



8th Annual

LEAD 2026

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Practice Changing Updates in Upper GI Malignancies and Pancreatic Adenocarcinoma

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Disclosures

Speaker: Incyte Corporation

Advisory Board: Guardant, Johnson & Johnson

Agenda

	Topic
1.	Upper Gastrointestinal Malignancies
	• HERIZON-GEA-1
	• ILLUSTRO (Cohort 4)
2.	Pancreatic Adenocarcinoma
	• RASolute-302



Upper GI Malignancies:

The Targeted Therapy Approach Continues

HER2-Positive Gastroesophageal Cancer:

- Gastroesophageal cancer: HER2+ 15-25%^{1,2}
- HER2+ higher in:
 - intestinal (31.8%) vs diffuse-type (6.0%)²
 - GEJ (32.2%) vs gastric (21.4%)²

1. Koopman et al. HER2 positivity in gastric and esophageal adenocarcinoma: clinicopathological analysis and comparison. J Cancer Res Clin Oncol. 2015 Aug;141(8):1343-51.
2. Van Cutsem et al. HER2 screening data from ToGA: targeting HER2 in gastric and gastroesophageal junction cancer. Gastric Cancer. 2015 Jul;18(3):476-84.

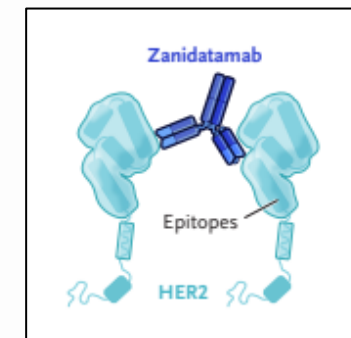
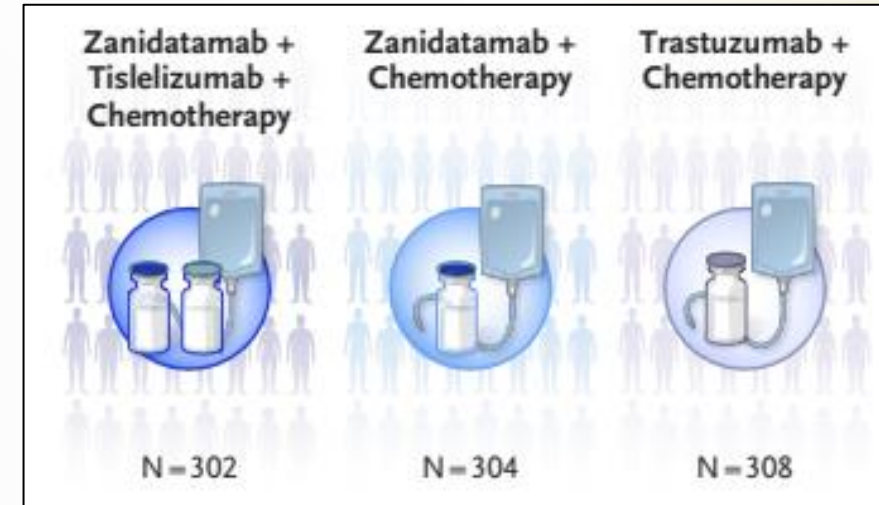
HER2-Positive Gastroesophageal Cancer: HERIZON-GEA-01

► 1st line HER2+ locally advanced, unresectable, or metastatic gastroesophageal adenocarcinoma

