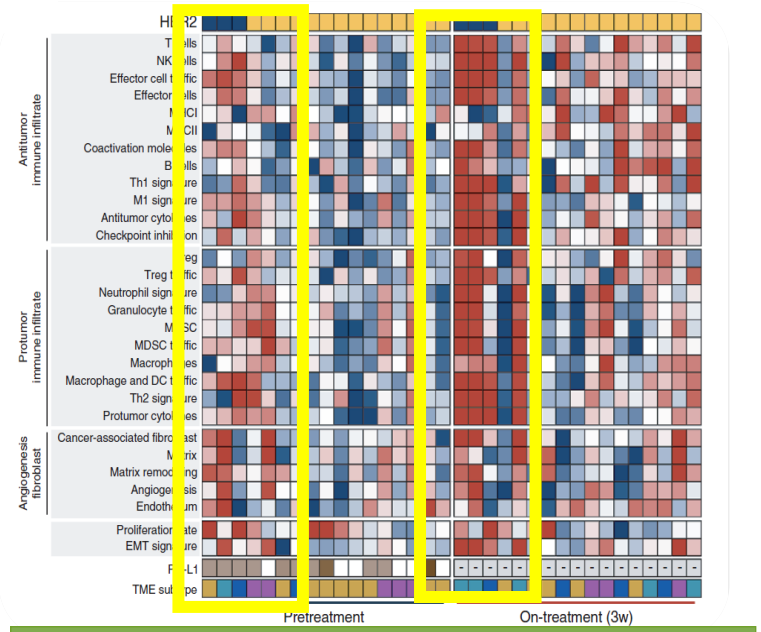
SYSA1801: Claudin 18.2-Directed ADC



Shi F, et al. *Drug Deliv*. 2022;29(1):1335-1344. Xu Y, et al. *Gastric Cancer*. 2021;24(4):913-925. Wang Y, et al. ASCO 2023. Abstract 3016.

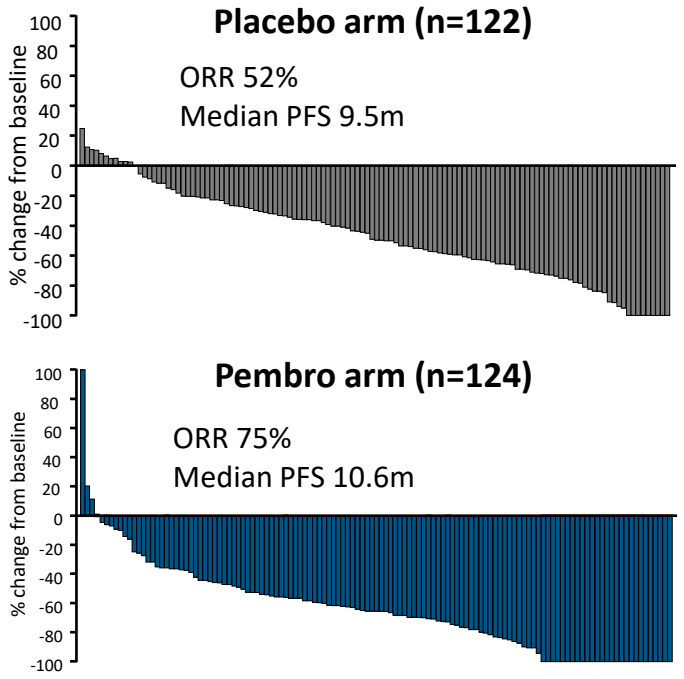
Will Changes in First Line Affect Second Line

KEYNOTE 811
Chemo+trastuzumab ± anti-PD-1



HER2 positive GEA is primed to respond to ICI
↑ immune infiltrates at baseline and further ↑ ↑ on response

Prevalence of immune activation in HER2 amplified GEA



Press release: met PFS endpoint in PD-L1+ve only #ESMO2023

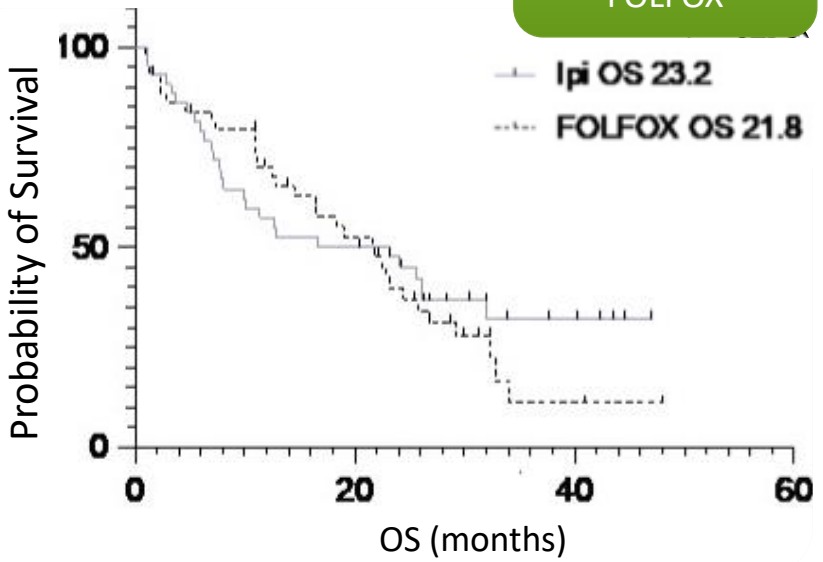
INTEGA
Trastuzumab + chemo + nivolumab vs trastuzumab-ipilimumab

Previously untreated HER2+ locally advanced or mEGA

R

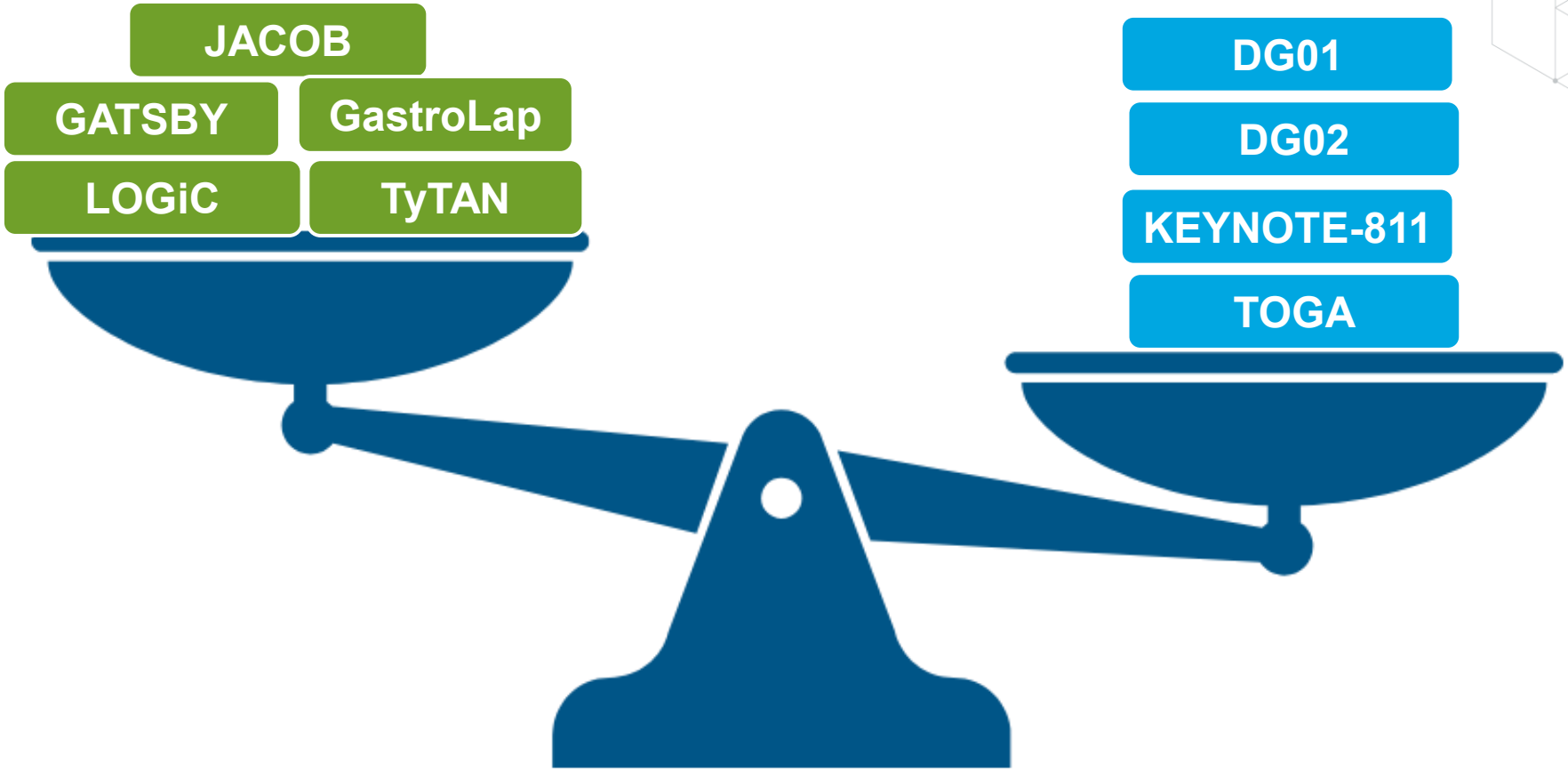
Trastuzumab
Nivolumab
Ipilimumab

Trastuzumab
Nivolumab
FOLFOX



Kim et al, Cancer Discovery 2021; Janjigian et al, Nature 2021; Lorenzen et al, ESMO 2022

HER2+ AGC Treatment: Balance Shift



Lorenzen S, et al. Eur J Cancer. 2015;51(5):569-576. Satoh T, et al. J Clin Oncol. 2014;32(19):2039-2049. Hecht JR, et al. J Clin Oncol. 2016;34(5):443-451.

