# Novel Therapies for Pancreatic Cancer

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# Disclosures

- Consulting and Advising: Exelixis, Natera, AstraZeneca, Intera/Boston Scientific
- Speaking: Exelixis, AstraZeneca, Bristol Myers Squibb

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# Objectives

- Review current treatment landscape
- Review ongoing unmet needs
- Highlight new/emerging therapies

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# Patient Case

- 62-year-old woman with history of obesity and type 2 diabetes
- Presents with progressive fatigue, weight loss, and new-onset abdominal/back pain
- ECOG PS 1

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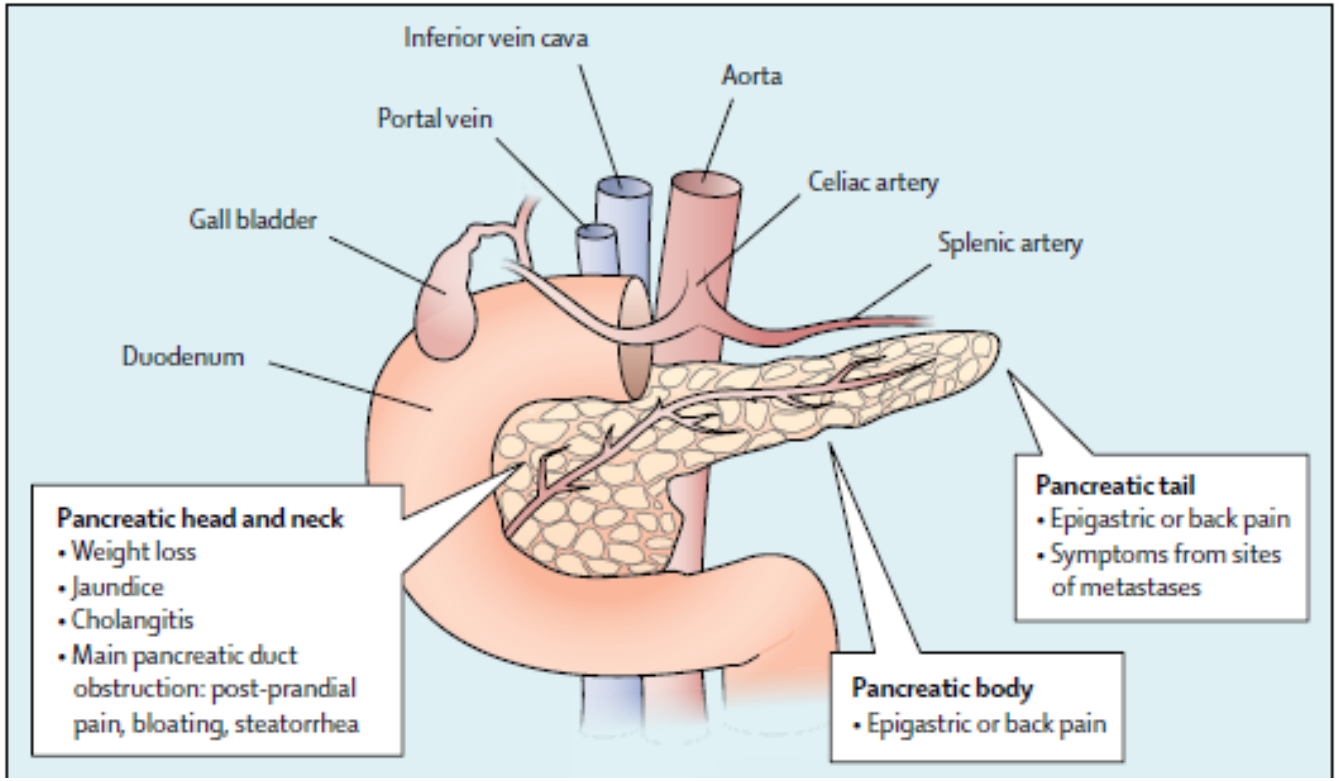
# Patient Case

- CT CAP: 2 x 3 cm mass in pancreatic body, bi-lobar hypodense liver lesions
- CA 19-9 4,000
- Biopsy: adenocarcinoma of pancreas




Mizrahi et al. Lancet 2020.