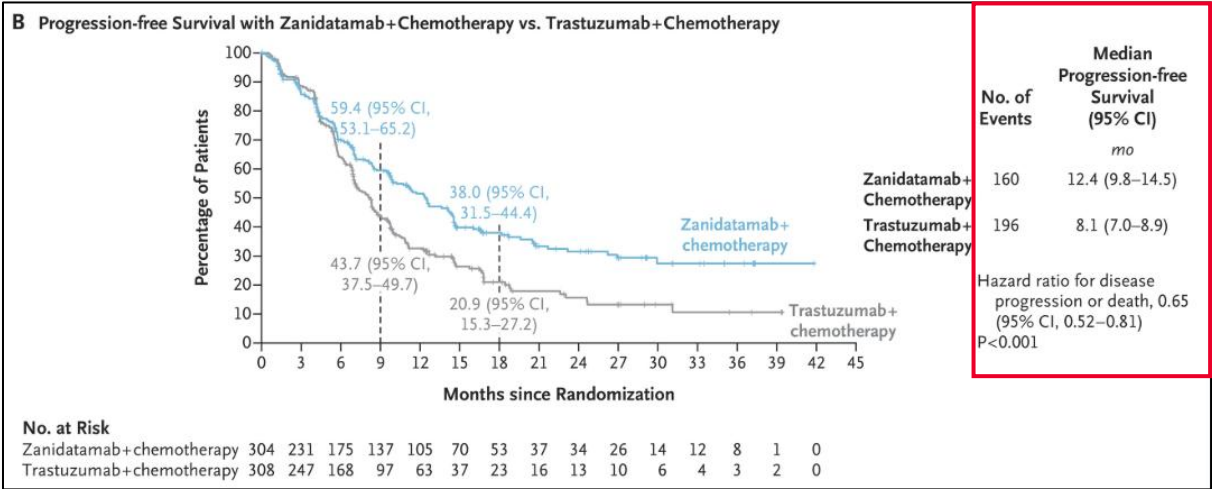
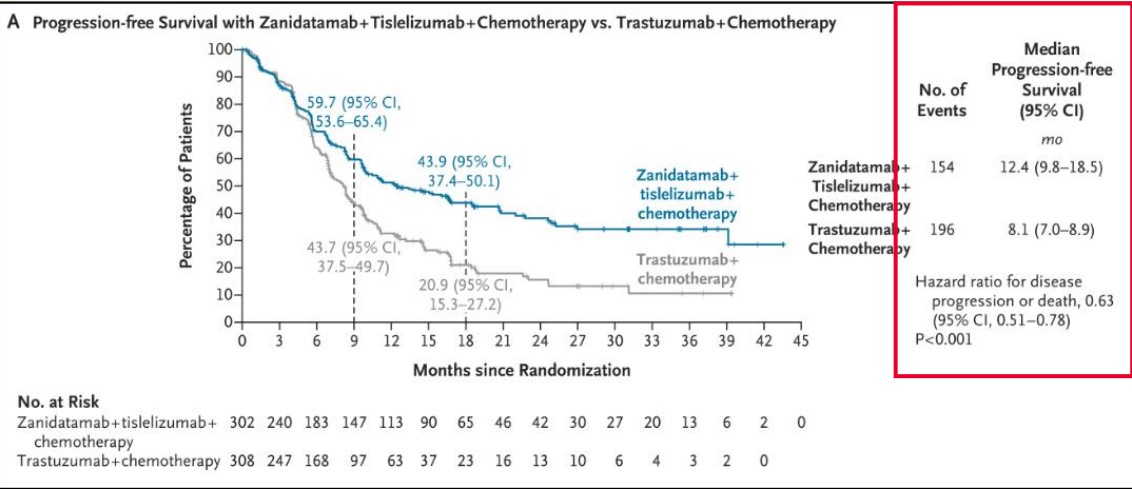
- Phase 3, randomized study
- Dual primary endpoints: PFS, OS

► Zanidatamab: a bispecific, biparatropic IgG1-like antibody against ECD4 and ECD2 of HER2

► Tislelizumab: an anti-programmed death 1 (PD-1 agent)

