



What's Next for Systemic Therapy in Gastroesophageal Cancer

Emerging systemic therapies and precision treatment

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Disclosures

Consultant for Amgen, AstraZeneca, BeOne Medicines, Daiichi Sankyo and Guardant Health, IQVIA

- This presentation and/or comments will be free of any bias toward or promotion of the above referenced companies or their product(s) and/or other business interests.
- This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.
- This presentation has been peer-reviewed and no conflicts were noted.



Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.



The clinical questions ahead

- GE cancers remain a leading cause of cancer mortality
- Survival has improved, but patients still die of metastatic disease
- We are entering a new era of biomarker –driven therapy



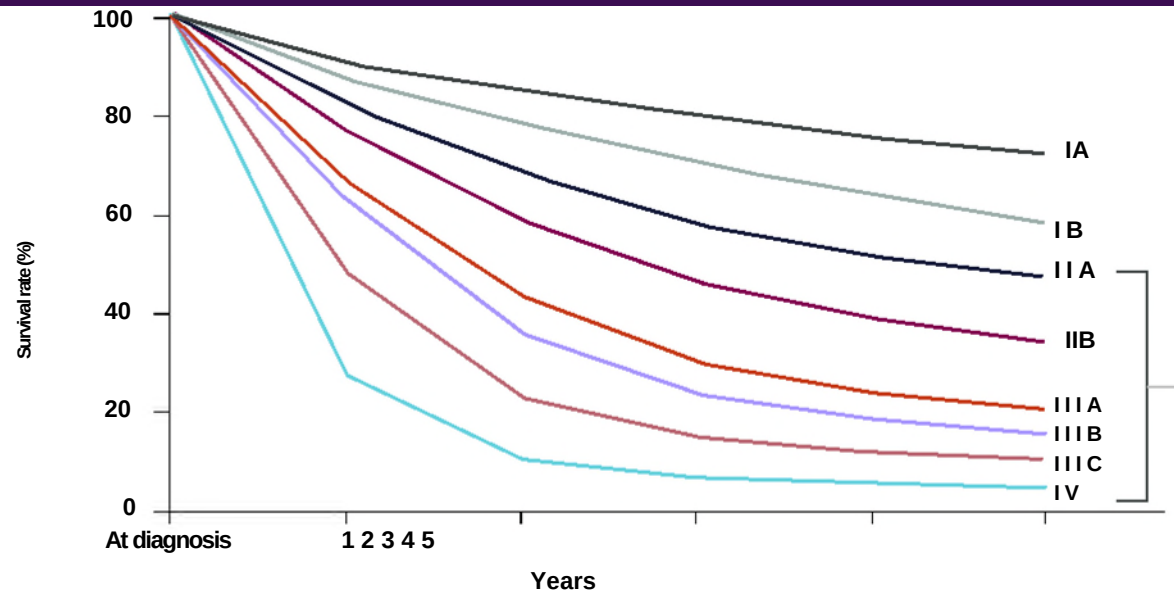
- Can earlier systemic therapy increase cure rates?
- Which biomarker should drive first-line treatment
- Can new drug platforms overcome acquired resistance
- How should sequence treatments as options expand



Each decision requires us to think several moves ahead

Recurrence rates are high and survival is poor for patients with resectable esophagogastric adenocarcinomas

Observed survival rates for surgically resected gastric adenocarcinomas (N=10,601; SEER, 1991–2000)*¹



Adapted from Washington K. 2010¹

The majority of patients with gastric cancer have poor prognosis with surgery alone

Outcomes after curative surgery for patients with localized GEA²



- **Survival declines with advancing stage**, highlighting the limitations of surgery alone in historical gastric cancer cohorts.
- **Recurrence remains a challenge after curative surgery**, with reported 5-year RFS of 55% and OS of 64%, supporting the need for more effective perioperative strategies.

*Data from the SEER 1973–2005 Public Use file diagnosed in 1991–2000.

OS=overall survival; RFS=recurrence-free survival; SEER=National Cancer Institute Surveillance, Epidemiology, and End Results Program.

1. Washington K. *Ann Surg Oncol*. 2010;17(12):3077–307. 2. Ve rslu is JM et al. *Nat Med*. 2020;26(4):475–484.



MATTERHORN study design

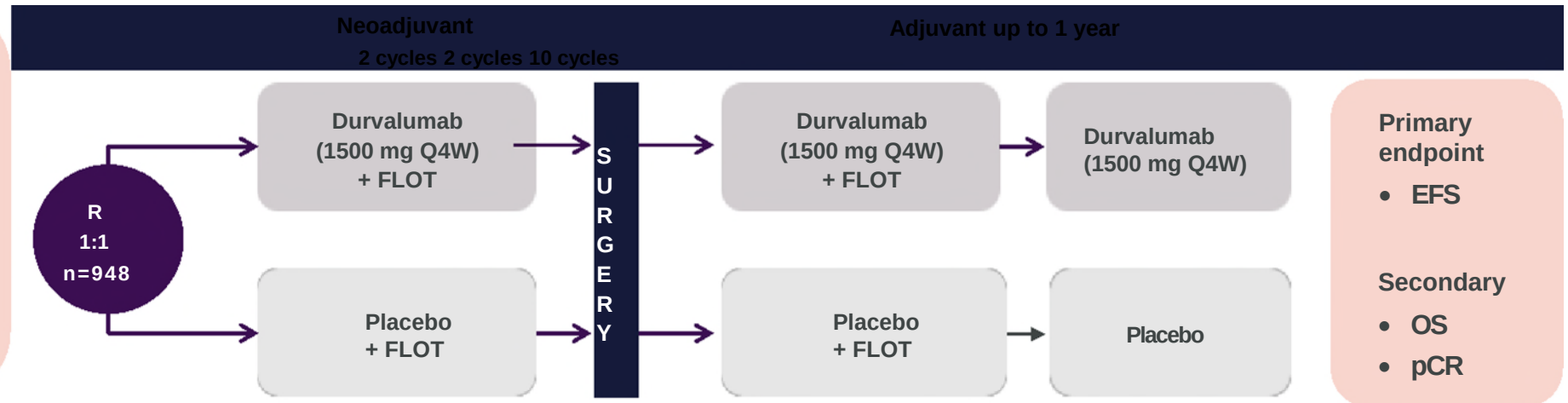
A global, Phase III, randomized, double-blind, placebo-controlled study

Study population

- Gastric and GEJ adenocarcinoma
- Stage II–IVa
- No evidence of metastasis
- No prior therapy
- ECOG PS 0 or 1
- Global enrolment in Asia, Europe, and North and South America