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# Current Standard of Care

- Resectable/Borderline Resectable Pancreatic Cancer:
  - Surgery + perioperative chemotherapy → observation
- Locally Advanced Pancreatic Cancer:
  - Systemic chemotherapy (5-FU or gem-based) induction
  - Consider consolidative chemoradiation if stable/response but not surgically resectable
- Metastatic Pancreatic Cancer:
  - First-line systemic therapy: FOLFIRINOX or NALIRIFOX vs gemcitabine/nab-paclitaxel
    - Primarily chosen based on performance status, comorbidities, discussion with patient
  - Second-line: 5-FU + liposomal irinotecan (if gem first-line) vs gemcitabine/nab-paclitaxel (if 5-FU first-line)
  - No standard third-line therapies

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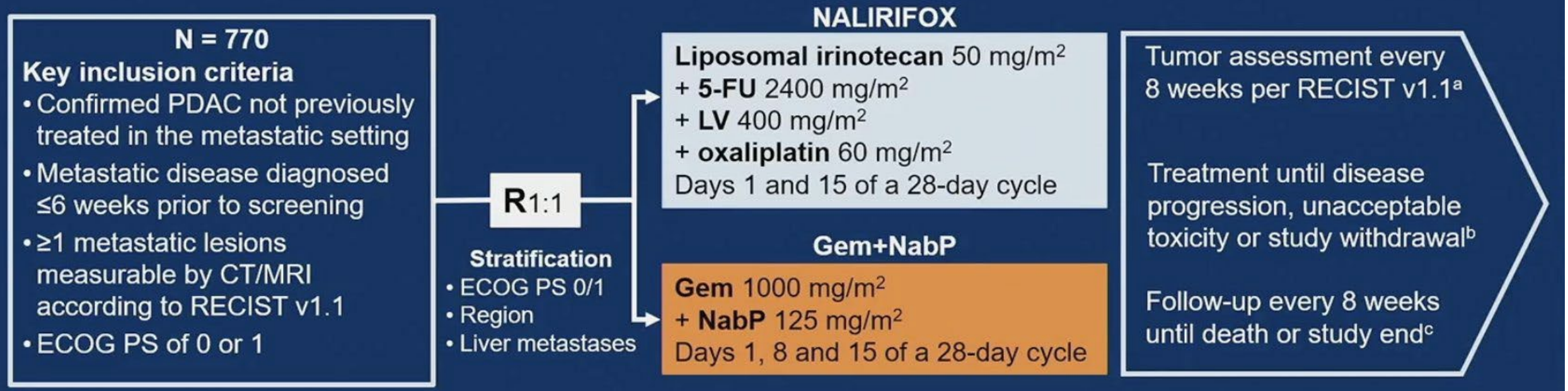
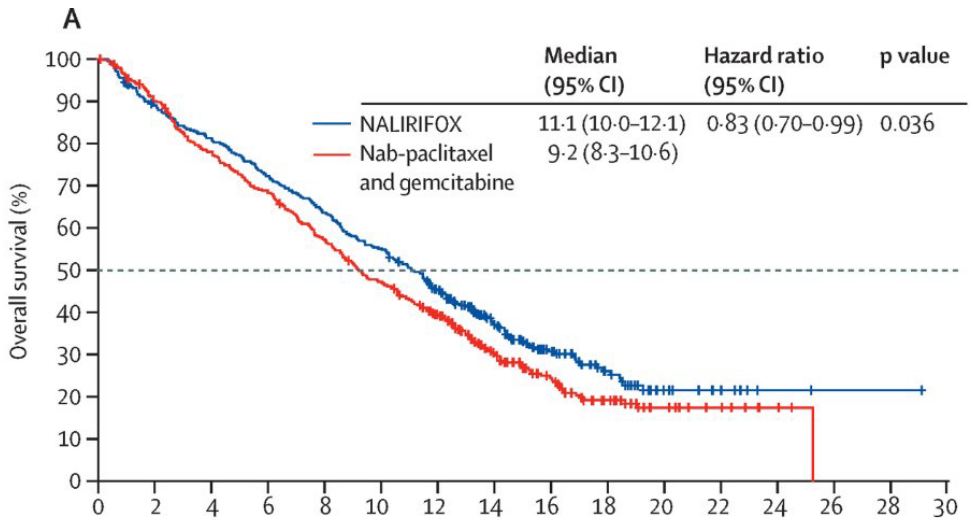
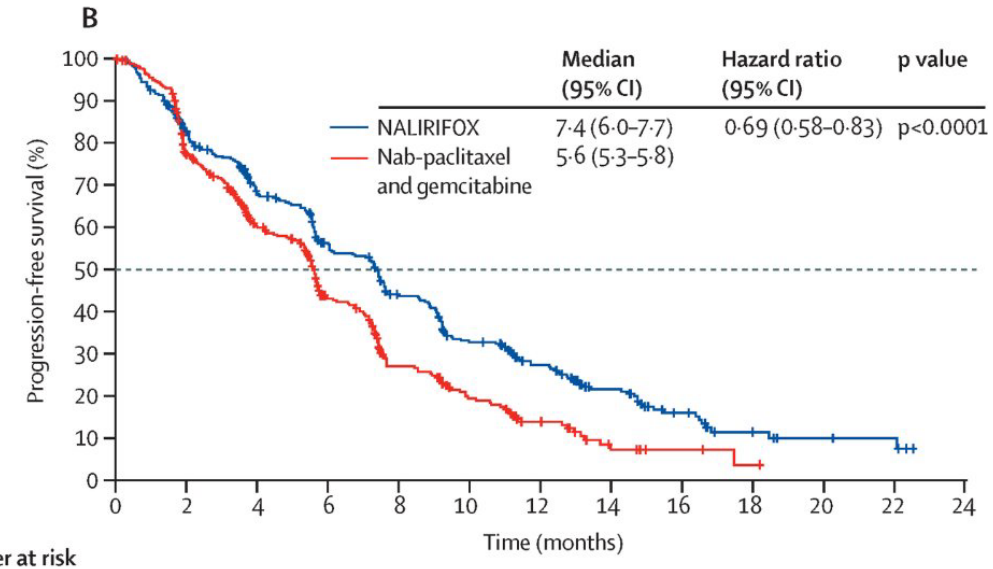
# NAPOLI 3: Study design