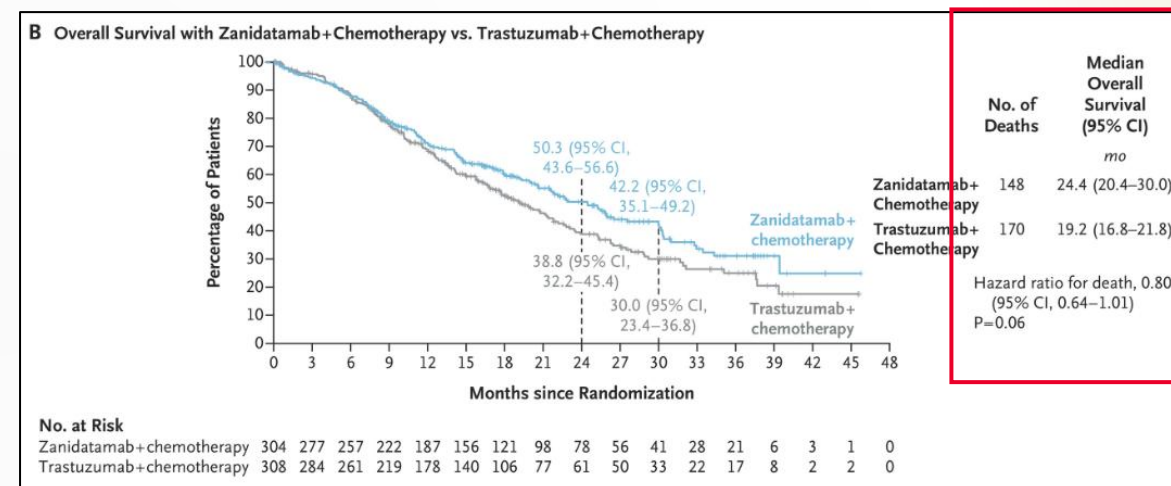
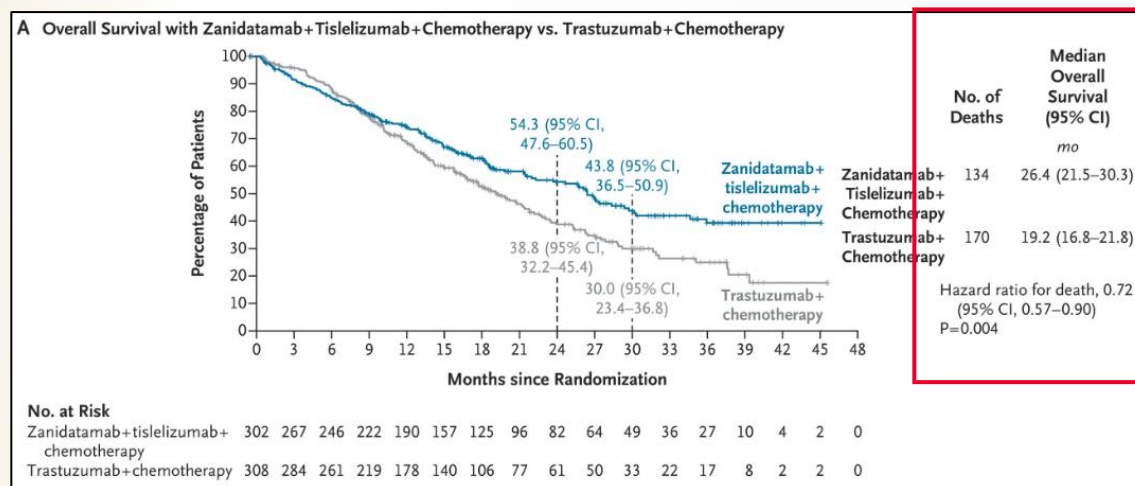


HERIZON-GEA-01: PFS as primary endpoint



Shitara et al. Zanidatamab with and without Tislelizumab in HER2-Positive Gastroesophageal Cancer. NEJM. 2026 May 28;394(20):2002-2014.

HERIZON-GEA-01: OS as primary endpoint



Shitara et al. Zanidatamab with and without Tislelizumab in HER2-Positive Gastroesophageal Cancer. NEJM. 2026 May 28;394(20):2002-2014.

HERIZON-GEA-01: Safety and Toxicity Profile

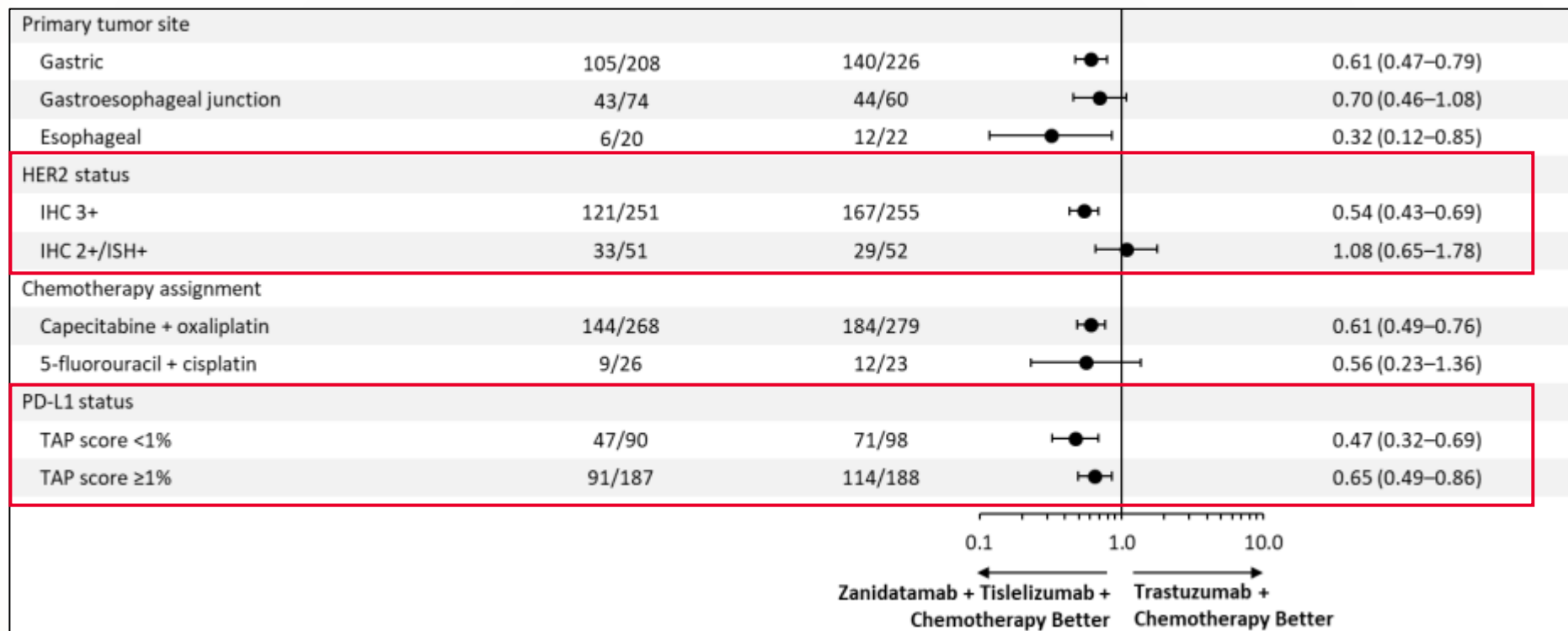
- Grade ≥ 3 treatment related adverse events:
 - 83.3% zanidatamab–tislelizumab–chemotherapy
 - 73.8% zanidatamab–chemotherapy
 - 74.5% trastuzumab–chemotherapy