Current Conundrums and Emerging Directions

John L. Marshall, MD

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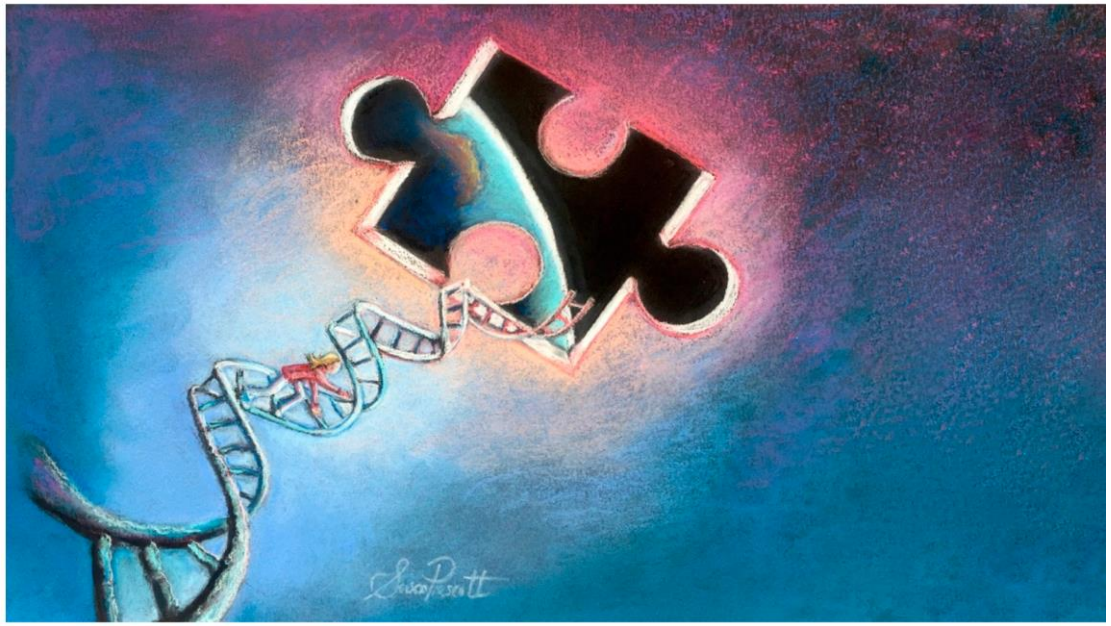
What a Difference a Decade Makes…

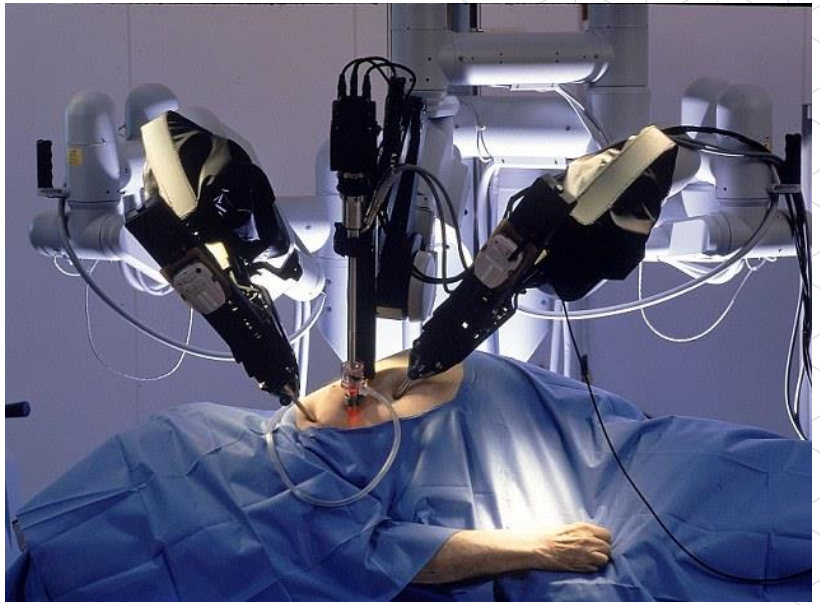
2010

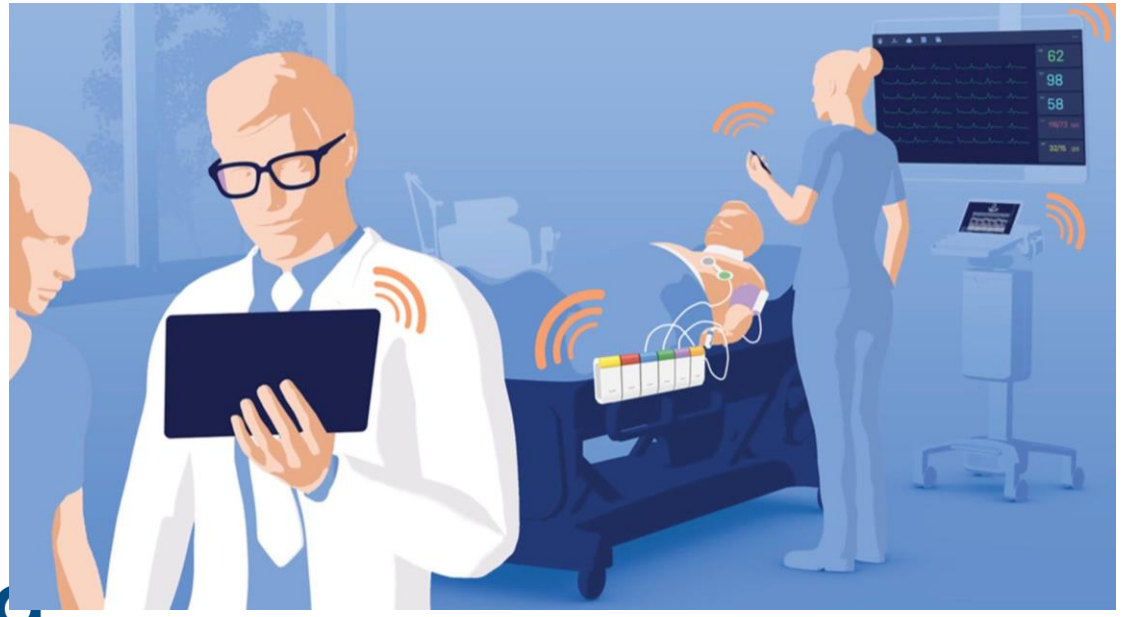
- Cancer is clonal
- All cancer is the same
- Immune therapies will never work
- Gene testing for some
- Randomized phase 3 trials
- Microbiome is disgusting
- Cancer treatment is expensive
- We love our jobs

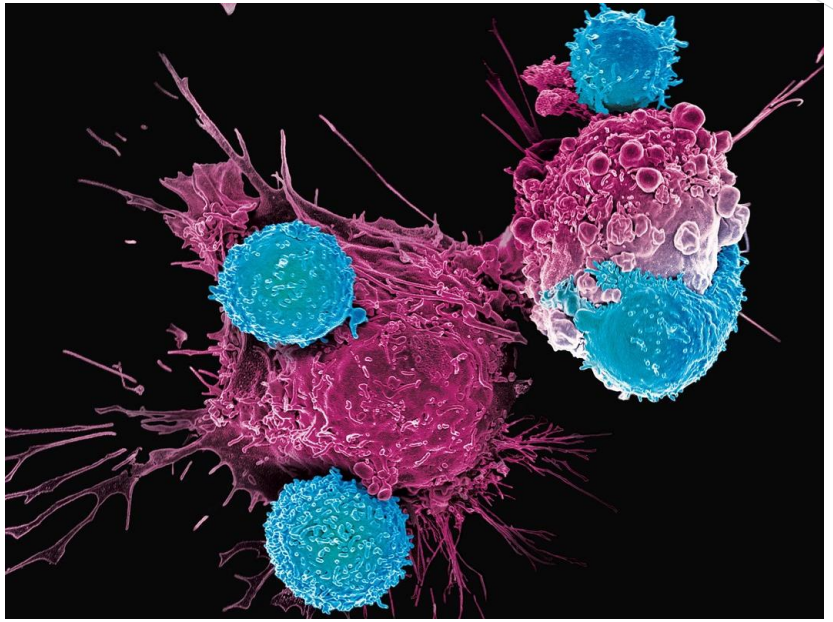
2020

- Cancer is polyclonal
- All cancer is different
- Immune therapies are miraculous
- Broad testing for many
- Small single-arm trials
- Microbiome is beautiful
- Cancer treatment is more expensive
- Highest burnout and suicide in medicine



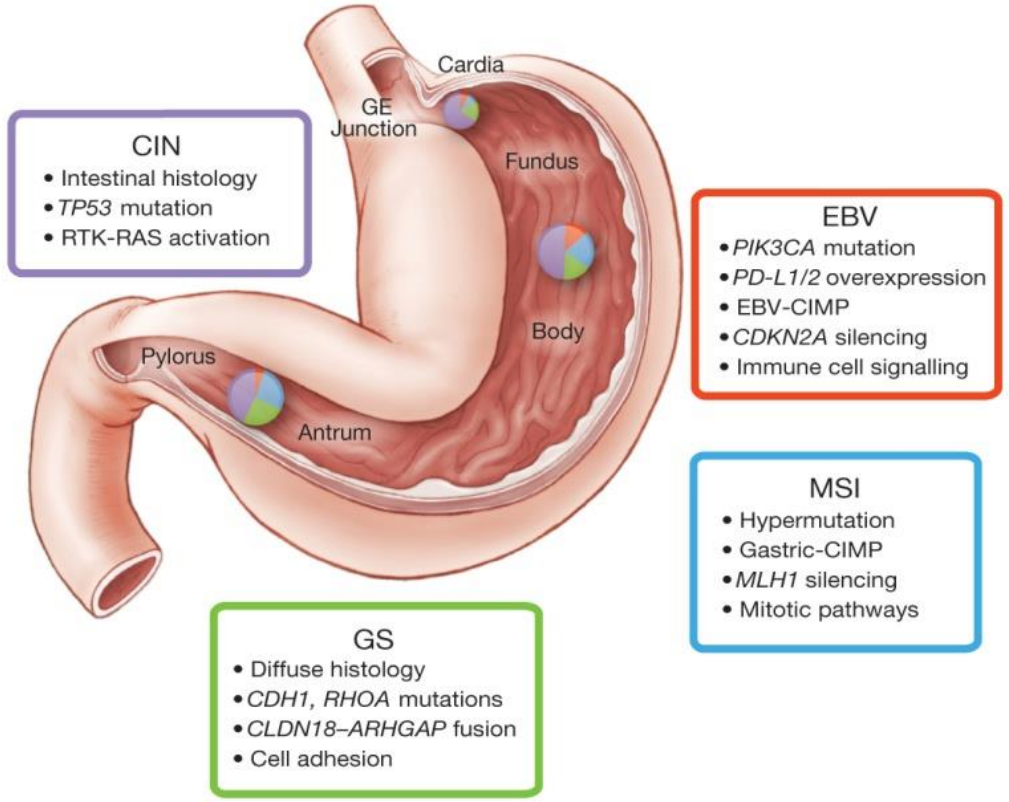



62
98
58



Unequal Access, Unequal Standards

Molecular Profiling Guides Treatment in Advanced GC



TCGA, Nature 2014

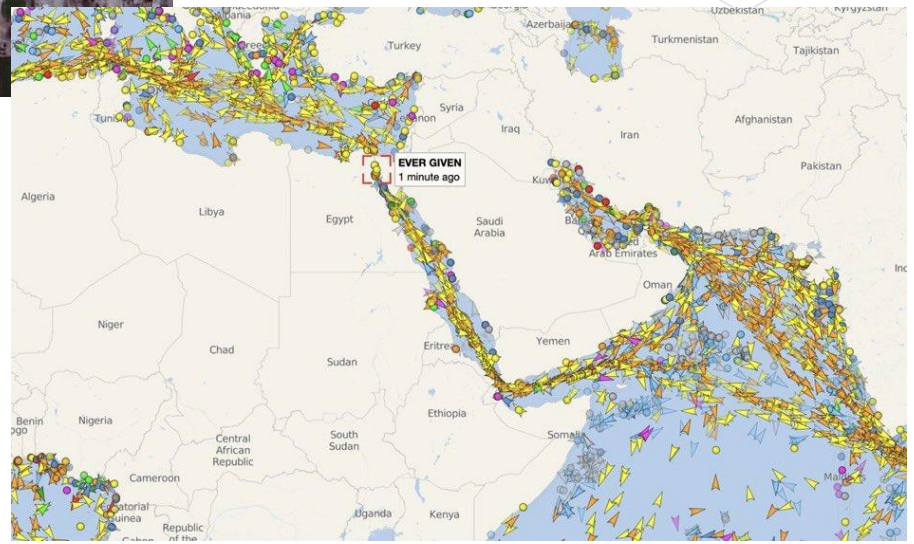
		Prevalence	Targeted therapies
Approved	**HER-2 amplification**	~22% (6%-30%)[1,2]	• Trastuzumab [1st line] • T-DXd [2nd line]
	MSI-H/dMMR	8%-11%[3]	• Pembrolizumab • Nivolumab • Dostarlimab
	PD-L1 positivity	~45%-60%[4,5]	• Nivolumab
	TMB ≥ 10 mut/Mb	~16%[6]	• Pembrolizumab
	NTRK fusion	<1%[7]	• Larotrectinib • Entrectinib
Promising	**FGFR2b overexpression**	~5%[8]	• Bemarituzumab
	Claudin 18.2	14%[9]	• CAR-T

1. Bang YJ, et al. *Lancet*. 2010;376(9742):687-697; 2. Gravalos C, et al. *Ann Oncol*. 2008;19(9):1523-1529; 3. Amonkar M. *J Clin Oncol*. 2019; 4. Liu X, et al. *Path Research and Practice*. 2020;216(4):152881; 5. Ahn S, et al. *Mod Pathol*. 2021;34(9):1719-1727; 6. Lee KW, et al. *Clin Cancer Res*. 2022;28(16):3489-3498; 7. Westphalen CB, et al. *NPJ Precis Oncol*. 2021;5(1):69; 8. Ahn S, et al. *Mod Pathol*. 2016;29(9):1095-1103; 9. Hong JY, et al. *Transl Cancer Res*. 2020;9(5):3367-3374.