Stratification factors

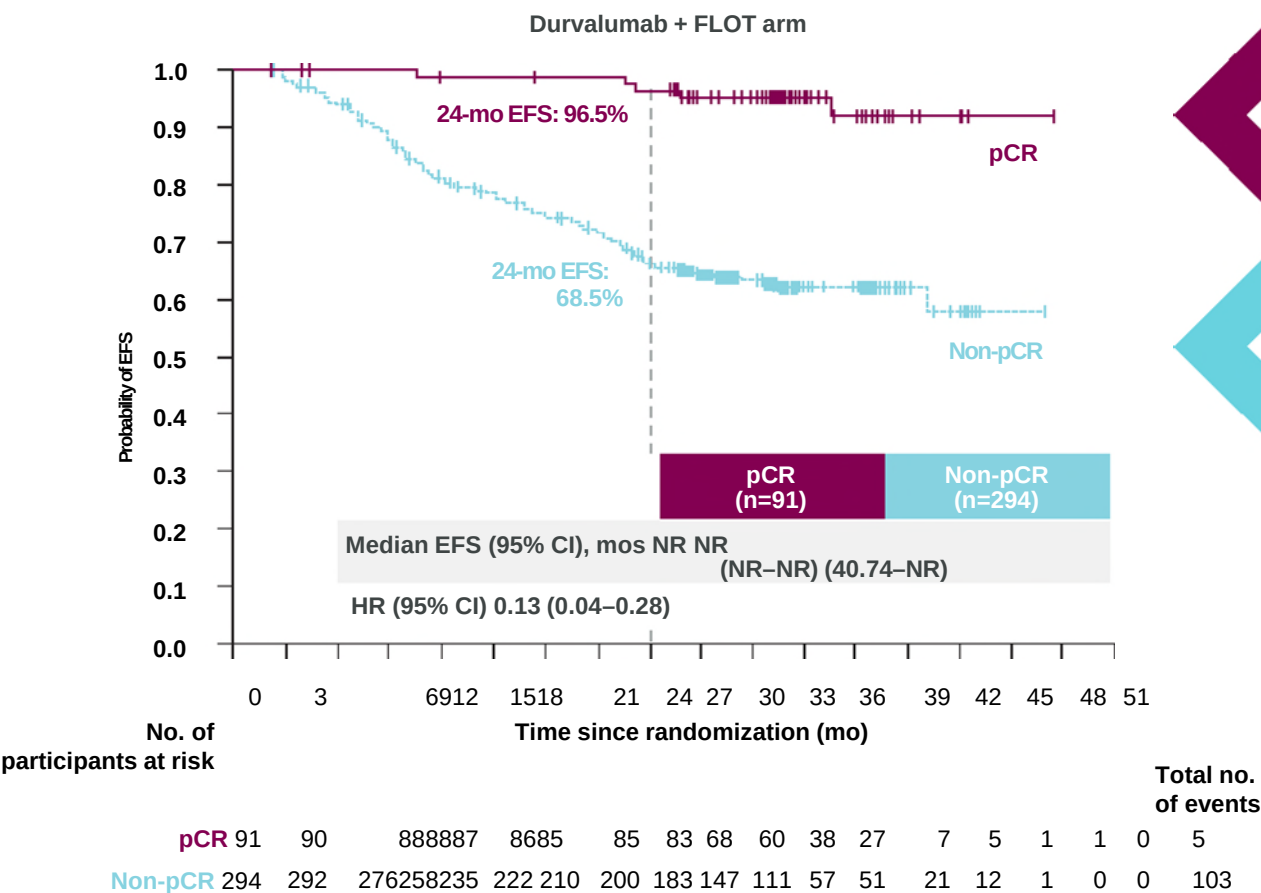
- Asia vs. non-Asia
- Clinical N+ vs. N-
- PD-L1: TAP <1% vs. TAP ≥1%*



FLOT dose flexibility was allowed in accordance with local standard clinical practice, or with the FLOT dose modification guidance contained within the FLOT4 protocol

Building on MATTERHORN: Exploring new treatment strategies with IO and ADC combinations in GEA

pCR matters it reflects a deep pathological response associated with favorable long-term outcomes. an early measure of treatment activity



Can we identify those patients?

How can pCR be improved?

That raises two questions.

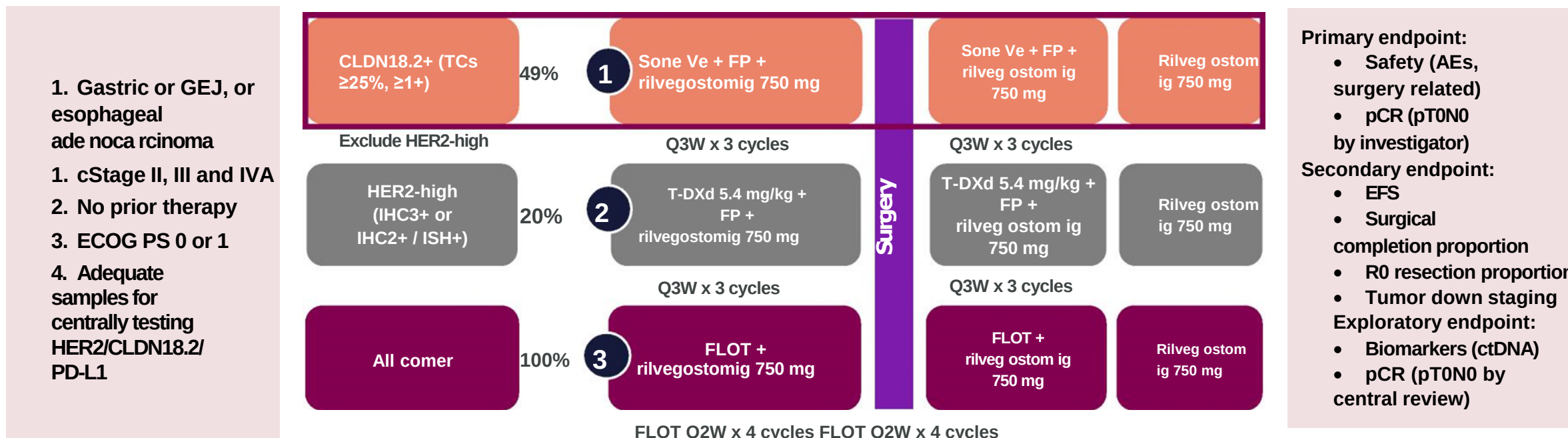
- Can pretreatment biomarkers or early response assessments identify patients likely to achieve pCR?
- For patients unlikely to achieve pCR, can we improve outcomes through alternative strategies, such as biomarker-selected ADC and immunotherapy combinations

- Within the durvalumab plus FLOT arm, patients who achieved a pathological complete response had a 24-month EFS of 96.5%, compared with 68.5% among those with residual disease.

Beyond PD-1: TIGIT,LAG-3,CTLA-4, novel immune agonists
PD-1 is chapter 1, not the final chapter