Most Common Adverse Events

Toxicity	Zanidatamab–Tislelizumab–Chemotherapy	Zanidatamab–Chemotherapy	Trastuzumab–Chemotherapy
Diarrhea	83.0%	79.0%	53.3%
Nausea	55.8%	54.4%	47.7%
Anemia	47.3%	44.3%	48.7%
Decreased appetite	45.9%	40.3%	36.1%
Vomiting	42.9%	43.6%	33.1%
Neutrophil count decreased	26.9%	23.3%	30.8%

Zanidatamab with and without Tislelizumab in HER2-Positive Gastroesophageal Cancer. Research Summary based on Shitara K et al. NEJM. May 28, 2026

HERIZON-GEA-01: Subgroup Analysis



Zanutamab with and without Tislelizumab in HER2-Positive Gastroesophageal Cancer. Research Summary based on Shitara K et al. NEJM. May 28, 2026

HERIZON-GEA-01: Take Aways

- mPFS >1 year when zanidatamab +/- tislizumab given with chemotherapy
- mOS >2 years when zanidatamab + tislelizumab given with chemotherapy
- Main AE was diarrhea
- **August 25, 2026 - FDA approved zanidatamab:**
 - In combination with fluoropyrimidine- and platinum-containing chemotherapy regimens with or without tislelizumab for 1st-line treatment for HER2+ (IHC 3+ or IHC 2+/ISH+) unresectable locally advanced or metastatic gastric, GEJ, or esophageal adenocarcinoma

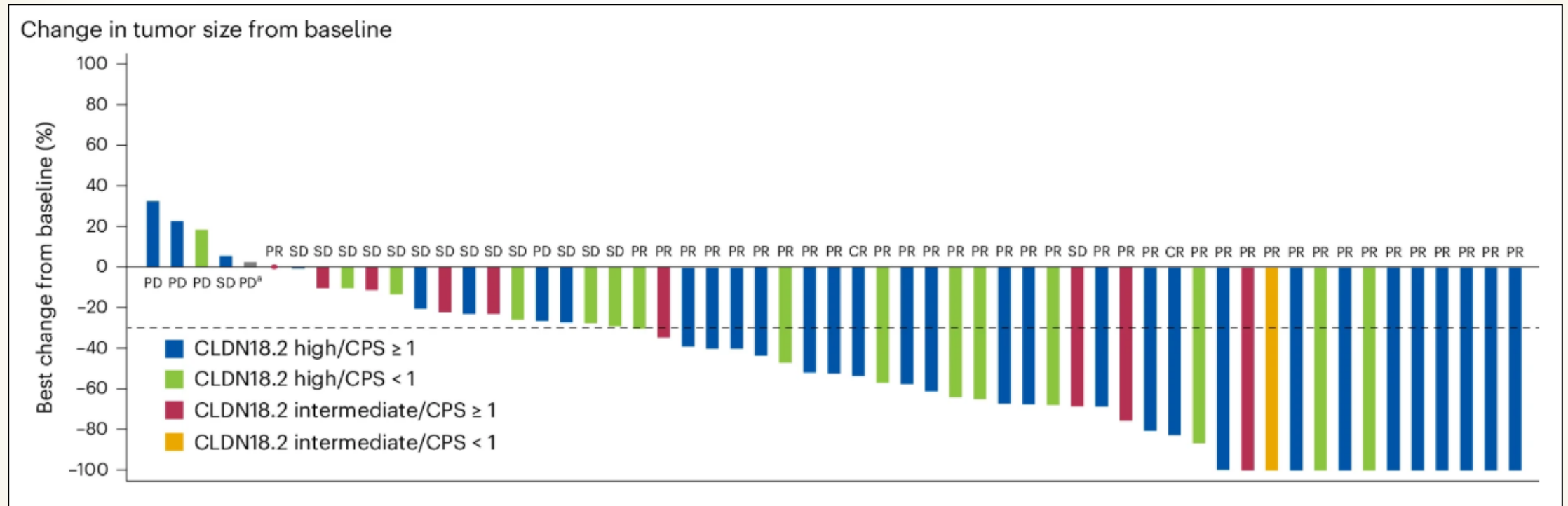
Shitara et al. Zanidatamab with and without Tislelizumab in HER2-Positive Gastroesophageal Cancer. NEJM. 2026 May 28;394(20):2002-2014.