[a]Tumor assessments (RECIST v1.1) were performed at baseline and every 8 weeks until radiologically progressive disease or until the start of another anti-cancer treatment, whichever came first. [b]Dose delays were permitted; if oxaliplatin was not well tolerated, patients in arm 1 could continue to receive liposomal irinotecan + 5-FU/LV. [c]The study will be completed once all patients have discontinued the study treatment and at least 543 OS events have occurred in randomized patients.
5-FU, 5-fluorouracil; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Gem, gemcitabine; LV, leucovorin; MRI, magnetic resonance imaging; NabP, nab-paclitaxel; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors.




| Number at risk (number censored) | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NALIRIFOX | 383 | 337 | 308 | 274 | 241 | 209 | 162 | 98 | 59 | 32 | 13 | 7 | 2 | 1 | 1 | 0 |
| | (0) | (4) | (4) | (4) | (4) | (4) | (15) | (53) | (77) | (97) | (111) | (117) | (122) | (123) | (123) | (124) |
| Nab-paclitaxel and gemcitabine | 387 | 345 | 298 | 261 | 218 | 179 | 140 | 80 | 50 | 28 | 15 | 10 | 3 | 0 | 0 | 0 |
| | (0) | (4) | (5) | (5) | (6) | (7) | (17) | (48) | (65) | (77) | (88) | (93) | (100) | (102) | (102) | (102) |




| Number at risk (number censored) | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NALIRIFOX | 383 | 271 | 210 | 164 | 122 | 87 | 61 | 39 | 20 | 9 | 5 | 4 | 0 |
| | (0) | (52) | (68) | (77) | (84) | (88) | (101) | (111) | (121) | (127) | (130) | (131) | (134) |
| Nab-paclitaxel and gemcitabine | 387 | 267 | 182 | 112 | 60 | 38 | 19 | 6 | 3 | 1 | 0 | 0 | 0 |
| | (0) | (40) | (68) | (89) | (102) | (108) | (117) | (123) | (126) | (127) | (128) | (128) | (128) |

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# Current Unmet Needs

- Early detection
- High risk of recurrence after curative-intent surgery
- Management of locally advanced but unresectable pancreatic cancer
- Limited durable responses
- Few targeted therapies
- High symptom burden