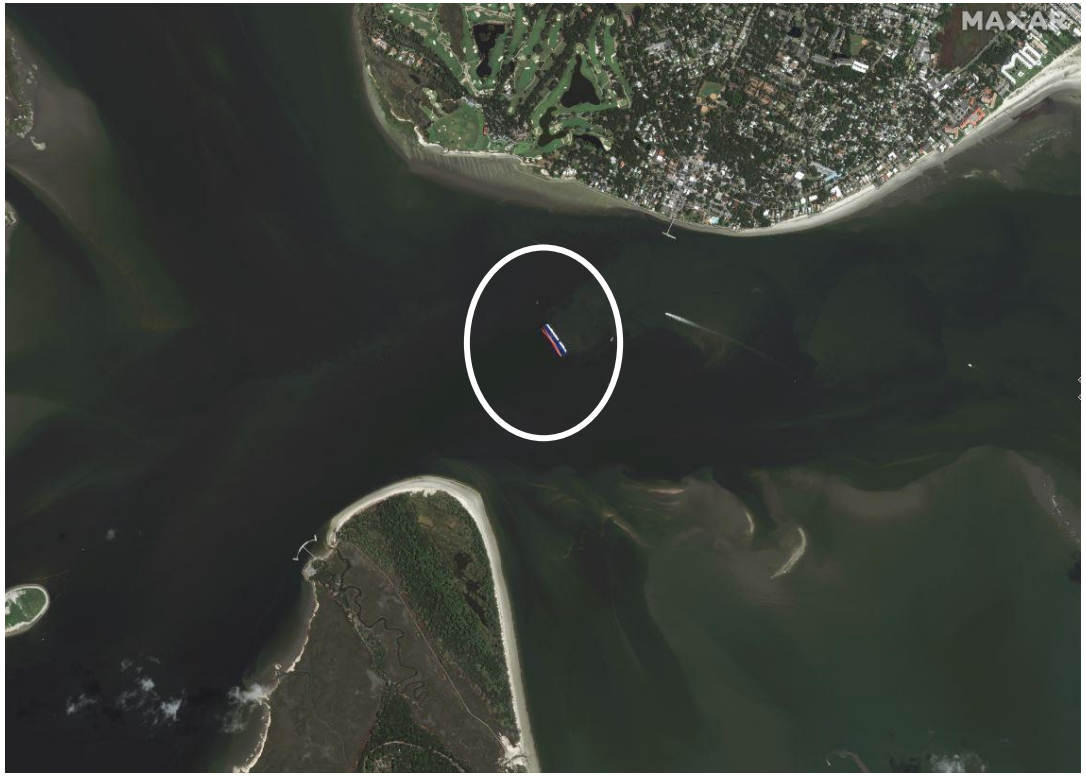
Why Is GI Cancer So Different?

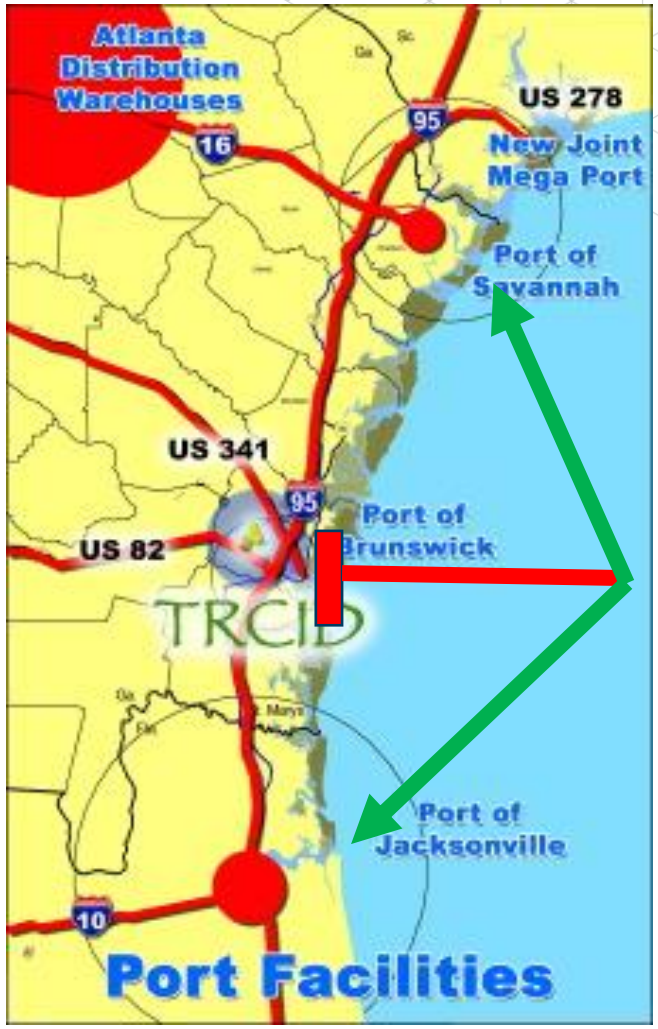
- Metastatic disease ≠ Local disease
- Are neo-adjuvant strategies Met or local biology?
- Esophageal ≠ EGJ ≠ Gastric
- Squamous ≠ Adenocarcinoma