ILLUSTRO (Cohort 4)

- ▶ Phase II: metastatic gastric/GEJ adenocarcinoma
 - Zolbetuximab plus mFOLFOX6 and nivolumab
- CLDN18.2 expression
 - High: moderate-to-strong membranous CLDN18 staining in $\geq 75\%$ of tumor cells
 - Intermediate: moderate-to-strong membranous CLDN18 staining in $\geq 50\%$ and $< 75\%$ of tumor cells
- PDL1 expression
 - CPS < 1 vs CPS ≥ 1

Shitara et al. First-line zolbetuximab plus mFOLFOX6 and nivolumab in unresectable CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: a phase 2 trial. Nat Med. 2026 Jun;32(6):2182-2190.

ILLUSTRO (Cohort 4)



Shitara et al. First-line zolbetuximab plus mFOLFOX6 and nivolumab in unresectable CLDN18.2-positive gastric or gastroesophageal junction adenocarcinoma: a phase 2 trial. *Nat Med.* 2026 Jun;32(6):2182-2190.

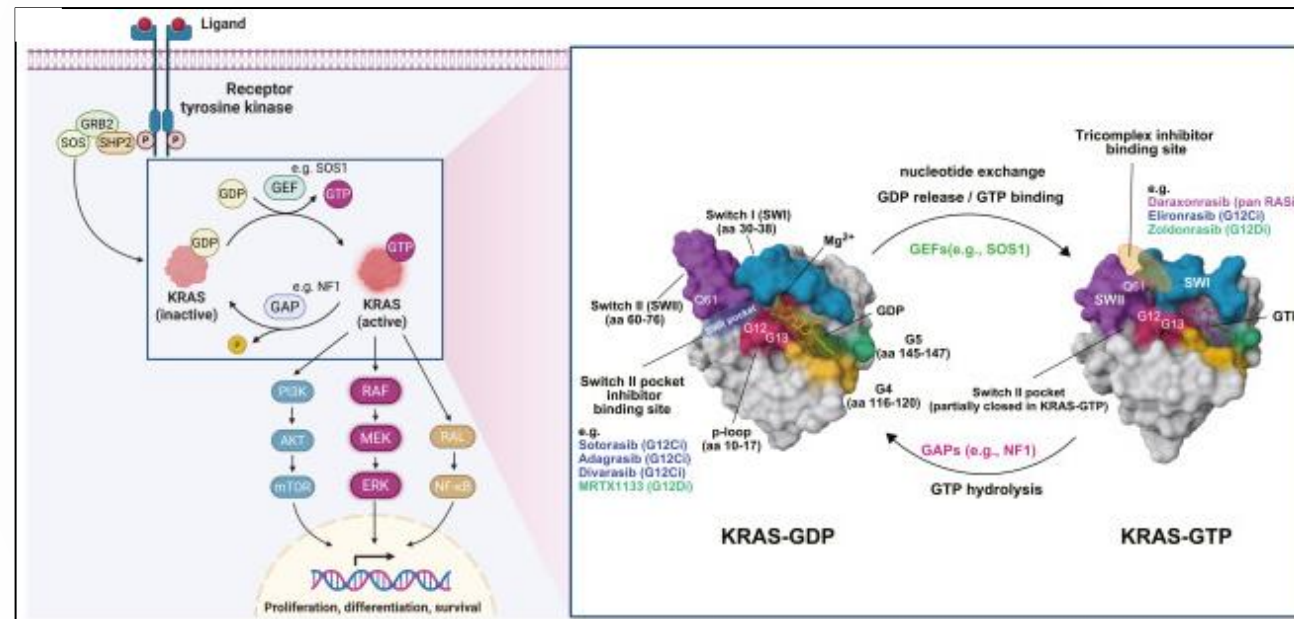
Pancreatic Adenocarcinoma:

“A Pill” A Day Keeps the Cancer At Bay



KRAS

- 90% of pancreas cancers have a KRAS mutation
- Long concerned ‘undruggable’



- Daraxonrasib: oral RAS(ON) multiselective, tri-complex inhibitor of active guanosine triphosphate-bound state of mutant and wild-type RAS

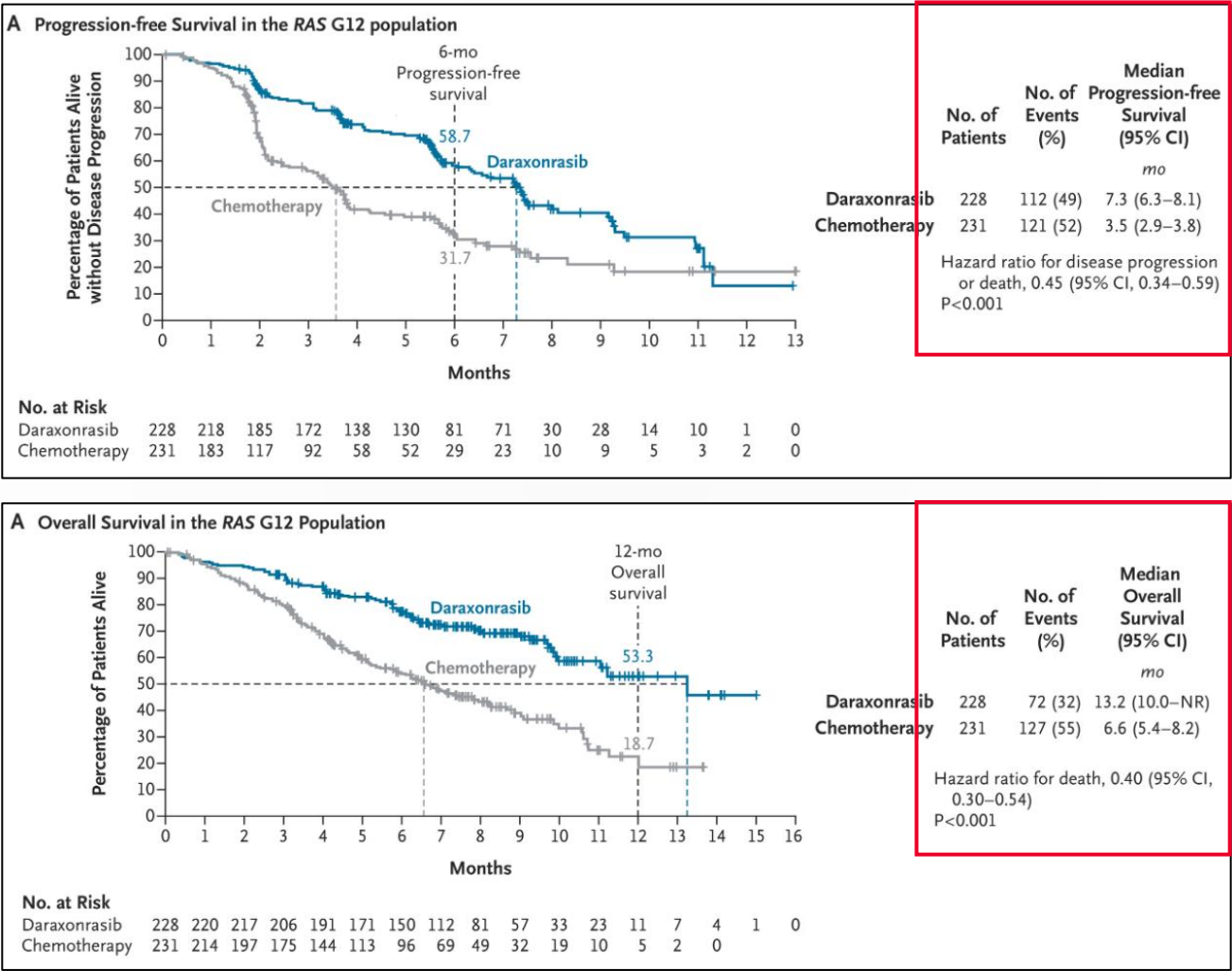
RASolute-302

- ▶ 2nd-line metastatic pancreatic adenocarcinoma (mPDAC)