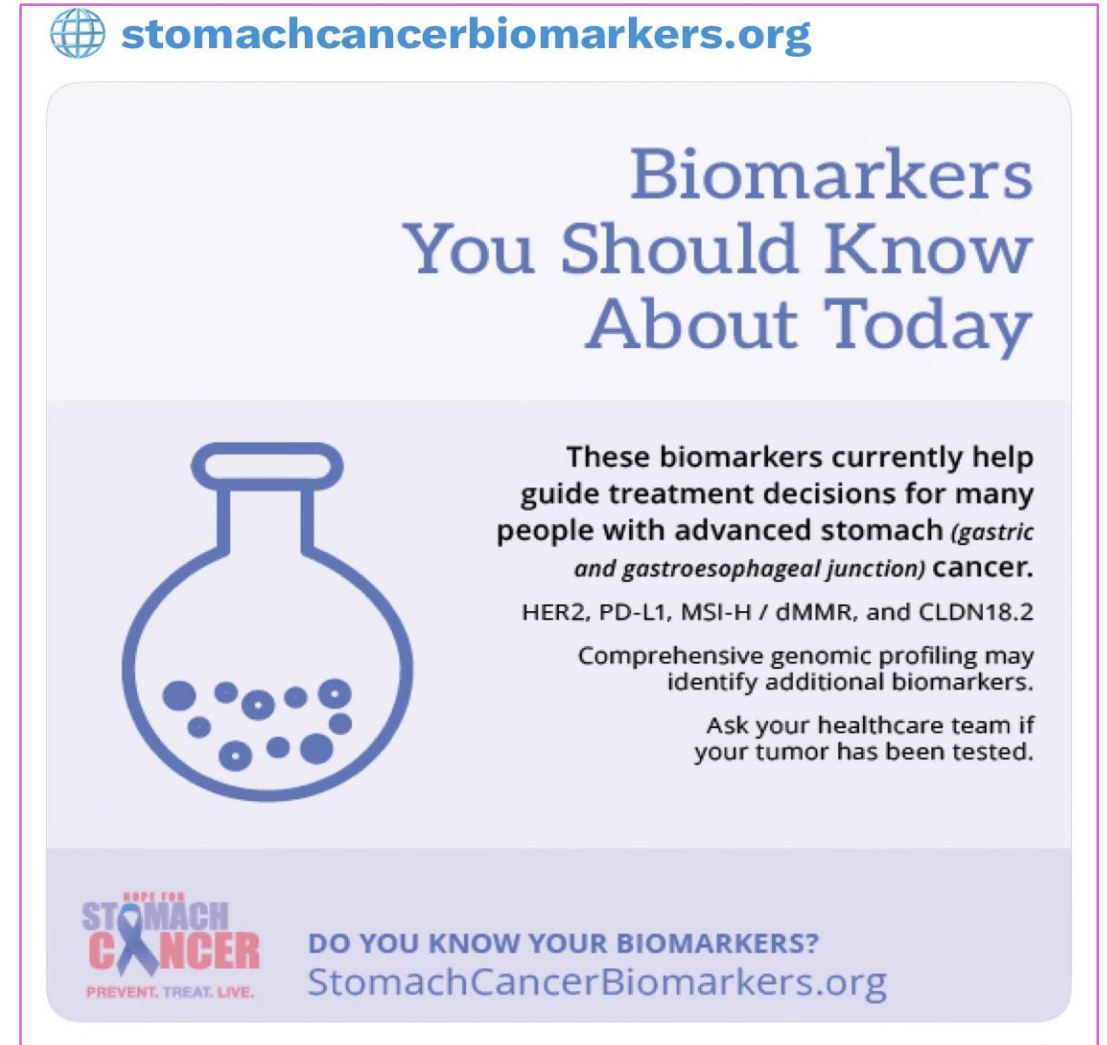
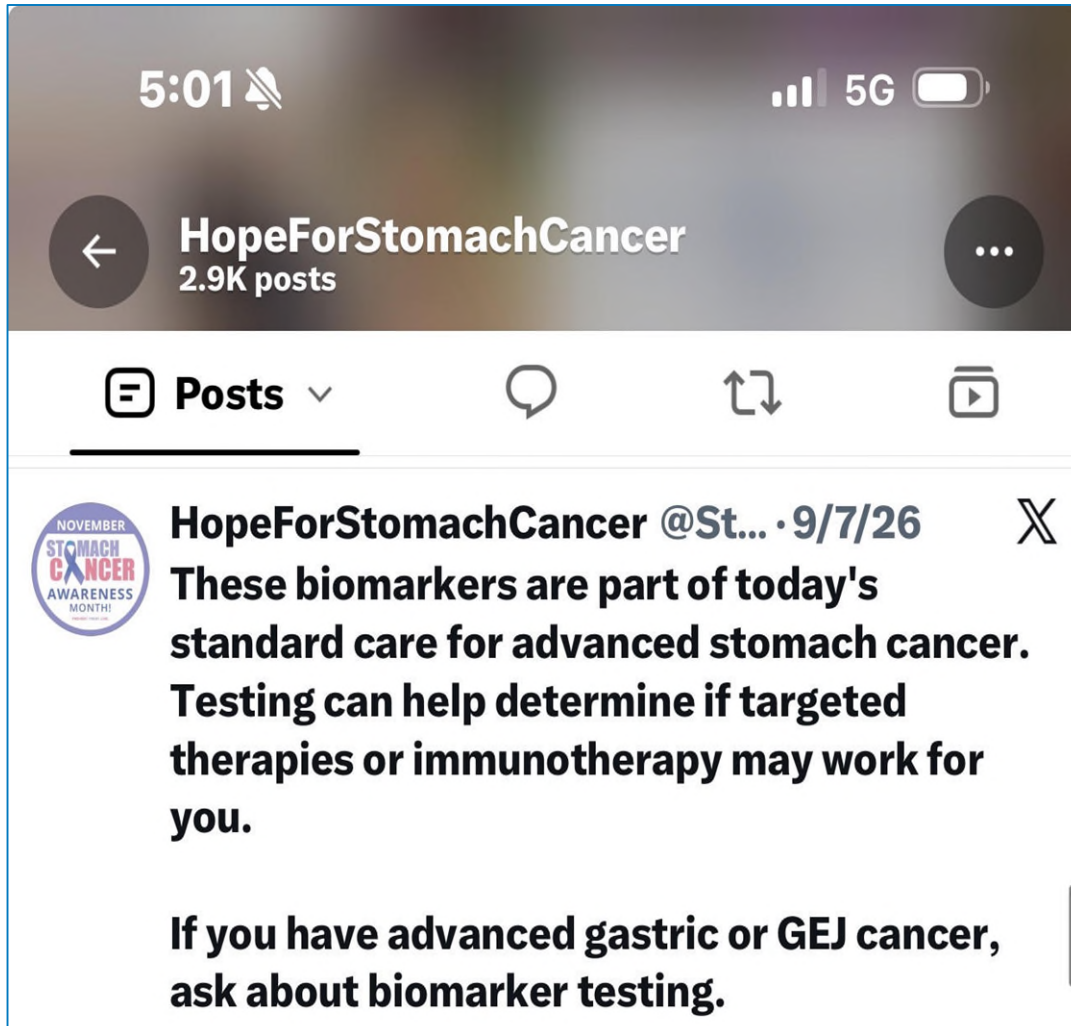