A Powerful Driver

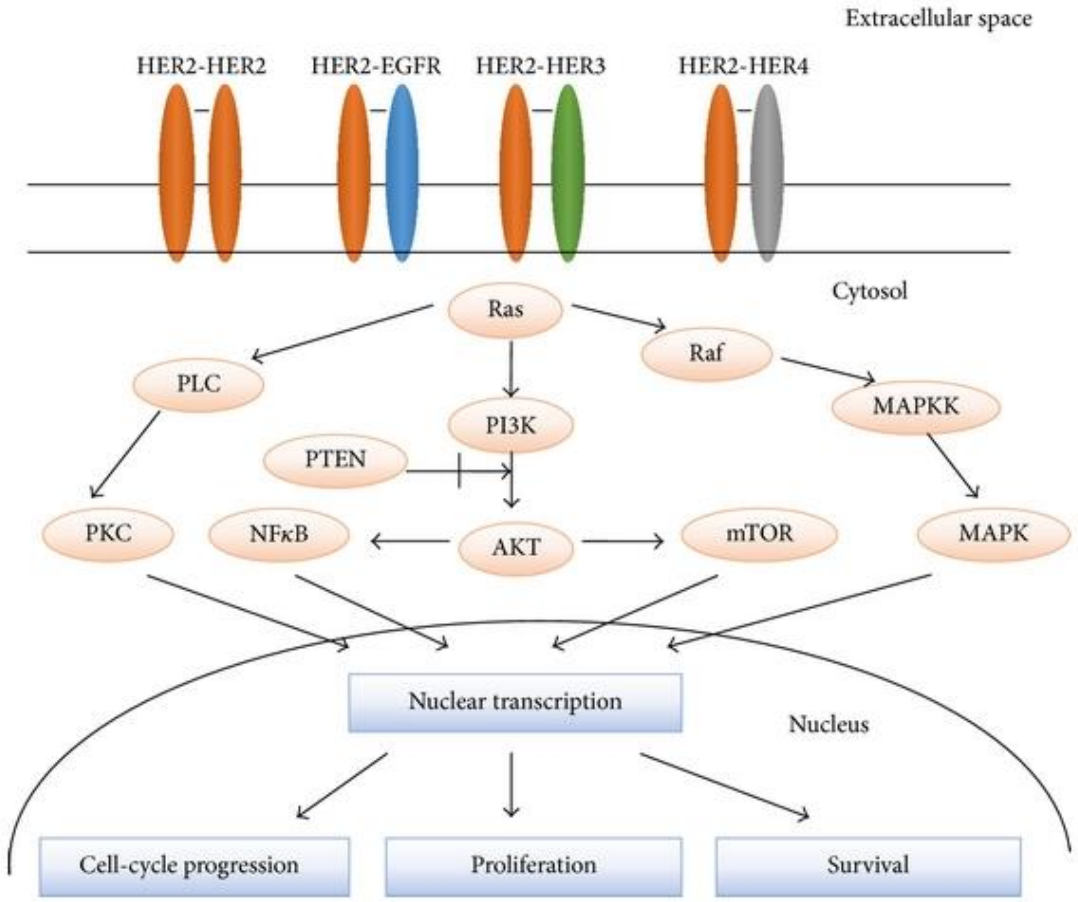


A GI Cancer Driver

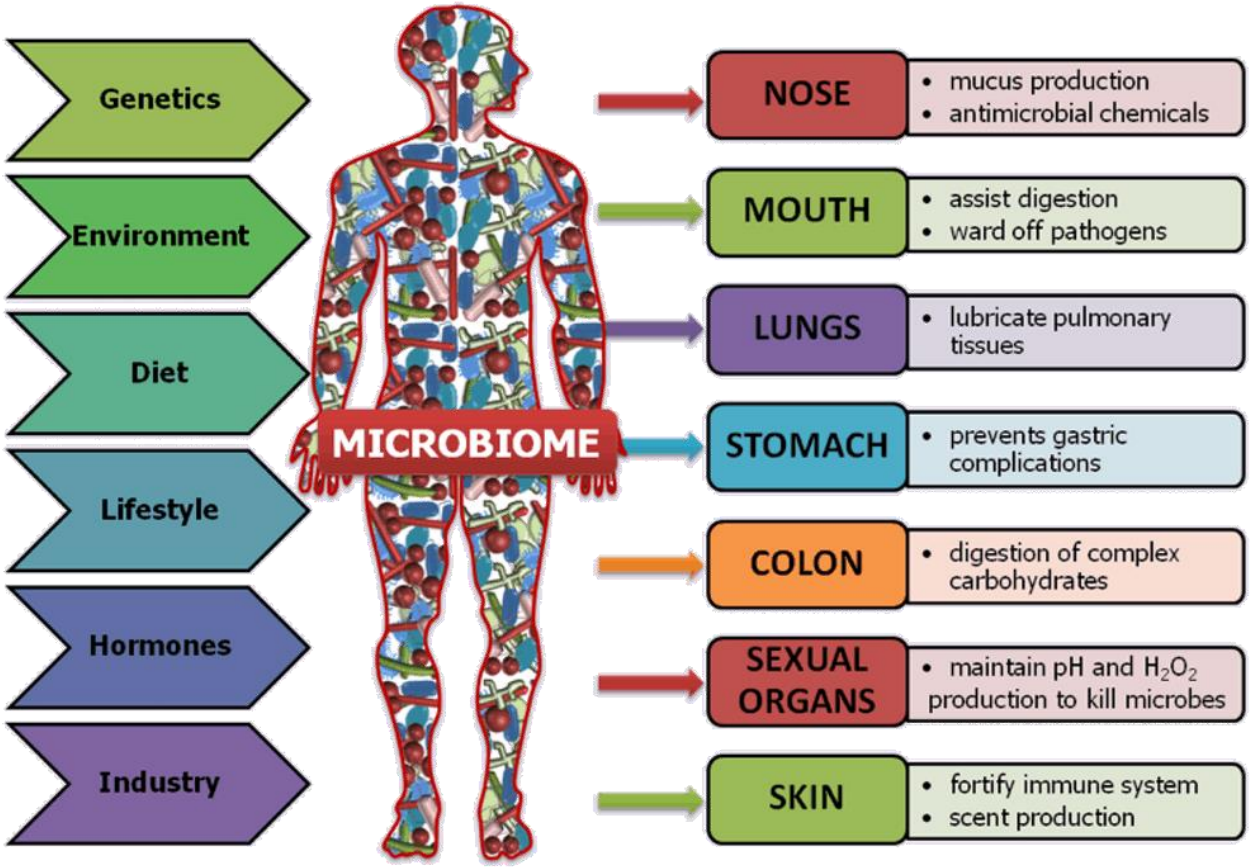


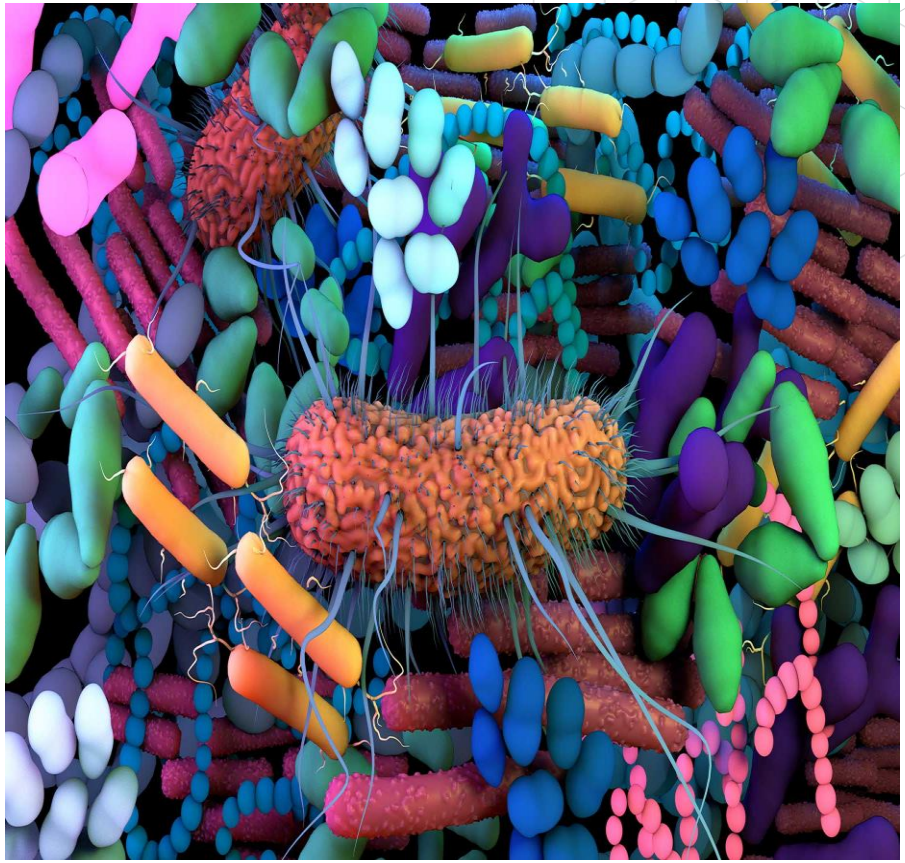


Let's Look at This Again...



The Role of the Microbiome





Historic Limited Successes with Targeted Therapies in Gastric Cancer

Study phase	Target	Intervention	ORR	OS benefit?
TOGA[1] / III	HER-2+	trastuzumab + chemo	47% (12% higher than chemo)	✓
DESTINY Gastric-01 / II	HER-2+	trastuzumab deruxtecan	51% (37% higher than physician choice)	✓
TRIO-013/LOGiC[2] III	HER-2+	lapatinib + chemo	53% (14% higher than chemo)	✗
METGastric[3] II/III	MET+/HER-2-	onartuzumab + chemo	41% (5% less than chemo)	✗
RILOMET-1[4] / III	MET+/HER-2-	rilotumumab + chemo	30% (9% less than chemo)	✗
SHINE[5] / II	FGFR2+	FGFR1-3 inhibitor	-	✗ (PFS)
FIGHT[6] / II	FGFR2b+	bemarituzumab + chemo	53% (13% higher than chemo)	✓
EXPAND[7] / III	Unselected (EGFR)	cetuximab + chemo	30% (1% higher than chemo)	✗
REAL3[8] / III	Unselected	panitimumab + chemo	46% (4% higher than chemo)	✗

Potential Reasons:

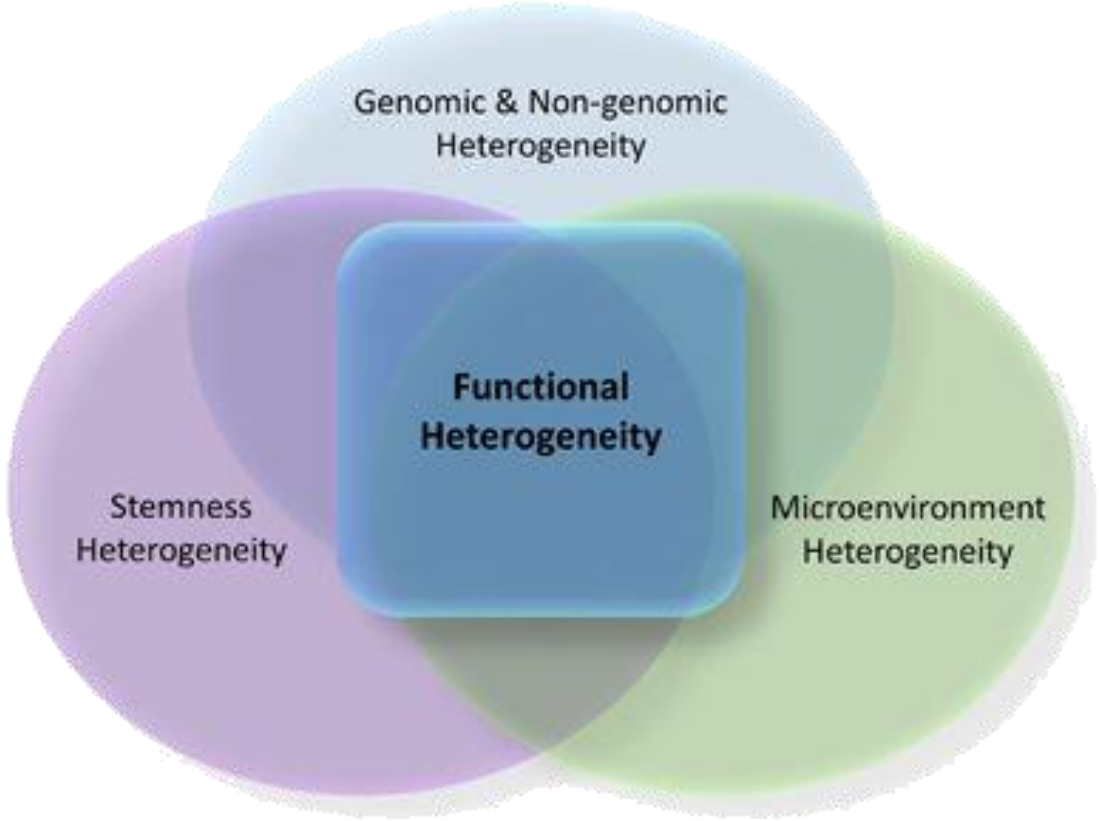
Wrong drug?
Wrong target?
Resistance mechanisms?
Unselected patients?

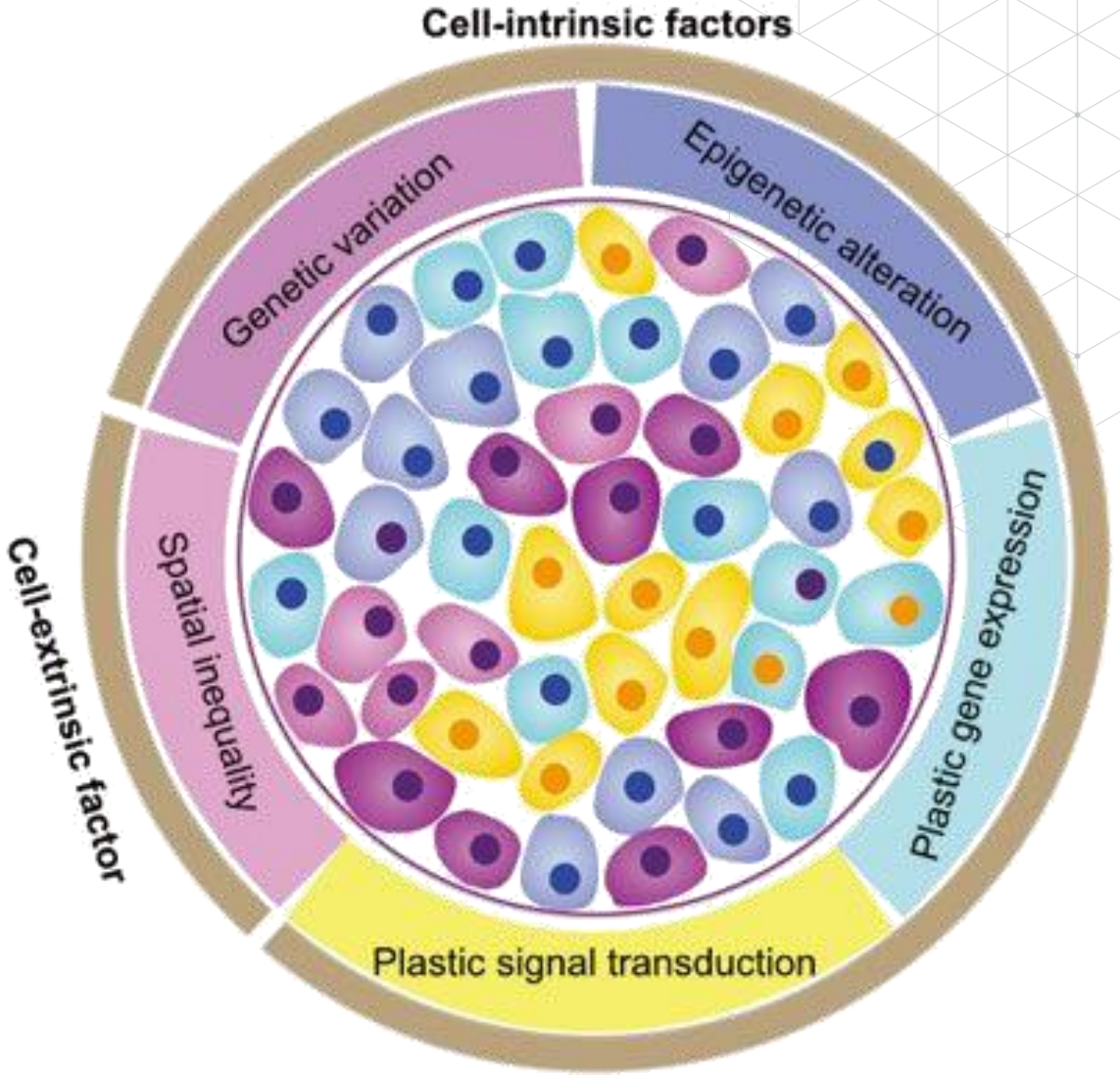
Molecular heterogeneity

1. Bang Y, et al. *Lancet*. 2010;376(9742):687-697; 2. Hecht JR, et al. *J Clin Oncol*. 2016;34(5):443-451; 3. Shah MA, et al. *J Clin Oncol*. 2015;33(33):3874-3879; 4. Cunningham D, et al. *J Clin Oncol*. 2015;33(15_suppl):4000; 5. Bang YJ, et al. *J Clin Oncol*. 2015;33(33):3858-3865; 6. Catenacci DVT, et al. *J Clin Oncol*. 2021;39(15_suppl):4010; 7. Lordick F, et al. *Lancet Oncol*. 2013;14(6):490-499; 8. Waddell T, et al. *Lancet Oncol*. 2013;14(6):481-489.