- ▶ Phase 3, randomized study: daraxonrasib vs chemotherapy
 - Dual primary endpoints: PFS, OS in *RAS* G12 population
 - Secondary endpoints:
 - PFS, OS in overall population (*RAS* G12, G13, or Q61 mutations or no *RAS* mutation)
 - Objective response and patient-reported outcomes in *RAS* G12 population and overall populations

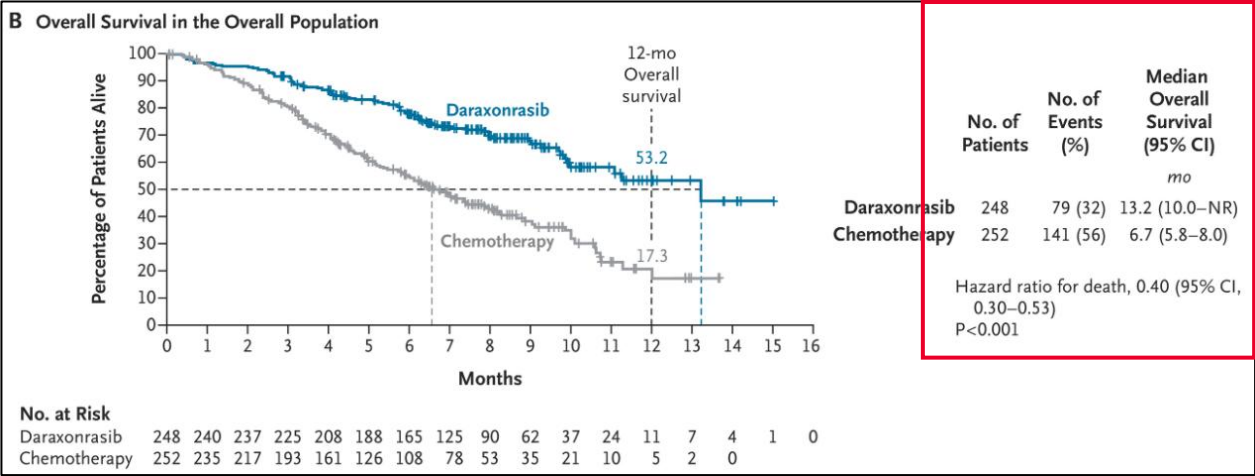
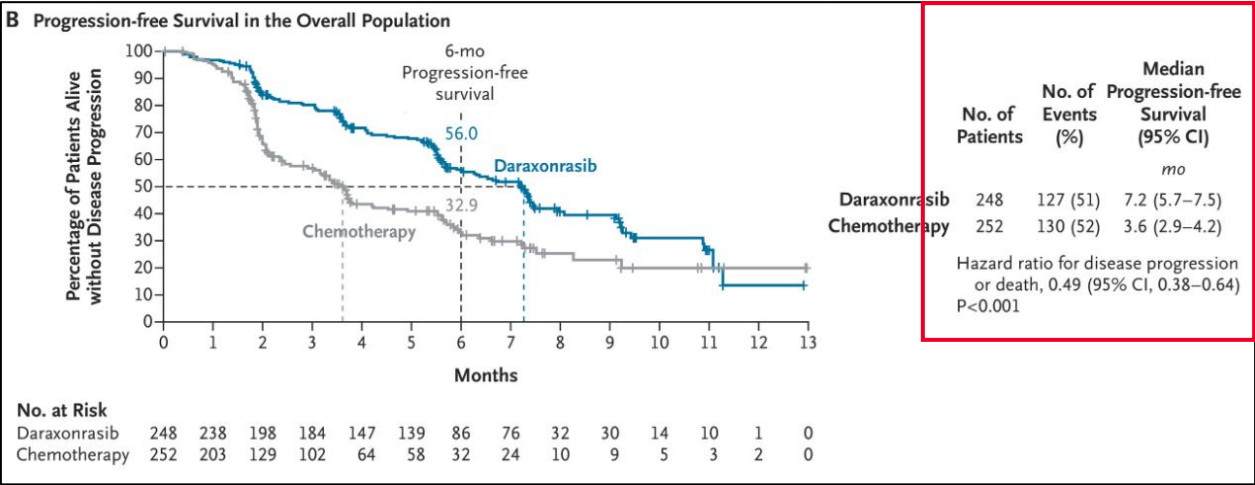
O'Reilly et al. Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer. NEJM. 2026 Jul 23;395(4):325-337.