GEMINI-PeriOp GC: biomarker-driven clinical trial



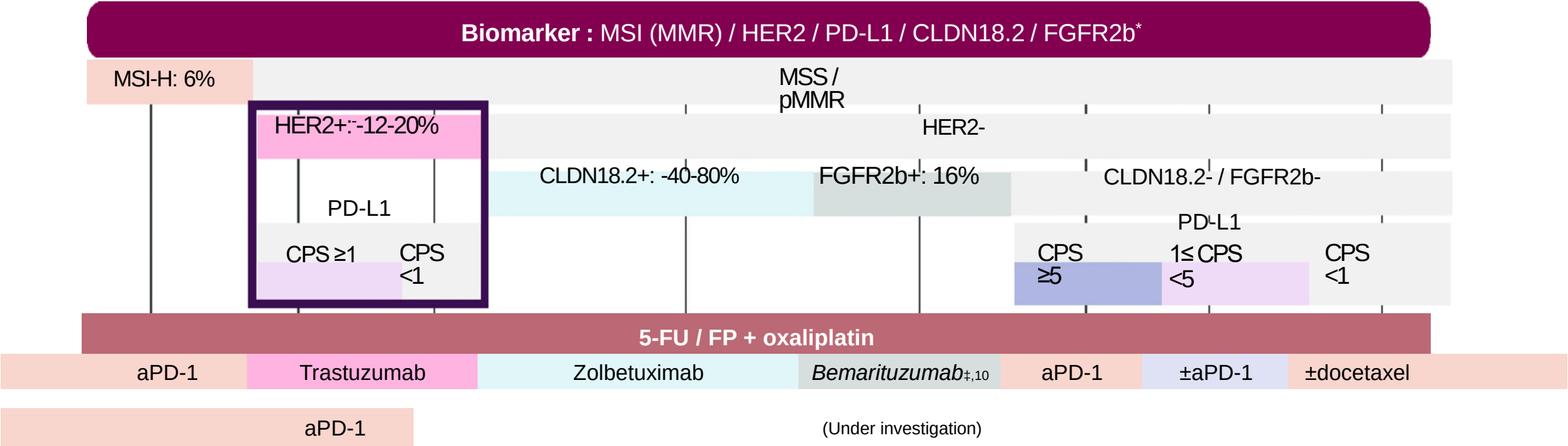
- It evaluates whether matching ADCs to HER2 or CLDN18.2 expression, together with CT and IO, can deepen pathological response while preserving surgical safety.
- Beyond pCR, EFS and exploratory biomarkers will help us understand whether these strategies offer durable benefit and which patients may benefit most.
- **AACR-ADOPT-GEA** : a phase II adaptive platform trial evaluating biomarker-matched targeted therapy plus IO and CT in resectable GEA. Its two-stage design first assesses pathological response and develops response predictors, then tests whether selected complete responders can safely omit surgery and preserve their stomach or esophagus.

Biomarker Awareness: Patients Are Asking—Are We Ready?



Patient selection and molecular stratification

1L SoC for advanced/metastatic GC/GEJC



FGFR2b is an emerging biomarker, with positivity defined here as moderate-to-strong (2+/3+) staining in ≥10% of tumor cells. Bemaritumab plus CT is not approved for 1L GEA

C

The Evolving Treatment Landscape in Gastroesophageal Cancer

One cancer, several molecular diseases

HER2+

An established target with new first-line regimens and an expanding role for ADCs

CLDN18.2+

Eligibility varies by drug, assay, staining intensity and expression cutoff.

FGFR2b

A selected population with a phase III signal that weakened with follow-up.

c-MET

Amplification identifies a small, distinct population; ADC programs study broader c-MET expression.

ESCC

ADCs are being evaluated after first-line chemoimmunotherapy.

GEA: histologically and molecularly diverse, which drives resistance and limits one-size-fits-all therapy.

ESCC: a distinct disease, frequently encountered in practice, and it deserves attention as new treatment strategies emerge

HER2: Van Cutsem, Gastric Cancer 2015 ·

CLDN18.2: AstraZeneca, Jul 2026; SPOTLIGHT/GLOW 2023 ·

FGFR2b: Rha, JCO Precis Oncol 2025 · MET: Lennerz, J Clin Oncol 2011 ·

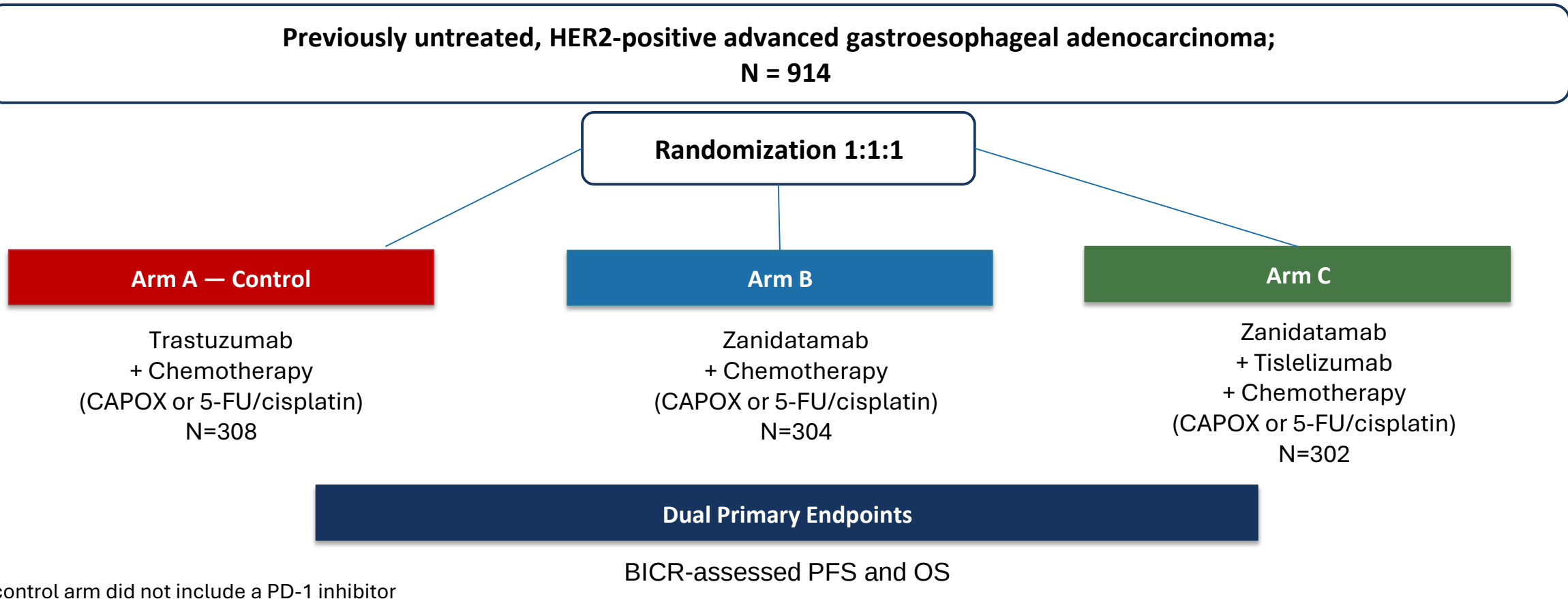
ESCC: CheckMate 648; KEYNOTE-590



HERIZON-GEA-01: Study Design

Global, open-label, randomized phase III trial

a new treatment horizon into view—and into routine practice



HERIZON-GEA-01: Progression-Free Survival

- Zanidatamab + CT: 35% relative reduction in the risk of progression or death versus trastuzumab + CT
- Zanidatamab + tislelizumab + CT: 37% relative reduction
- Both comparisons were statistically significant: $P < .0001$

Replacing trastuzumab with zanidatamab substantially prolonged disease control in first-line HER2-positive disease.