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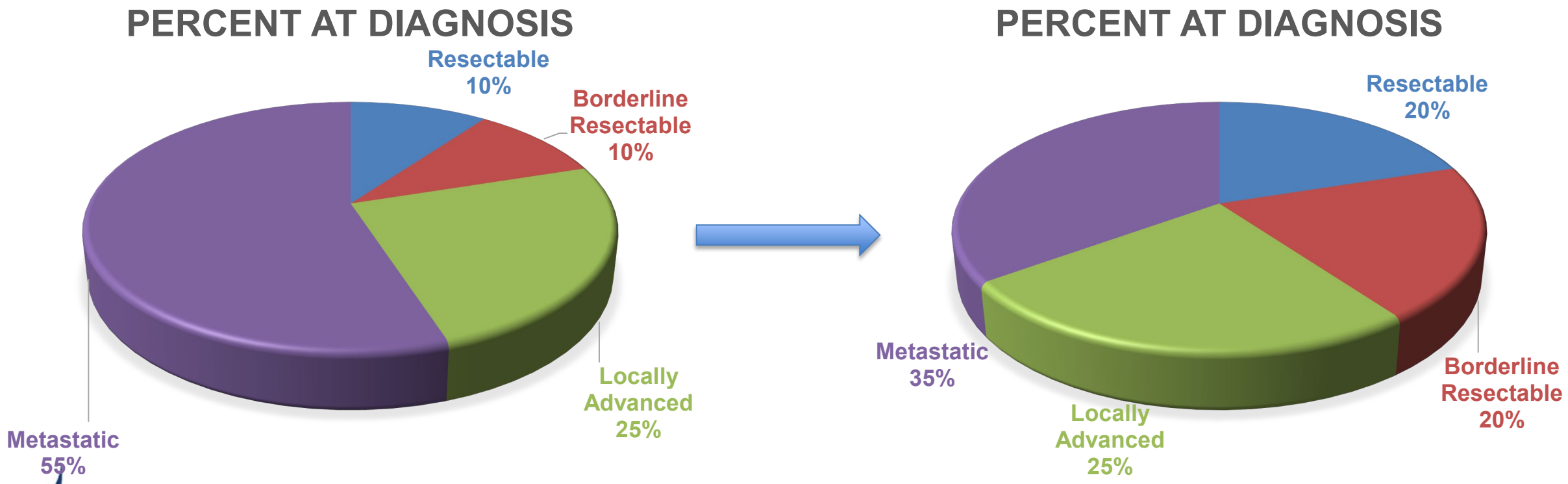
# Current Unmet Needs

- **Early detection**

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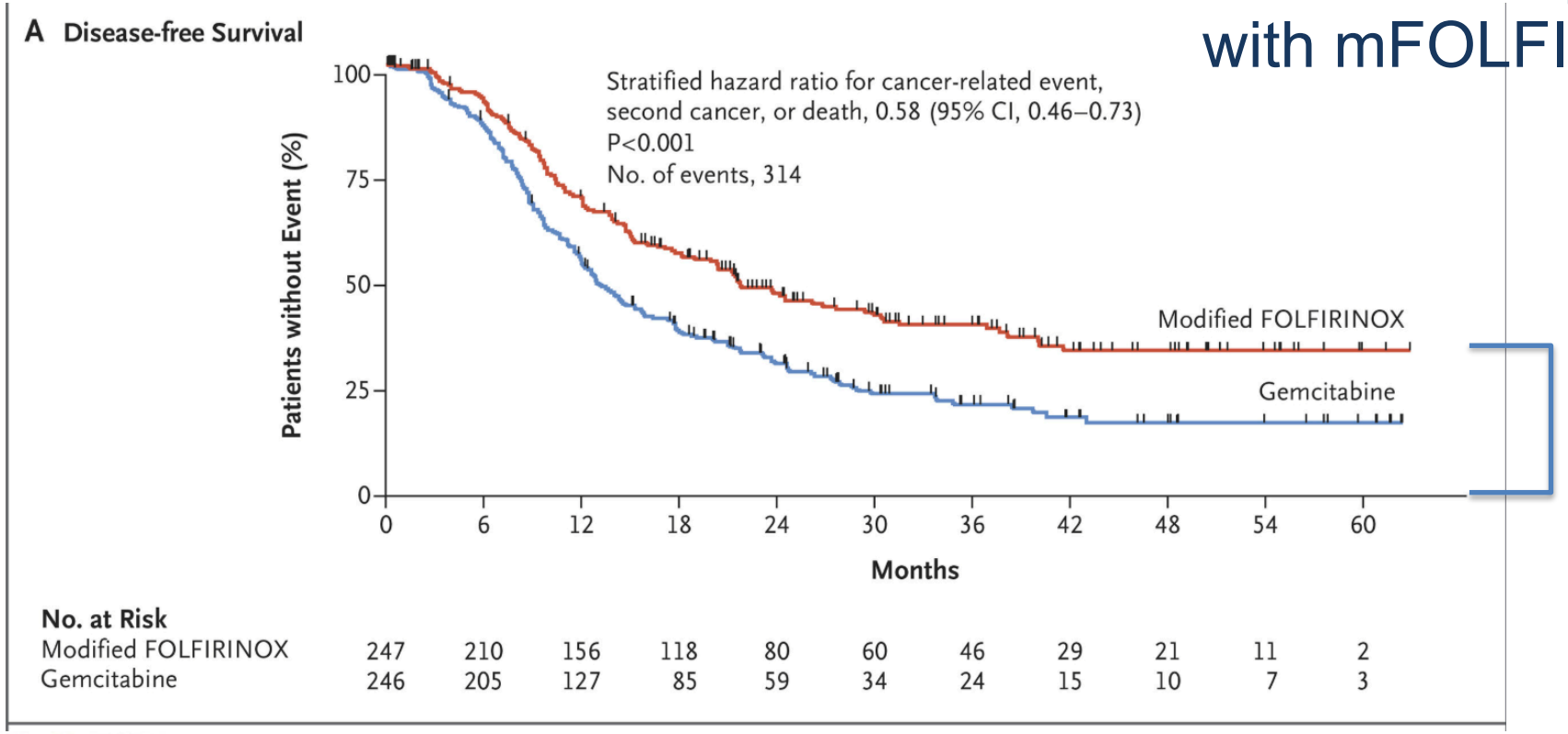
# Current Unmet Needs