Capturing Temporospatial Heterogeneity

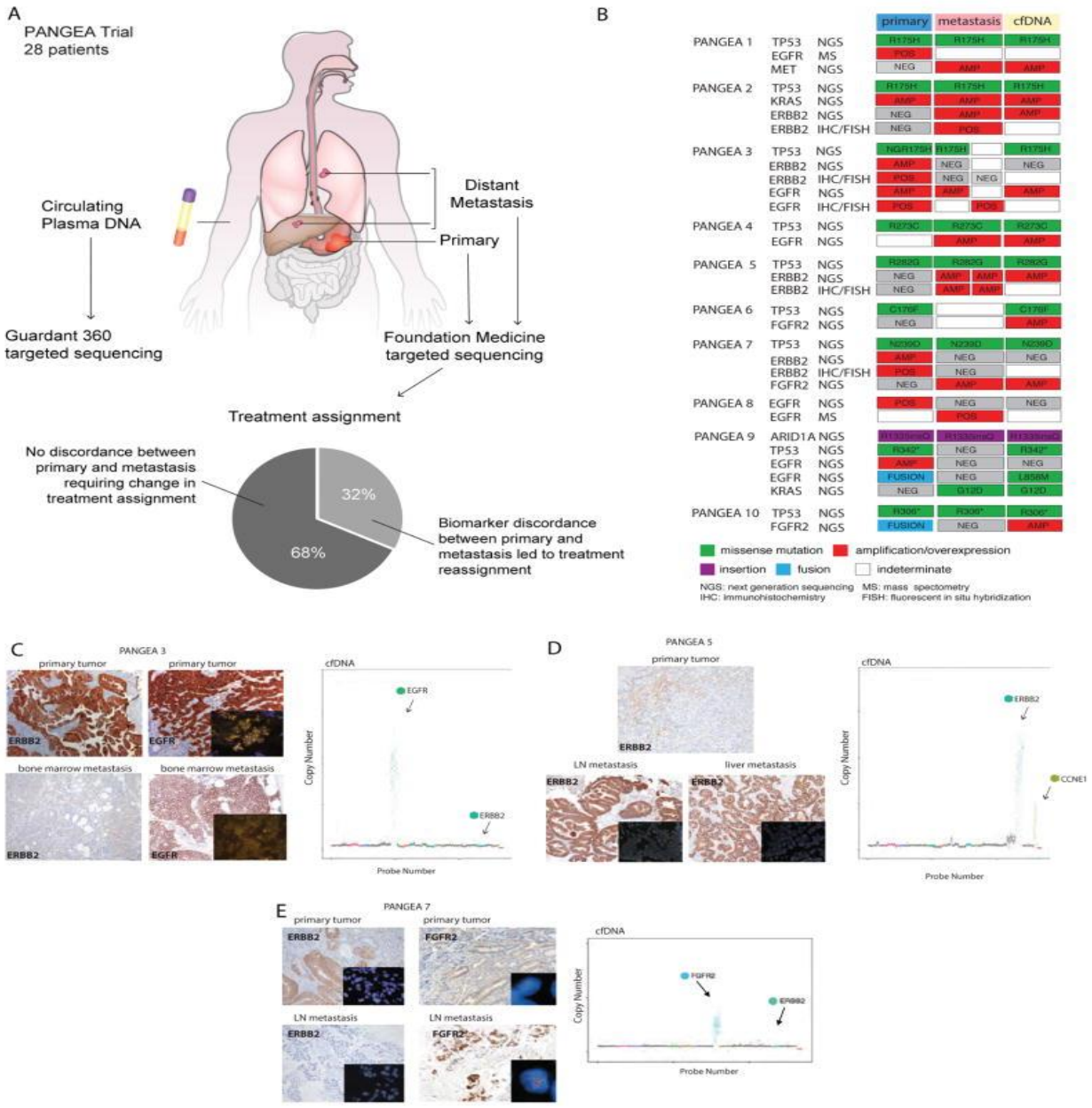
Heterogeneity





Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma

- Frequent baseline heterogeneity in targetable genomic alterations in GEA
- Current tissue sampling practices for biomarker testing do not effectively guide precision medicine in this disease
- Routine profiling of metastatic lesions and/or cfDNA should be systematically evaluated



Pectasides E, et al. *Cancer Discov*. 2018;8(1):37-48.

ctDNA Has the Potential to Predict Treatment Efficacy

Trastuzumab deruxtecan

- Approved for HER2-amplified gastric cancer (IHC2+/FISH+ or IHC 3+) based on Destiny-Gastric01

Destiny-Gastric01 post hoc exploratory ctDNA analysis

Liquid biopsy	N	Response Rate, %
ERBB2 amplified	71	60.6
ERBB2 copy number >6	33	75.8
ERBB2 copy number < 6	76	40.8
ERBB2 non-amplified	38	34.2

Other studies with anti-HER2-directed therapy also demonstrate plasma ERBB2 amplification correlates with responses and survival

Pts who lack plasma amplification still may benefit

- False negatives?
- Low shedding?
- Dilution?
- Poor sensitivity assay?

Bemarituzumab

- Improved OS 1st line when added to chemo in FGFR2b+ gastric cancer patients based on FIGHT

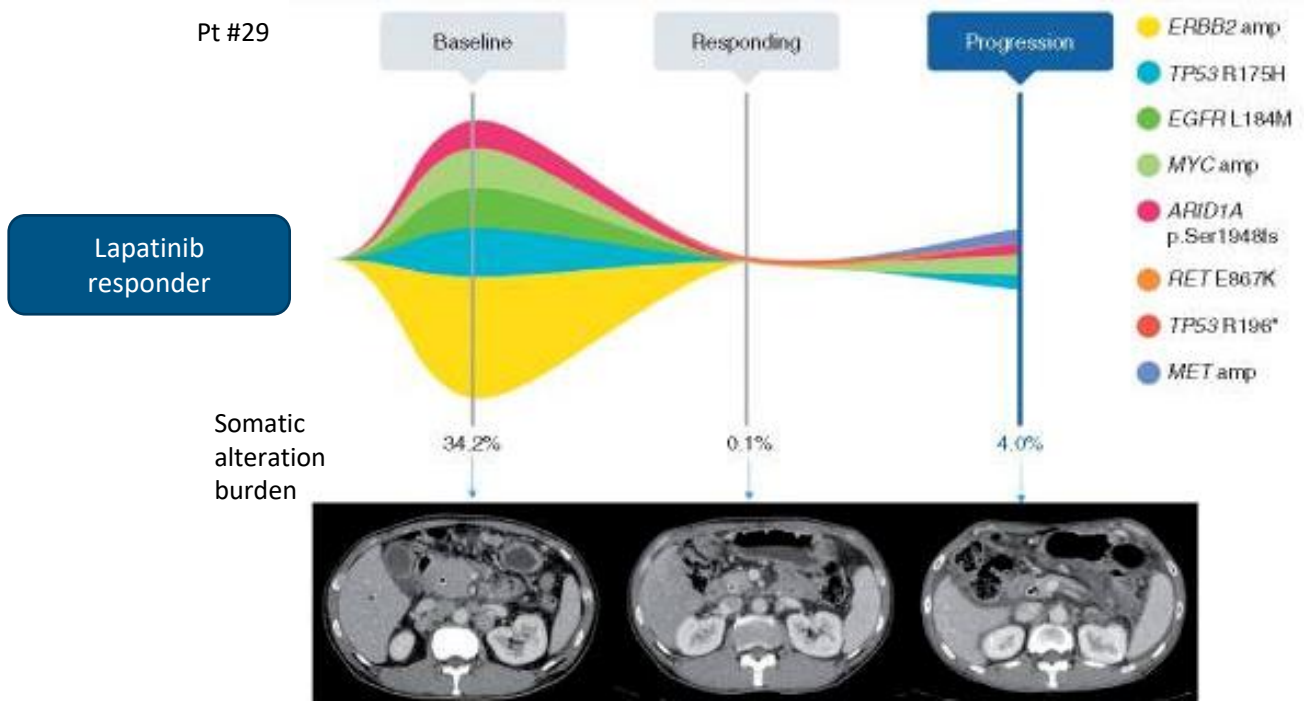
FIGHT subgroup analysis

Profile	PFS HR (95% CI)	OS HR (95% CI)
Tumor IHC+/ctDNA-	0.63 (95% CI 0.4-0.99)	0.66 (95% CI 0.39-1.12)
Tumor IHC+/ctDNA+	0.15 (95% CI 0.02-1.18)	0.10 (95% CI 0.01-0.83)

Shitara K, et al. *N Engl J Med*. 2020;382(25):2419-2430. Shitara K, et al. *Ann Oncol*. 2021;32(9):1127-1136. Joubert N, et al. *Pharmaceuticals (Basel)*. 2020;13(9):245. Kim ST, et al. *Ann Oncol*. 2018;29(4):1037-1048; Maron SB, et al. *Clin Cancer Res*. 2019;25(23):7098-7112. Wang H, et al. *Eur J Cancer*. 2018;88:92-100.

Catenacci DVT, et al. *J Clin Oncol*. 2021;39(15 suppl):4010.

ctDNA May Identify Emerging Resistance Mechanisms



- Emerging MYC and new MET amplification
- Other resistance mutations reported in literature:
  - EGFR amplifications
  - PIK3CA/R1/C3
  - ERBB2/4 mutations
  - NF1 mutations

Potential application

- Guide subsequent targeted therapies on progression
- Facilitate novel therapeutic discovery
- Predict responses to subsequent therapies

Kim ST, et al. *Ann Oncol*. 2018;29(4):1037-1048. Wang DS, et al. *Gut*. 2019; 68(7):1152-1161.

Investigational/Emerging HER2-Targeting Options

Select Novel HER2-Directed Strategies

Strategy	Selected Agents
Monoclonal antibodies (with augmented ADCC)	Margetuximab
Bispecific antibodies	ZW25
Tyrosine kinase inhibitors	Tucatinib Neratinib (+ trastuzumab or cetuximab)
Immunotherapy combinations	Numerous

Courtesy Dr. Marshall

HER2 + IO

Why did this work in GEJ/Gastric and not Breast?