Treatment	Median PFS	HR vs control
Trastuzumab + CT	8.1 mo	—
Zanidatamab + CT	12.4 mo	0.65
Zanidatamab + tislelizumab + CT	12.4 mo	0.63

Both zanidatamab regimens prolonged PFS versus trastuzumab + chemotherapy



HERIZON-GEA-01:OS benefit with the tislelizumab triplet

Treatment	Median OS	HR vs trastuzumab + chemotherapy
Trastuzumab + CT	19.2 mo	—
Zanidatamab + CT	24.4 mo	0.80
Zanidatamab + tislelizumab + CT	26.4 mo	0.72

- Significant OS benefit with zanidatamab + tislelizumab + CT. Median OS was 26.4 versus 19.2 months with trastuzumab + CT, with a 28% reduction in the hazard of death (HR 0.72).
- Zanidatamab + CT showed numerically longer OS, but did not reach statistical significance at this interim analysis.
- This trial does not establish superiority over pembrolizumab plus trastuzumab and CT, or prove the incremental benefit of tislelizumab over zanidatamab plus CT

CT: chemotherapy



HERIZON-GEA-01: triplet outcomes across PD-L1

Zanidatamab + tislelizumab + chemotherapy vs trastuzumab + chemotherapy

- The numerically stronger HR in TAP <1% is a subgroup observation
- It does not establish that PD-L1-negative tumors benefit more; the subgroup comparisons were not adjusted to prove a treatment-effect difference

PD-L1 TAP	Median PFS	PFS HR	Median OS	OS HR
<1%	18.5 vs 7.9 mo	0.47	29.7 vs 15.8 mo	0.49
≥1%	11.3 vs 8.3 mo	0.65	26.4 vs 21.2 mo	0.82

HERIZON-GEA-01: Safety & Clinical Implications

- The triplet improved OS versus trastuzumab + chemotherapy, with more high-grade treatment-related toxicity
- For US patients with CPS ≥ 1 , trastuzumab + chemotherapy + pembrolizumab is also an approved first-line regimen; HERIZON did not compare these approaches head to head
- As of August 2026, zanidatamab + tislelizumab + chemotherapy is FDA approved for HER2 IHC 3+ or IHC 2+/ ISH^+ disease

Regimen	Grade ≥ 3 TRAEs	HER2 therapy stopped for related AEs
Zanidatamab + tislelizumab + chemotherapy	71.8%	11.9%
Zanidatamab + chemotherapy	59.0%	8.5%
Trastuzumab + chemotherapy	59.6%	2.3%

The control arm lacked PD-1 inhibition

T-DXd improved OS versus ramucirumab + paclitaxel

n = 494	T-DXd 6.4 mg/kg	Ram + paclitaxel
Median OS	14.7 mo	11.4 mo
OS hazard ratio	0.70 (p = 0.0044)	reference
Median PFS	6.7 mo	5.6 mo
PFS hazard ratio	0.74	reference
Confirmed ORR	44.3%	29.1%
Disease control	91.9%	75.9%

- First randomized phase 3 to show OS benefit for a HER2-directed drug in 2L;
- it converts the DESTINY-Gastric01 3L signal (OS 12.5 vs 8.4 months, HR 0.59, Japan/Korea) into a global standard.
- Absolute gain is 3.3 months with a 30% reduction in risk of death.
- Re-biopsy or ctDNA to confirm HER2 status at progression, because HER2 loss after trastuzumab is described.

The question is no longer whether T-DXd works, but how early to use it.



T-DXd moves into first-line trials

DESTINY-Gastric05

Phase 3 · HER2+ · 1L · primary: PFS (BICR)

- T-DXd 5.4 mg/kg + 5-FU or capecitabine + pembrolizumab
- vs trastuzumab + platinum chemo + pembrolizumab
- Platinum-free: T-DXd replaces trastuzumab and platinum
- CPS <1: exploratory cohort without pembrolizumab
- Results expected ~2028

DESTINY-Gastric03

Phase 1b/2 · HER2+ and HER2-low · 1L

Part 2F (HER2+, n = 32): T-DXd 5.4 + FP + pembrolizumab

- ORR 75.0% (CPS ≥1 70.6%; CPS <1 72.7%)
- mPFS 12.1 mo; mDoR 12.3 mo
- Drug-related grade ≥3 AEs 34.4%; no drug-related ILD

Part 5 (HER2-low): T-DXd + volrustomig (PD-1/CTLA-4) + FP, under evaluation

If T-DXd combinations succeed in first line, how will HER2-directed therapy be sequenced after progression?



ARTEMIDE-Gastric01: first-line phase III design

Population

- HER2-positive advanced gastric/GEJ adenocarcinoma
- PD-L1 CPS ≥ 1
- Planned N = 700

Randomization
2:2:1

**T-DXd 5.4 mg/kg + fluoropyrimidine +
rilvegostomig**

N = 280

**Trastuzumab + chemotherapy +
pembrolizumab**

N = 280

**Trastuzumab + chemotherapy +
rilvegostomig**

N = 140 · new contribution of components

Primary Endpoints

- BICR-assessed PFS and OS

Status

- Trial design shown; phase III efficacy results pending

Rilvegostomig : PD-1 × TIGIT bispecific antibody



What's Next for CLDN18.2-Directed Therapy?

- **Antibody:** Zolbetuximab + chemotherapy in first line; SPOTLIGHT/GLOW selected tumors with $\geq 75\%$ moderate-to-strong staining (CLDN18.2-high tumors)
- **ADC:** Sone-ve and IBI343 are being studied after prior therapy. **Sone-ve: $\geq 25\%$ at any intensity in CLARITY-Gastric01. IBI343 (exatecan/topoisomerase I inhibitor payload): 2+/3+ in $\geq 75\%$ in G-HOPE-001 (ESMO 2026)**
- **Bispecific:** CLDN18.2-directed immune-engaging combinations Givastomig (CLDN18.2 $\times$ 4-1BB) remain investigational
- **CAR-T:** atri-cel is now approved in China, while CLDN18.2 CAR-T remains investigational in the US.



ILUSTRO: Efficacy & Clinical Implications

Design: Global, open-label phase II cohort in previously untreated, HER2-negative advanced gastric/GEJ adenocarcinoma

Biomarker: CLDN18.2 moderate-to-strong staining in ≥50% of tumor cells; high subgroup defined as ≥75%

Regimen: Zolbetuximab + nivolumab + mFOLFOX6

Cohorts: 4A safety lead-in, n = 6; 4B expansion, n = 71

Cohort 4B outcome	Overall	CLDN18.2 high ≥75%	Intermediate 50–<75%
ORR in measurable disease	62.1%	68.1%	40.0%
Median PFS	14.8 mo	18.0 mo	6.7 mo
Median OS	18.0 mo	Not reached	9.6 mo

ORR and survival use different evaluable populations. The intermediate subgroup is small: about 10 patients for response and 11 for expression-stratified survival. Treat those estimates as exploratory.