RASolute-302: RAS G12 population - PFS & OS



O'Reilly et al. Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer. NEJM. 2026 Jul 23;395(4):325-337.

RASolute-302: Overall population - PFS & OS



O'Reilly et al. Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer. NEJM. 2026 Jul 23;395(4):325-337.

RASolute-302: Adverse Events

- Grade ≥ 3 less common with daraxonrasib (43.6%) than chemotherapy (57.5%)
- Serious treatment-related adverse events (TRAE) less common with daraxonrasib (26.1% vs. 57.5%)
- TRAE leading to discontinuation less common with daraxonrasib (2.4% vs. 11.1%)

Rash			(%)
Diarrhea			(%)
Stomatitis			
Nausea			(%)
Vomiting			)
		Thrombocytopenia	33.2% (9.8%)
		Peripheral neuropathy	25.2% (3.3%)

~2.4% ILD/pneumonitis (0.9% grade 3; 1 fatal) with daraxonrasib

*Grade ≥ 3 TRAE

O'Reilly et al. Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer. NEJM. 2026 Jul 23;395(4):325-337.

RASolute-302: Prophylaxis

Prior to and during treatment with daraxonrasib, prophylactic and concomitant medications are recommended to reduce the risk of dermatologic reactions:

- Topical corticosteroid (applied to the face and chest) and emollient creams
- Limit sun exposure and use broad-spectrum sunscreen (SPF 30 or higher)
- Consider prophylactic oral antibiotics (e.g., doxycycline or minocycline)

RASolute-302: Drug interactions

- Strong CYP3A Inhibitors with P-gp Inhibition: Avoid concomitant use.
- Strong CYP3A Inhibitors without P-gp Inhibition: Reduce daraxonrasib dosage.
- Moderate CYP3A Inhibitors with or without P-gp Inhibition: Reduce daraxonrasib dosage.
- P-gp Inhibitors: Reduce daraxonrasib dosage.
- Cyclosporine A: Avoid concomitant use.
- Strong CYP3A Inducers: Avoid concomitant use. Increase daraxonrasib dosage if concomitant use cannot be avoided.
- Moderate CYP3A Inducers: Increase daraxonrasib dosage.
- P-gp Substrates: Take at least 4 hours apart from daraxonrasib.

<https://ir.revmed.com/news-releases/news-release-details/us-fda-approves-revolution-medicines-rasonquetm-daraxonrasib>

RASolute-302: Take Aways

- *RAS* G12 population
 - mPFS daraxonrasib vs chemotherapy: 7.3 mo vs 3.5 mo
 - mOS daraxonrasib vs chemotherapy: 13.2 mo vs 6.6 mo
- Prophylaxis for rash prevention – start before, continue during treatment
- **August 26, 2026 - FDA approved daraxonrasib:**
 - Metastatic PDAC who have received at least 1 prior systemic therapy or are not candidates for multiagent systemic therapy

O'Reilly et al. Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer. NEJM. 2026 Jul 23;395(4):325-337.

RASolute-302: Next steps

- **RASolute 303:** Study of Daraxonrasib and Daraxonrasib + GnP as First-line Treatment in Patients With Metastatic Pancreatic Adenocarcinoma
- **RASolute 304:** A phase III multicenter, open-label, randomized study of adjuvant daraxonrasib versus observation following completion of neoadjuvant and/or adjuvant chemotherapy in patients with resected pancreatic adenocarcinoma (PDAC)
- **RASolute 309:** Study of Zoldonrasib (RMC-9805) Plus Daraxonrasib (RMC-6236) Versus Gemcitabine and Nab-Paclitaxel as First-Line Treatment in Metastatic *KRAS* G12D-Mutated Pancreatic Adenocarcinoma
- **Phase 1b/2 Study** of Elironrasib and Daraxonrasib as Monotherapies and Combination Therapy in Participants With Advanced *KRAS* G12C Mutant Solid Tumors

Final Thoughts

- Zanidatamab + tislelizumab with chemotherapy improved metastatic/unresectable HER2+ locally advanced/metastatic GEA to >2 year mOS
- Zanidatamab +/- tislelizumab with chemotherapy is FDA approved 1st line therapy for HER2+ locally advanced or metastatic GEA
- Daraxonrasib is now FDA approved for 2nd line therapy in mPDAC regardless of *KRAS* status
- Ongoing studies to move these novel therapies to earlier lines of therapy



Thank you!