Select Novel Immunotherapy Combinations for HER2-Positive Gastric Cancer

Study	Identifier	Regimen	Phase
MAHOGANY	NCT04082364	Margetuximab ± PD-1 inhibitor ± chemotherapy ± dual checkpoint inhibitor	II/III
INTEGA	NCT03409848	Ipilimumab or FOLFOX + nivolumab + trastuzumab	II
DESTINY-Gastric03	NCT04379596	Trastuzumab deruxtecan ± chemotherapy ± durvalumab	Ib/II
DESTINY-Gastric04	NCT04704934	Trastuzumab deruxtecan vs ramucirumab + paclitaxel	III
MOUNTAINEER-02	NCT04499924	Tucatinib + trastuzumab or placebo + ramucirumab + paclitaxel	II/III
	NCT04276493	Zanidatamab + chemotherapy ± tislelizumab	I/II

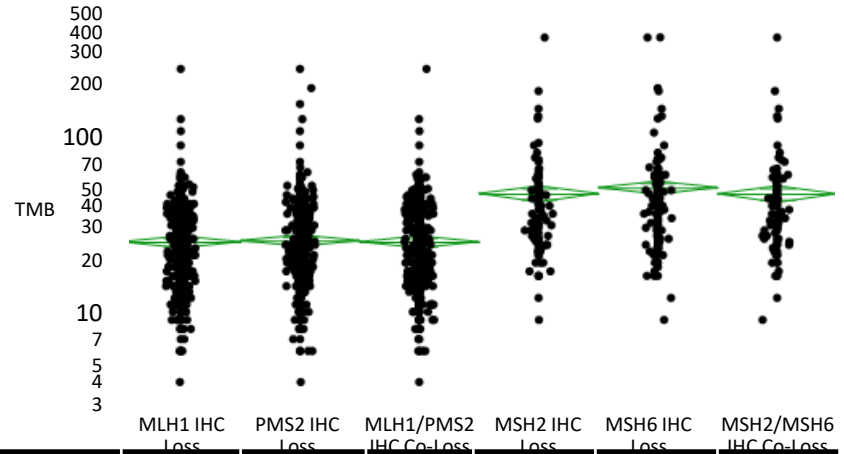
Courtesy Dr. Marshall

IO Biomarkers

- MSI-H
  - 57% RR (KN-059)
- PDL-1
  - Higher is better
- TMB
  - Higher is better

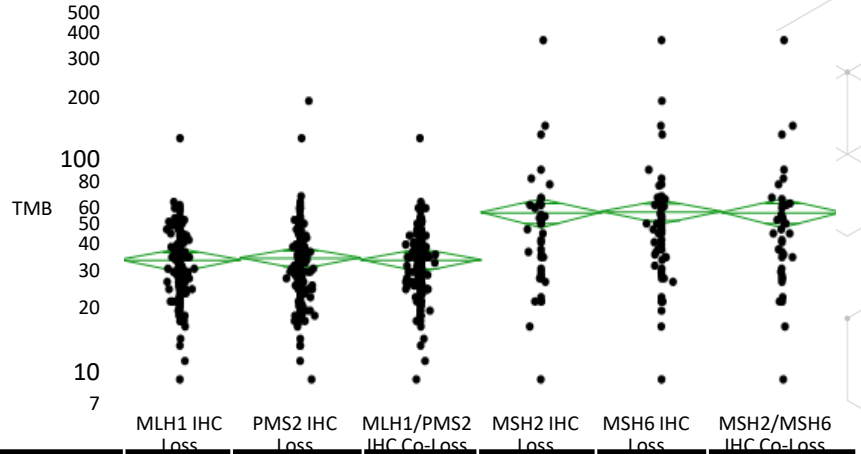
MSI-H Tumors Are Not Created Equal

All Tumors



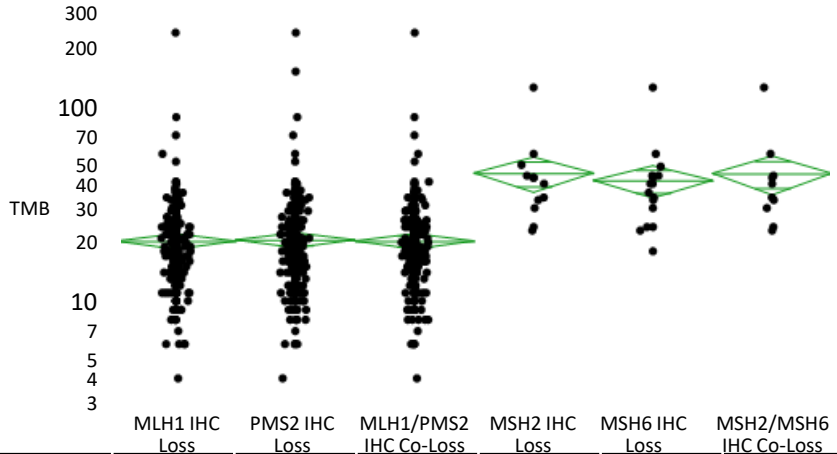
Mean mt/Mb	MLH1 IHC Loss	PMS2 IHC Loss	MLH1/PMS2 IHC Co-Loss	MSH2 IHC Loss	MSH6 IHC Loss	MSH2/MSH6 IHC Co-Loss
	25	25	25	47	51	47

CRC



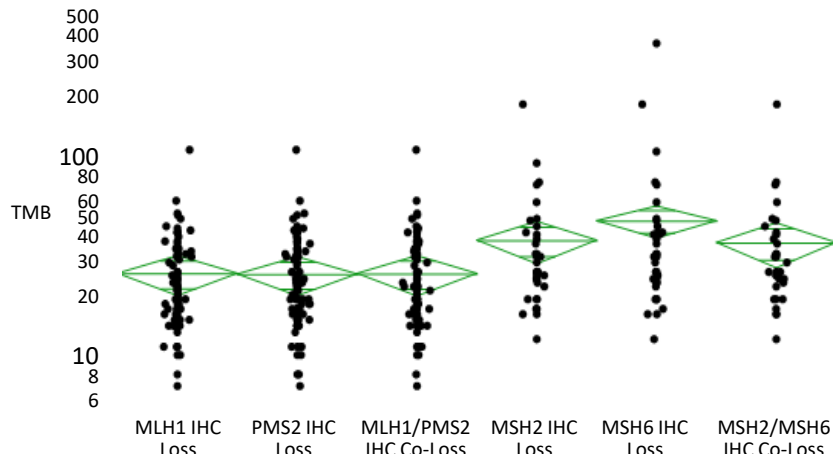
	MLH1 IHC Loss	PMS2 IHC Loss	MLH1/PMS2 IHC Co-Loss	MSH2 IHC Loss	MSH6 IHC Loss	MSH2/MSH6 IHC Co-Loss
	33	34	33	55	56	55

Endometrial



Mean mt/Mb	MLH1 IHC Loss	PMS2 IHC Loss	MLH1/PMS2 IHC Co-Loss	MSH2 IHC Loss	MSH6 IHC Loss	MSH2/MSH6 IHC Co-Loss
	20	21	20	46	42	45

Other Cancers

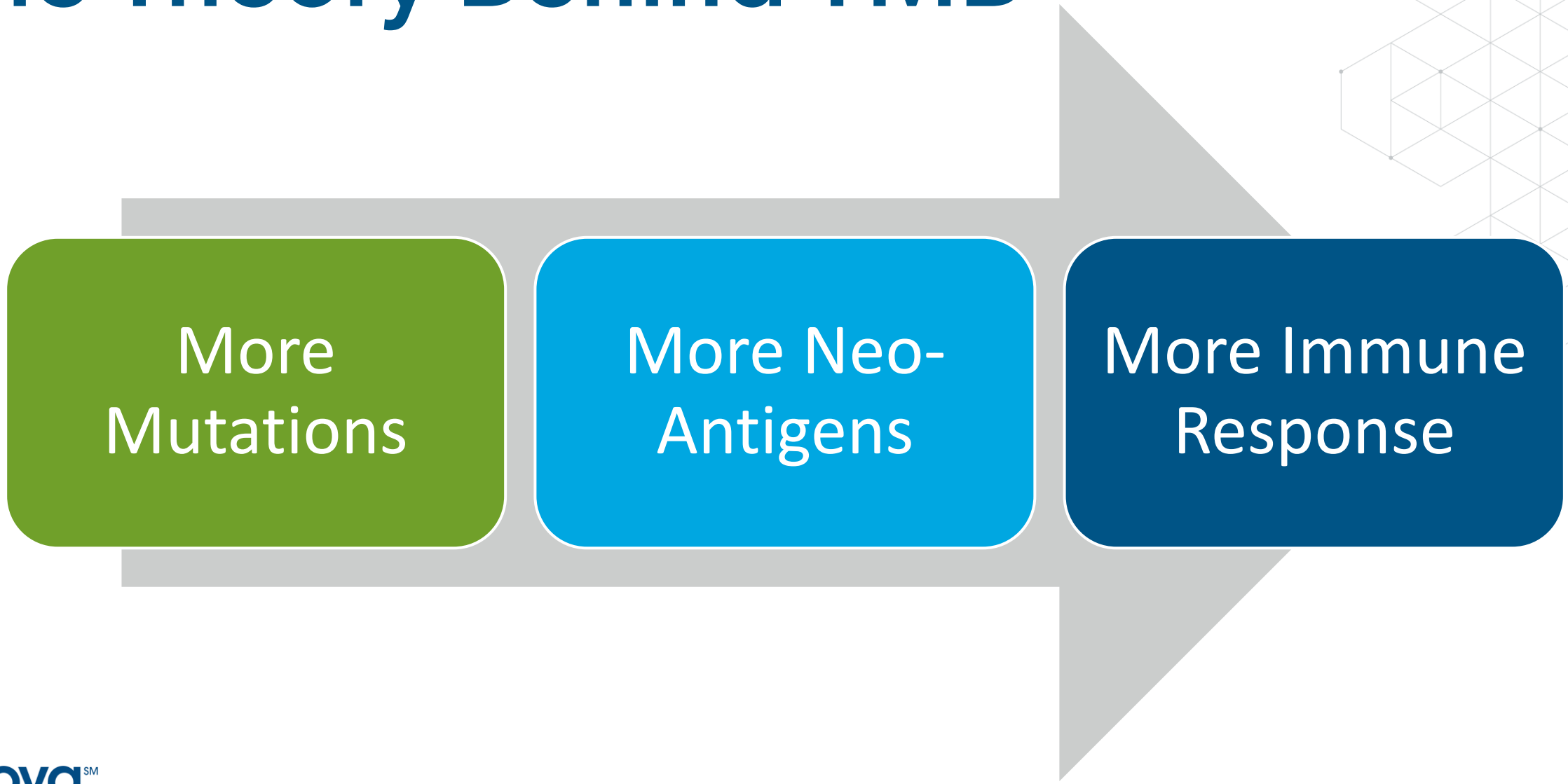


	MLH1 IHC Loss	PMS2 IHC Loss	MLH1/PMS2 IHC Co-Loss	MSH2 IHC Loss	MSH6 IHC Loss	MSH2/MSH6 IHC Co-Loss
	26	25	26	38	47	37

prova℠ EDUCATION

Hall. ASCO GI 2019. Abstr 505.