The triplet showed encouraging activity and is being evaluated in the randomized phase 3 LUCERNA trial



MET: Block the Driver or Deliver the Payload

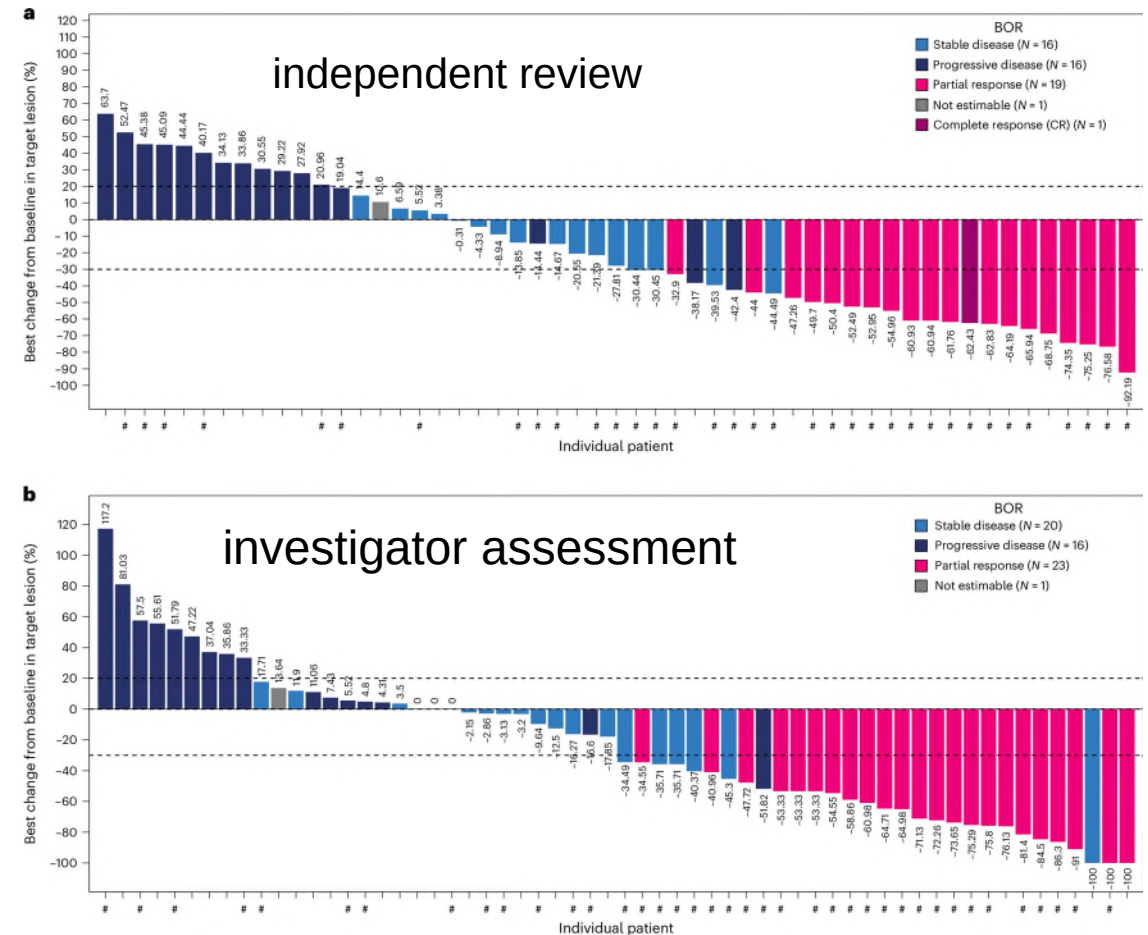
Savolitinib, MET TKI: shows activity in a narrowly selected, MET-amplified gastric/GEJ.

- Pivotal phase II; MET copy number ≥ 10 after ≥ 2 prior lines
- IRC-assessed ORR 32.3%, n = 65; median DoR 9.7 months
- Median PFS/OS 4.0/6.9 months
- cfDNA MET-amplified subgroup, n = 42: ORR 45.2%
- Grade ≥ 3 TRAEs 34.5% in the safety population; one possibly related death

Temab-A, c-MET ADC

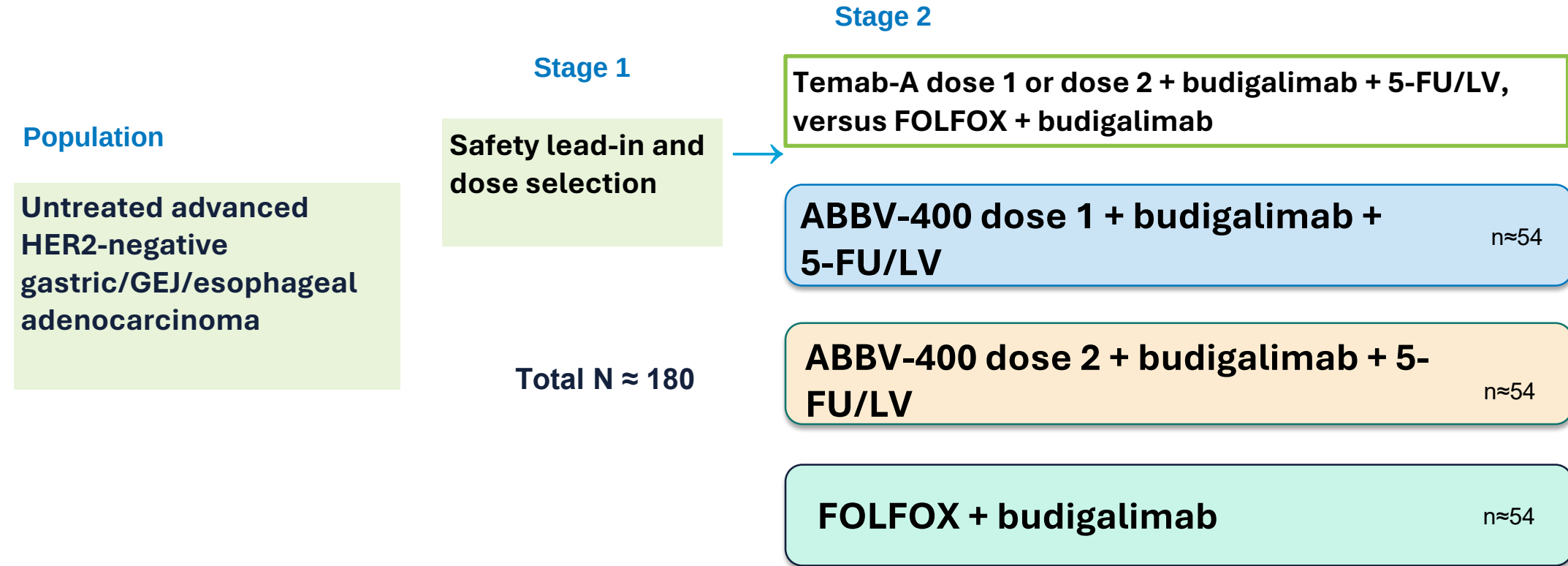
- Phase I GEA cohort: ORR 28.6%, n = 42.
- Median DoR 8.3 months; median PFS/OS 5.7/14.5 months
- First-line combination testing is underway

Savolitinib: best change in target-lesion size



AndroMETa-GEA-977: Phase II dose-finding / randomized study

Temab-A/ABBV400 : adizutecan, topoisomerase I inhibitor



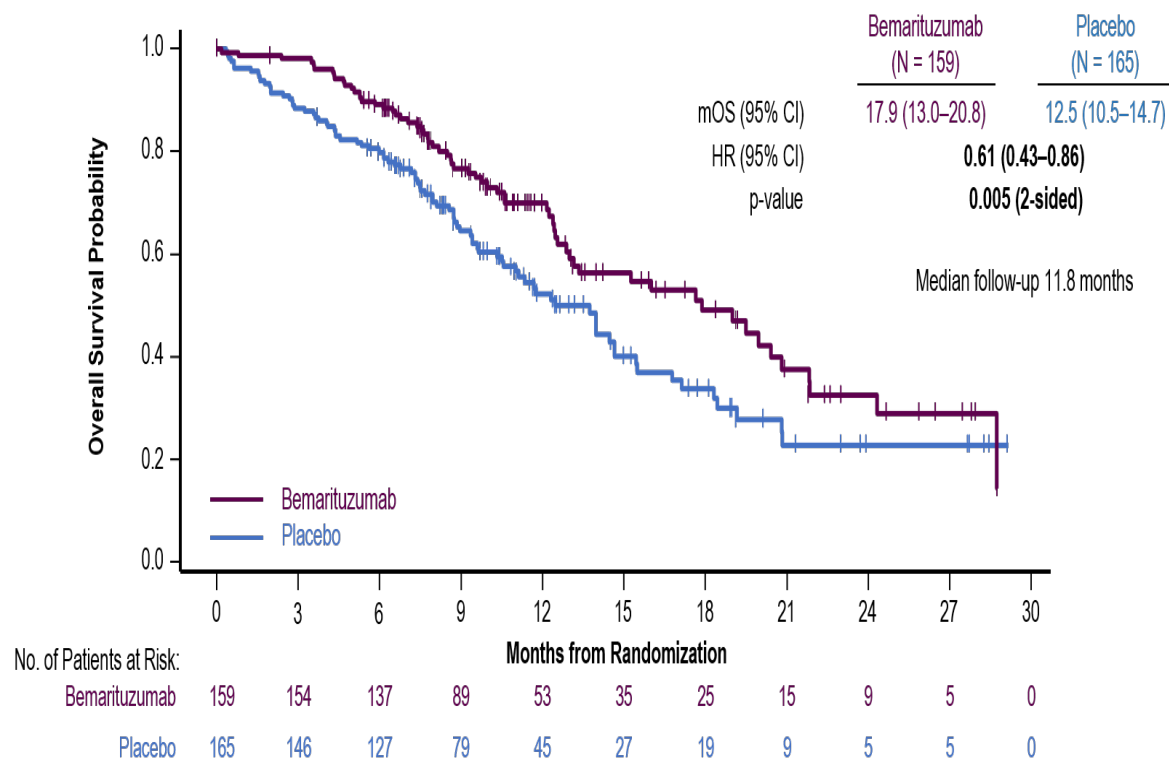
- COH participated in this study, completed accrual.
- The results being evaluated to determine whether to proceed with phase III development.

Primary endpoints: PFS and ORR

Exploratory biomarker: c-MET expression



FGFR2b: An Early Survival Signal That Weakened With Follow-up



PRIMARY ANALYSIS · 11.8 MO FOLLOW-UP

HR 0.61

Median OS 17.9 vs 12.5 months

FINAL ANALYSIS · 19.4 MO FOLLOW-UP

HR 0.82

Median OS 14.5 vs 13.2 months

- **Initial efficacy signal:** FORTITUDE-101 met its primary OS endpoint
- **Longer follow-up tempered enthusiasm:** HR attenuated to **0.82** (95% CI **0.62–1.08**)
- **Tolerability matters:** Corneal toxicity contributed substantially to adverse events; reduced treatment exposure is a plausible contributor to attenuation, **but causality is unproven.**

- **PANKU-Esophagus01: an EGFR × HER3 ADC after chemoimmunotherapy**

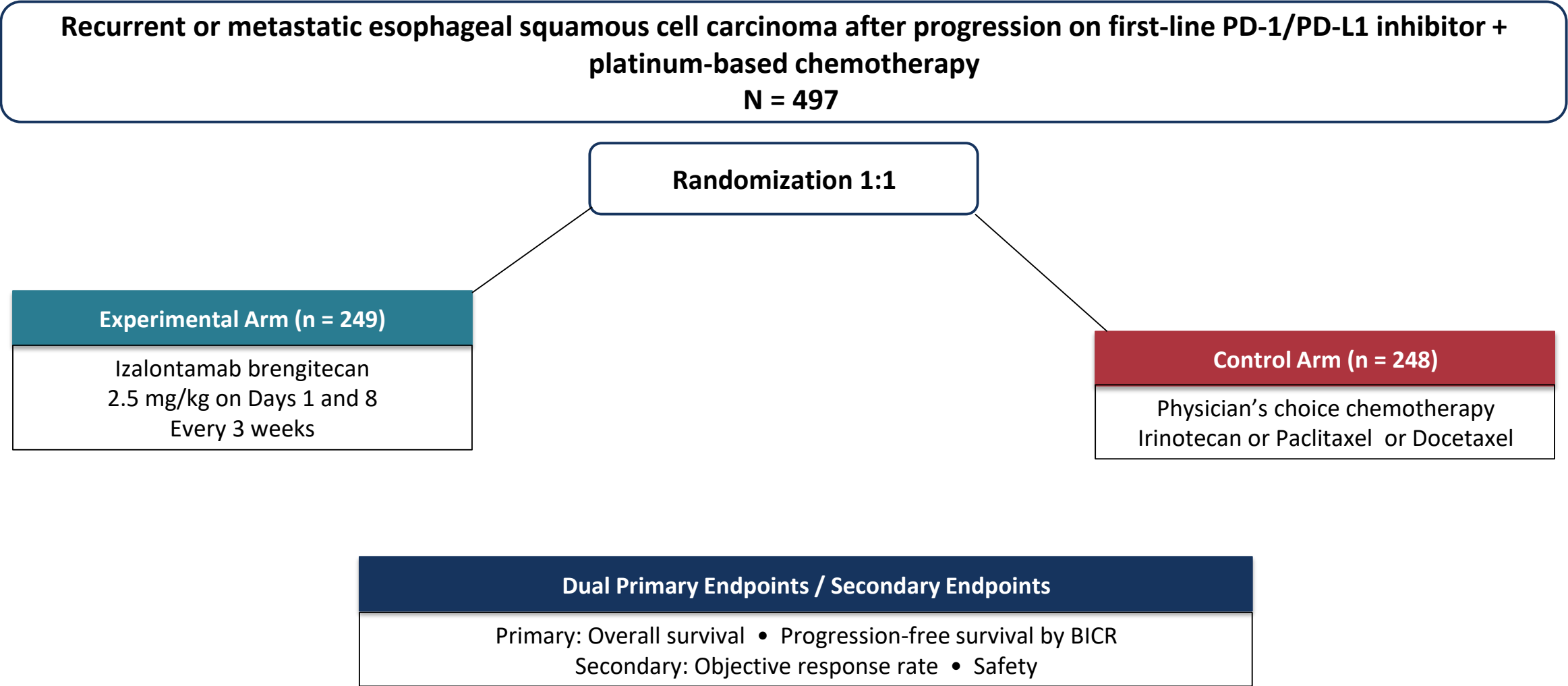
Most patients eventually develop resistance, and outcomes with 2L chemotherapy remain poor

- **Setting:** Recurrent or metastatic ESCC after first-line platinum chemotherapy plus PD-1/PD-L1 inhibition
- **Agent:** Izalontamab brengitecan (iza-bren) is an EGFR × HER3 bispecific ADC with a topoisomerase I inhibitor payload
- PANKU-Esophagus01 evaluated whether this novel ADC could improve outcomes compared with standard second-line chemotherapy
- **Question:** Can iza-bren improve survival versus physician's choice chemotherapy?