The Theory Behind TMB



The Big Unknown

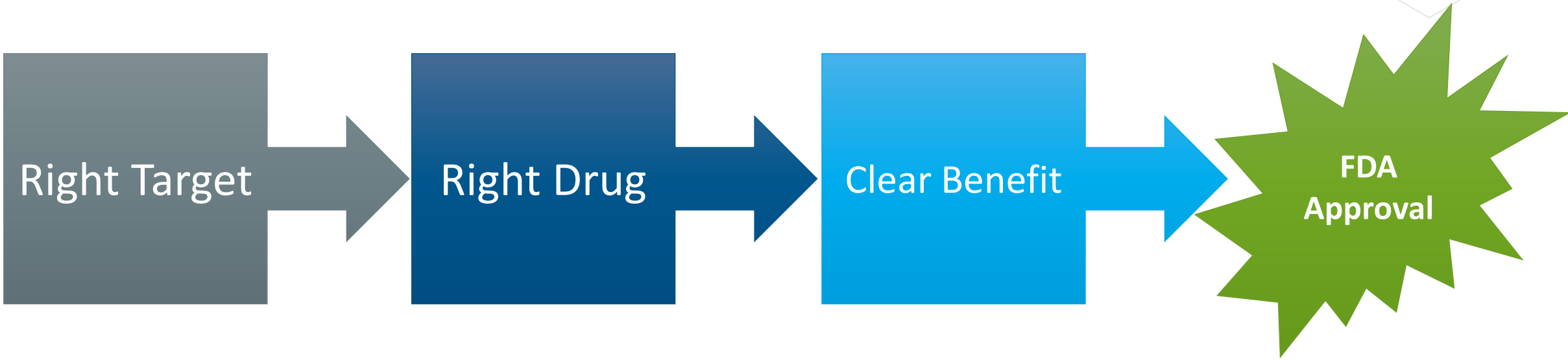
Precision Medicine

Prospective incorporation of molecular profiling will transform global cancer care

Maturation of Precision Medicine

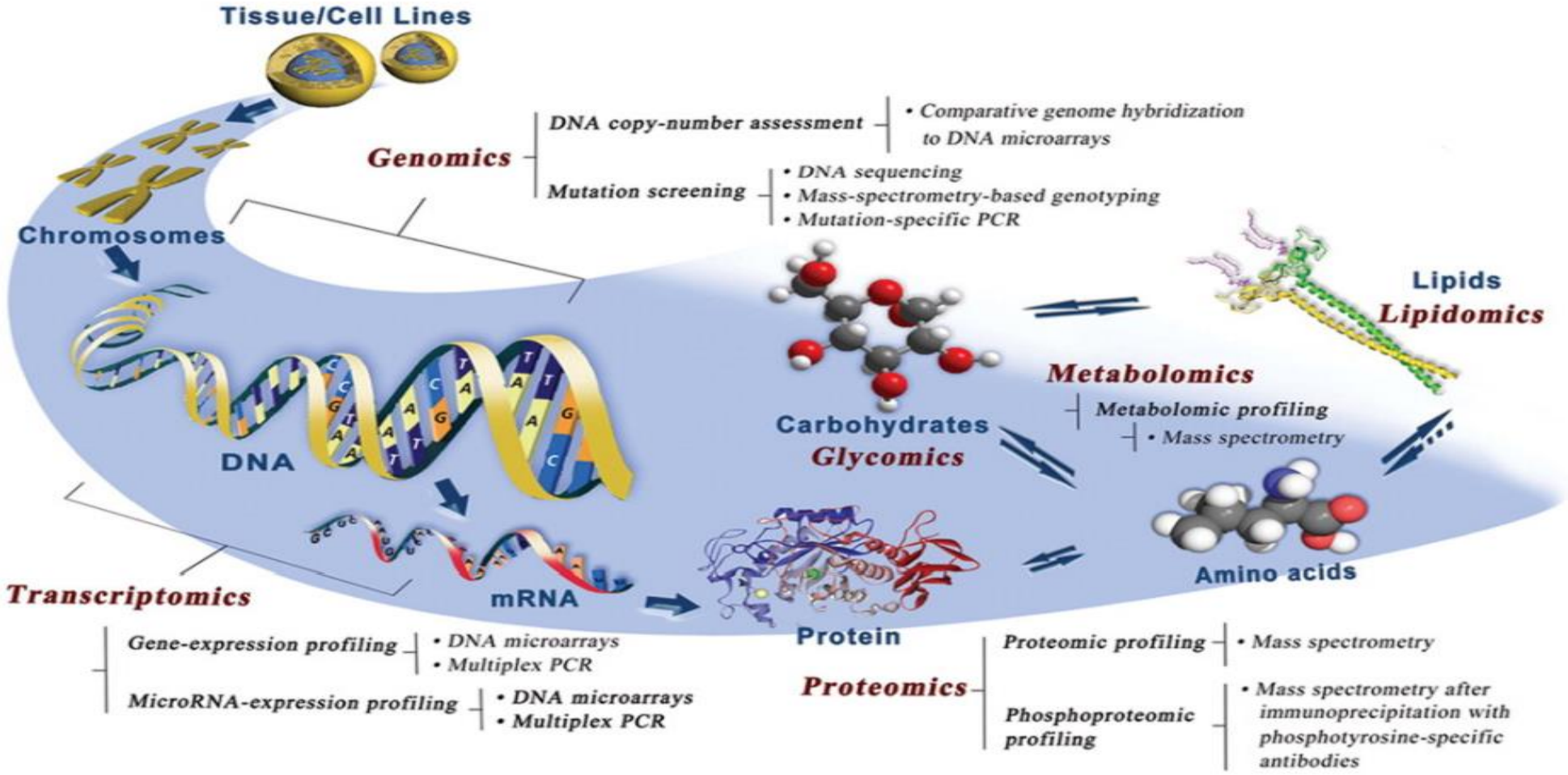
The New Order of Clinical Research

- Phase 3 trials are less necessary
- Drugs are approved for biomarkers, not cancer types
- Guidelines may be just as important as regulatory approval



Why DNA Mutations Only Tell Part of the Story

Multi-Omics

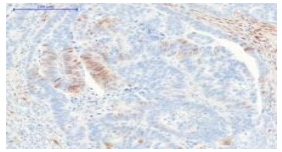


Thies J. *Soil Biota*. 2015:10.1016/B978-0-12-415955-6.00006-2.

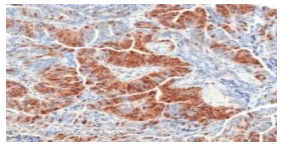
Standard of Biobanking: It Is All About the Tissue

Tissue ischemia and protein phosphorylation

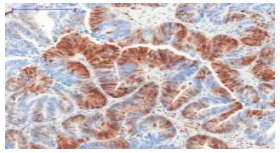
10 min



20 min



60 min



- ✓ Exact documented and very short tissue cold ischemia times of < 12 min (mean 7 min)
- ✓ Exact tissue localization and standardized fixation
- ✓ Complete biospecimen sets
- ✓ Highest tissue quality monitored by visual inspection, H&E staining,
- ✓ and microscopic assessment
- ✓ Native and rapid fluid preparations
- ✓ Complete specimen data
- ✓ Complete clinical data
- ✓ Patients' confidentiality assured following international standards