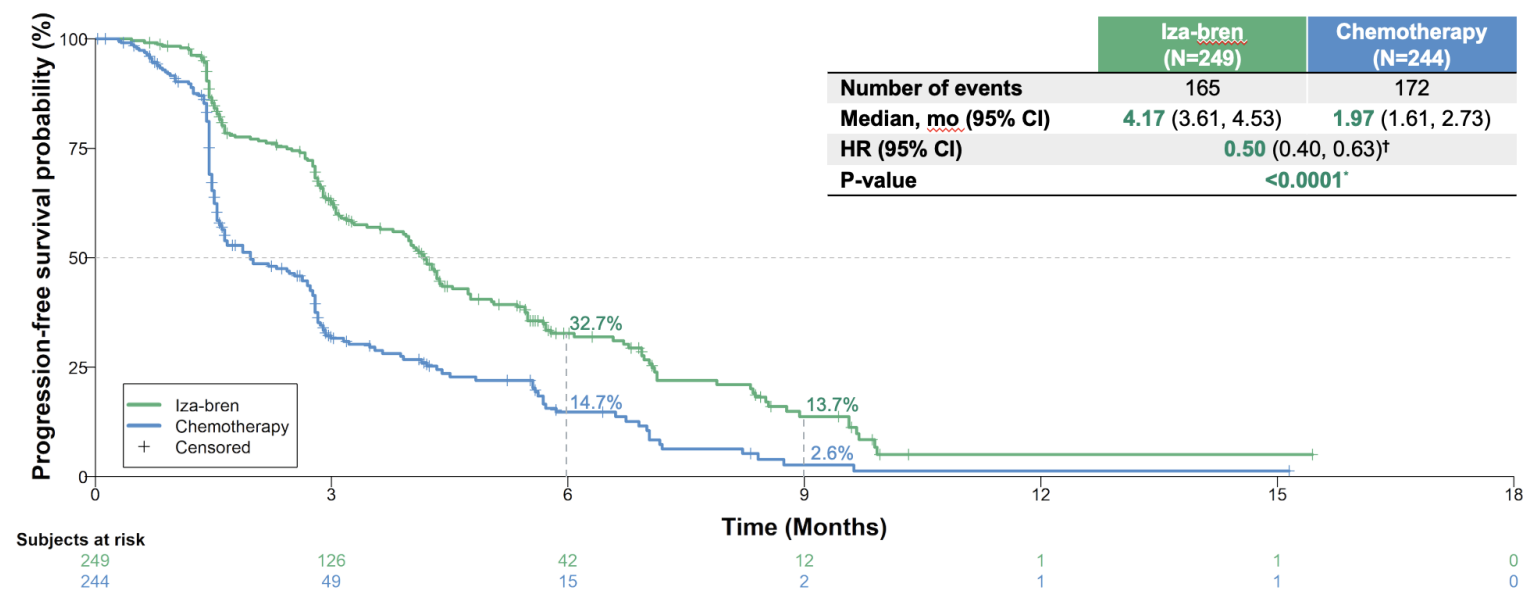


PANKU-Esophagus01:phase III design

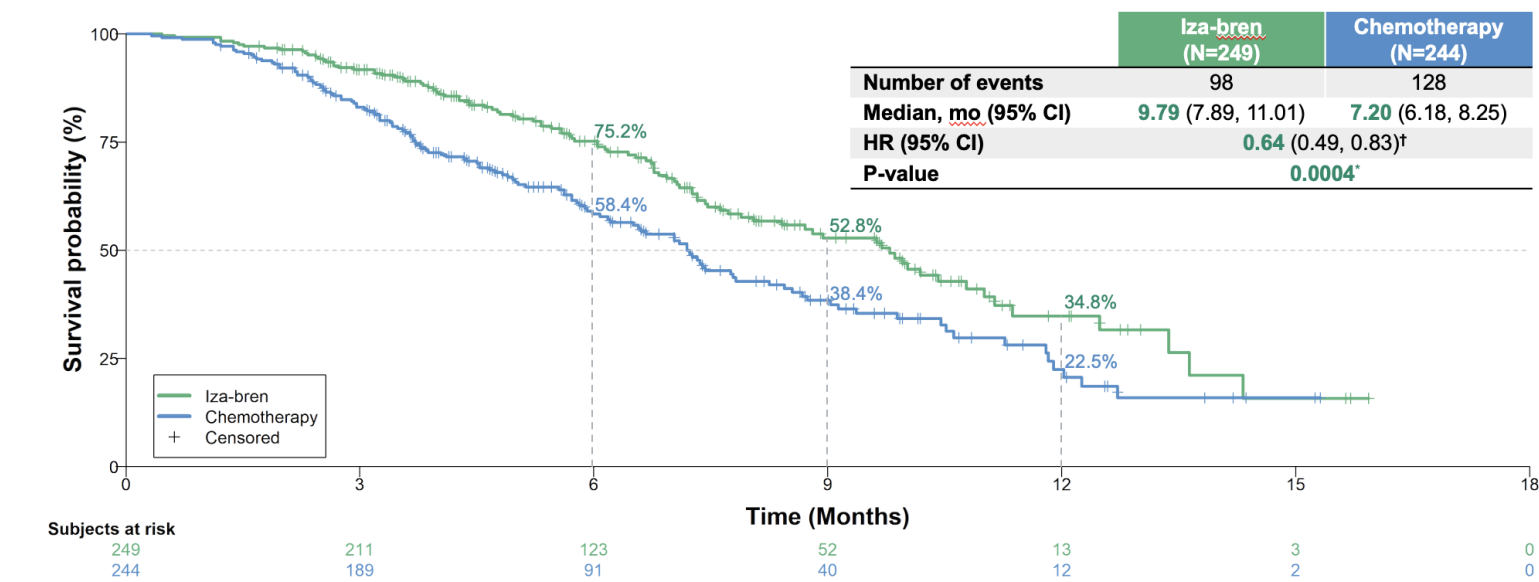
Phase III, randomized, open-label, multicenter trial in China



PANKU-Esophagus01: Progression-free and overall survival



- PFS, upper curve: 4.2 vs 2.0 months; HR 0.50
- OS, lower curve: 9.8 vs 7.2 months; HR 0.64
- ORR: 35.3% vs 13.1%
- Iza-bren significantly improved OS, PFS, and objective response compared with chemotherapy



PANKU-Esophagus01: Safety

Safety	Iza-bren	Chemotherapy
Grade ≥3 TRAEs	85.1%	60.2%
Discontinuation due to TRAEs	2.0%	3.3%
Treatment-related death	1.2%	1.6%

- The trial met both primary endpoints, improving OS and PFS versus chemotherapy
- High-grade treatment-related toxicity, predominantly hematologic, was frequent
- The study was conducted in China; additional global data will help assess generalizability

PANKU-Esophagus01 demonstrates that EGFR/HER3-directed ADC therapy can significantly improve survival and tumor control compared with chemotherapy in previously treated advanced ESCC



Take-home messages

Treat earlier: Perioperative therapy is evolving toward more cures and biomarker-guided treatment.

HER2 options are expanding: Choosing the best first-line regimen and treatment sequence remains a key question.

CLDN18.2 is moving beyond antibodies: ADCs, bispecifics, and CAR-T are expanding the treatment landscape.

Selection and safety matter: The right biomarker and manageable toxicity are essential to meaningful benefit.

Reassess as tumors evolve: Repeat biomarker testing may help guide the next treatment.

The goal: Longer survival with treatment patients can tolerate.



Thank You

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