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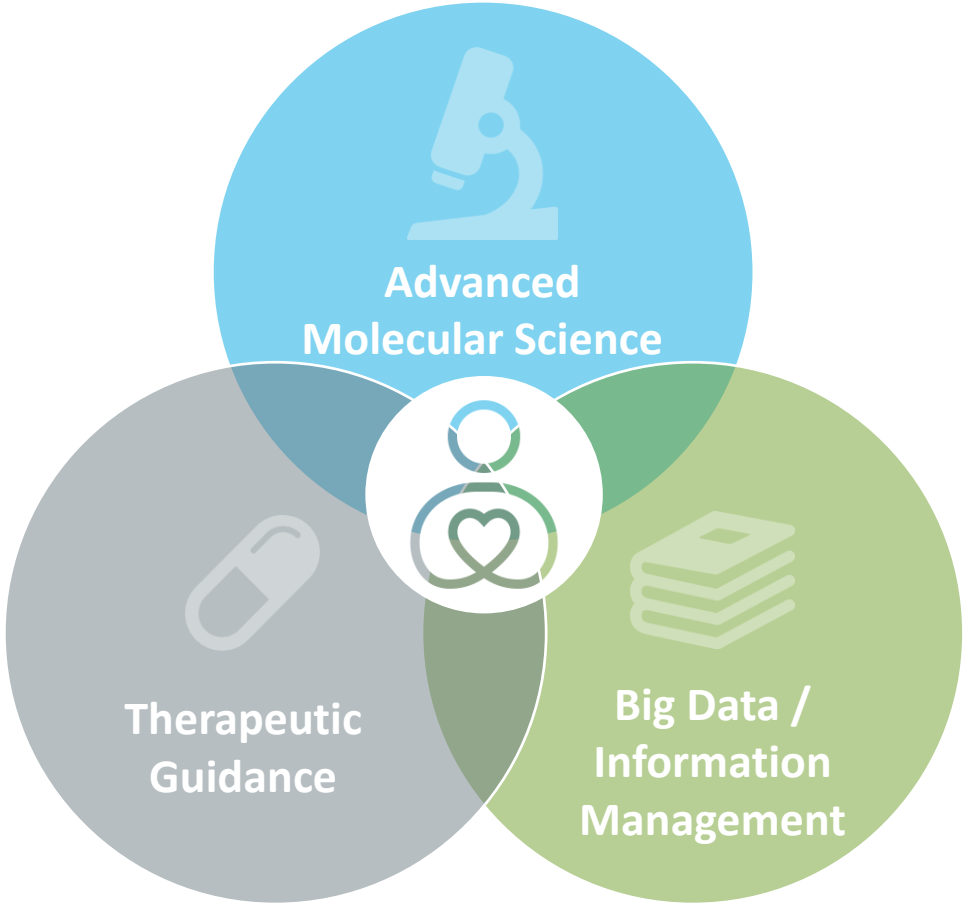
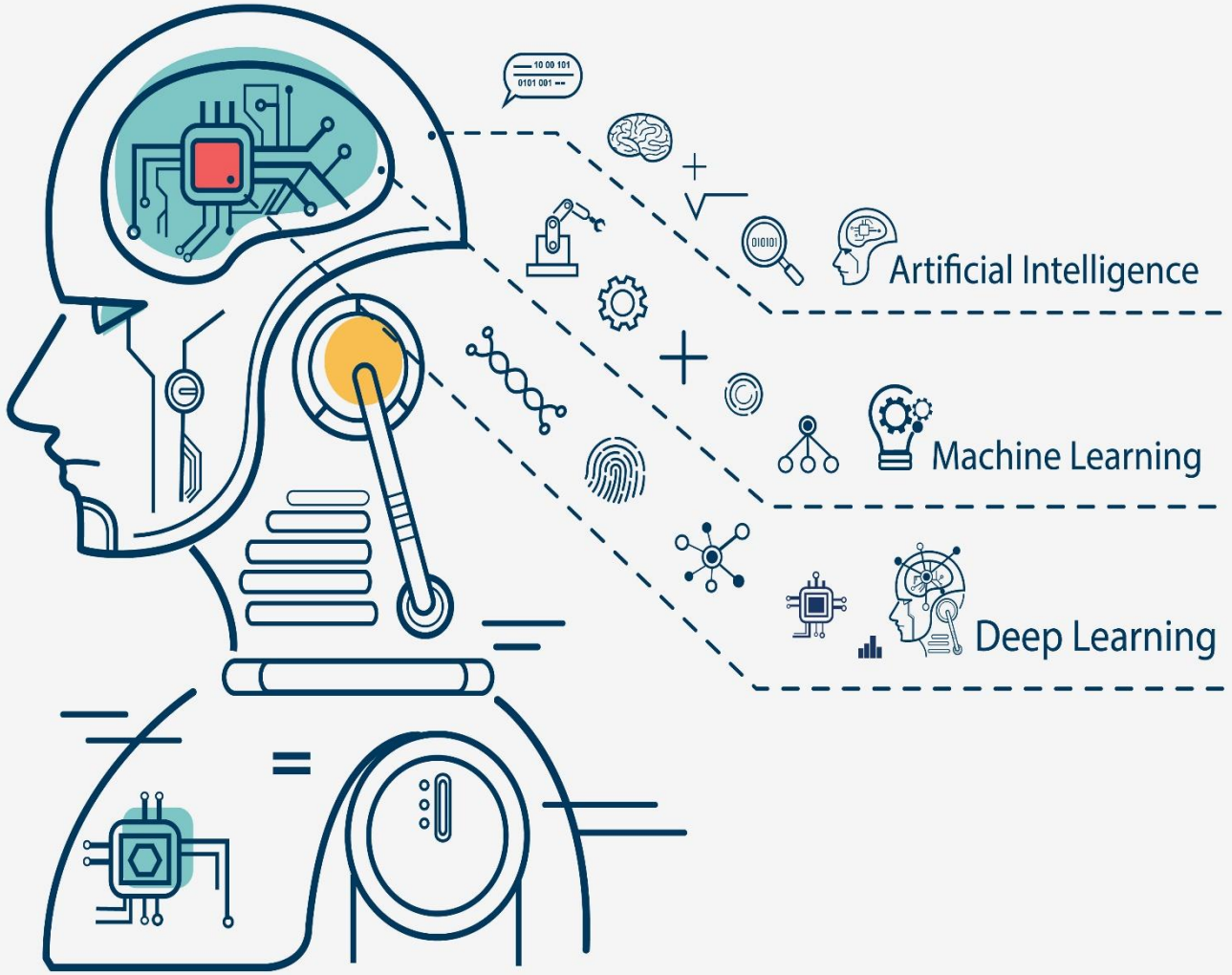
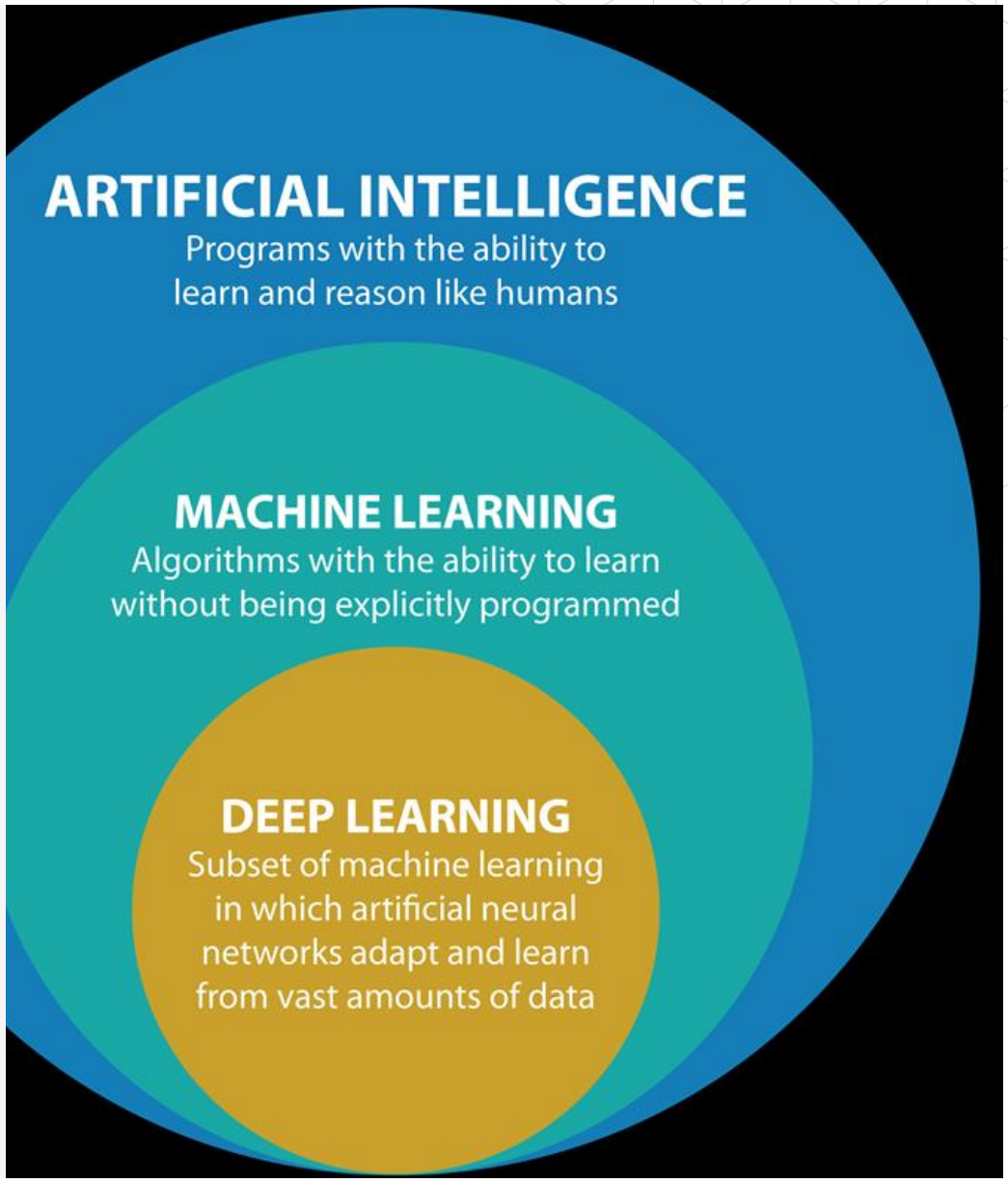
The Precision Medicine Era




Artificial Intelligence
Machine Learning
Deep Learning


ARTIFICIAL INTELLIGENCE
Programs with the ability to learn and reason like humans
MACHINE LEARNING
Algorithms with the ability to learn without being explicitly programmed
DEEP LEARNING
Subset of machine learning in which artificial neural networks adapt and learn from vast amounts of data

Now Published

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Clinical Validation of a Machine-learning–derived Signature Predictive of Outcomes from First-line Oxaliplatin-based Chemotherapy in Advanced Colorectal Cancer

Jim P. Abraham[1], Daniel Magee[1], Chiara Cremolini[2], Carlotta Antoniotti[2], David D. Halbert[1], Joanne Xiu[1], Phillip Stafford[1], Donald A. Berry[3], Matthew J. Oberley[1], Anthony F. Shields[4], John L. Marshall[5], Mohamed E. Salem[6], Alfredo Falcone[2], Axel Grothey[7], Michael J. Hall[8], Alan P. Venook[9], Heinz-Josef Lenz[10], Anthony Helmstetter[1], W. Michael Korn[1], and David B. Spetzler[1]

ABSTRACT

Purpose: FOLFOX, FOLFIRI, or FOLFOXIRI chemotherapy with bevacizumab is considered standard first-line treatment option for patients with metastatic colorectal cancer (mCRC). We developed and validated a molecular signature predictive of efficacy of oxaliplatin-based chemotherapy combined with bevacizumab in patients with mCRC.

Experimental Design: A machine-learning approach was applied and tested on clinical and next-generation sequencing data from a real-world evidence (RWE) dataset and samples from the prospective TRIBE2 study resulting in identification of a molecular signature, FOLFOX*ai*. Algorithm training considered time-to-next treatment (TTNT). Validation studies used TTNT, progression-free survival, and overall survival (OS) as the primary endpoints.

Results: A 67-gene signature was cross-validated in a training cohort ($N = 105$) which demonstrated the ability of FOLFOX*ai* to distinguish FOLFOX-treated patients with mCRC with increased benefit from those with decreased benefit. The signature was predictive of TTNT and OS in an independent RWE dataset of 412 patients who had received FOLFOX/bevacizumab in first line and inversely predictive of survival in RWE data from 55 patients who had received first-line FOLFIRI. Blinded analysis of TRIBE2 samples confirmed that FOLFOX*ai* was predictive of OS in both oxaliplatin-containing arms (FOLFOX HR, 0.629; $P = 0.04$ and FOLFOXIRI HR, 0.483; $P = 0.02$). FOLFOX*ai* was also predictive of treatment benefit from oxaliplatin-containing regimens in advanced esophageal/gastro-esophageal junction cancers, as well as pancreatic ductal adenocarcinoma.

Conclusions: Application of FOLFOX*ai* could lead to improvements of treatment outcomes for patients with mCRC and other cancers because patients predicted to have less benefit from oxaliplatin-containing regimens might benefit from alternative regimens.

Introduction

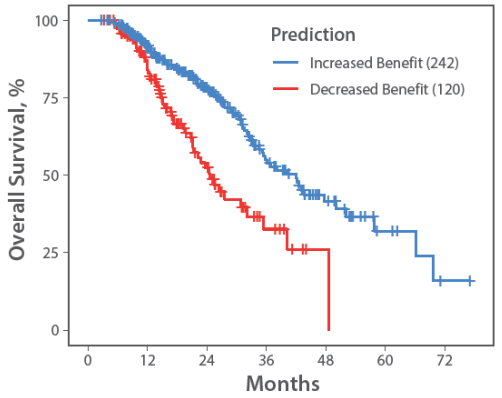
Over the last 2 decades, conventional chemotherapies (e.g., oxali-

Abraham JP, et al. *Clin Cancer Res*. 2021;27(4):1174-1183.

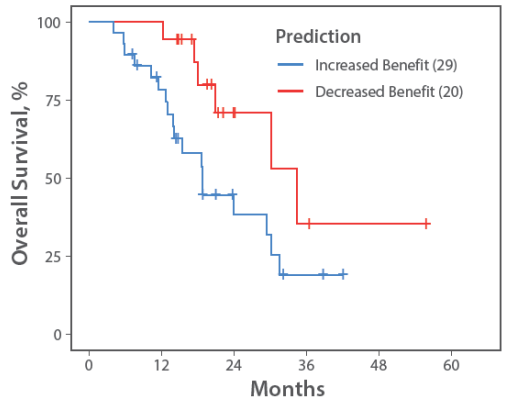
First Clinically Validated AI-Driven Frontline Chemotherapy Predictor

- Median OS ↑ = 17.5 months in patients treated in manner consistent with AI predictor vs patients treated counter to the prediction
- Demonstrated ~71% difference in median OS for patients in the FOLFOX 1st arm compared to the FOLFIRI 1st arm
- Demonstrated the impact of how FOLFOX and FOLFIRI are sequenced in patient treatment
- 2 independent data sets:
  - 412 manually curated cases with RWE
  - 149 cases analyzed retrospectively from the randomized, prospective phase 3 TRIBE2 study

mCRC RWE FOLFOX+BV–FOLFIRI+BV



mCRC RWE FOLFIRI+BV–FOLFOX+BV



	AI Results Indicate:	
	FOLFOX + BV 1st → FOLFIRI + BV 2nd (FOLFOX/BV RWE cohort)	**FOLFIRI + BV 1st → 2nd FOLFOX + BV** (FOLFIRI/BV RWE cohort)
OS When Patient Received: FOLFOX/BV 1st → FOLFIRI + BV 2nd	**42.0 months**	18.7 months
OS When Patient Received: FOLFIRI+BV 1st → FOLFOX 2nd	24.5 months	**34.4 months**

Abraham JP, et al. *Clin Cancer Res*. 2021;27(4):1174-1183.

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