- **High risk of recurrence after curative-intent surgery**

5-year disease-free survival was **only 26%** with mFOLFIRINOX

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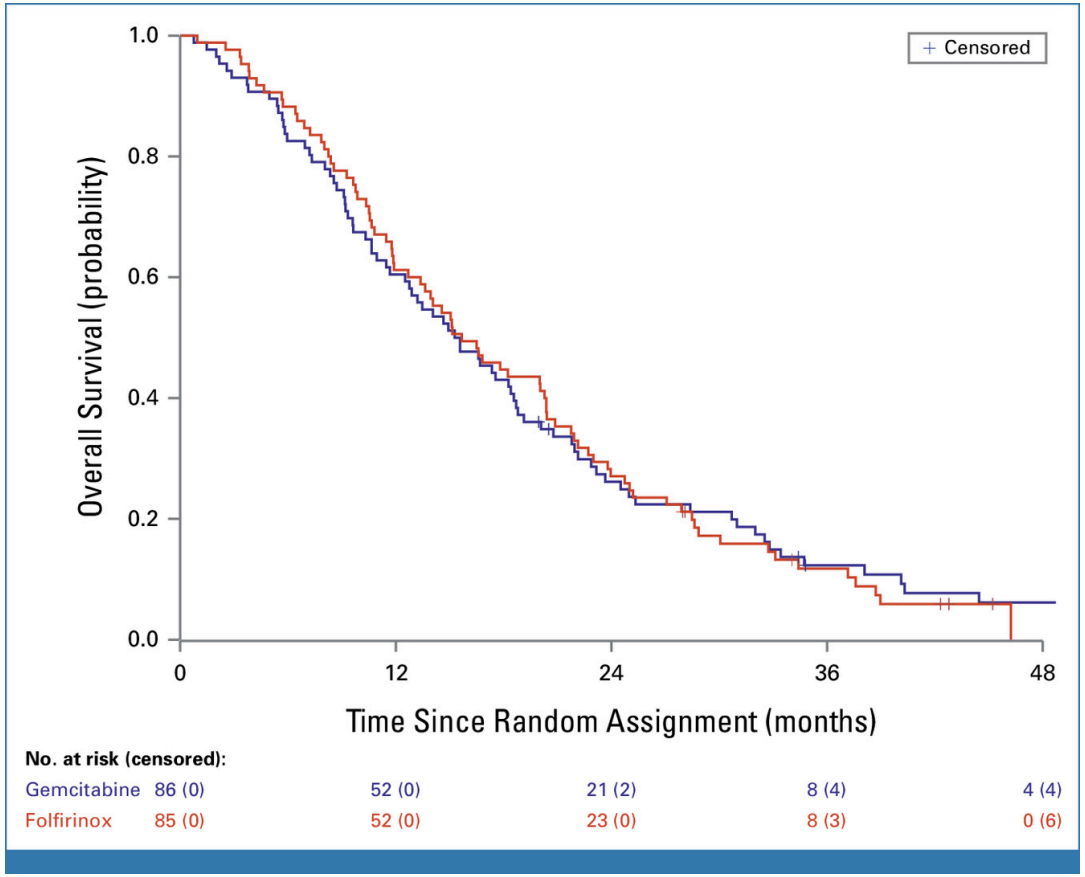
Conroy et al. N Engl J Med 2018.

# Current Unmet Needs

- **Management of locally advanced but unresectable pancreatic cancer**




**NEOPAN** study:

- mOS was ~ 15 months in both gemcitabine and FOLFIRINOX arms
- Only ~ 12% alive at 3 years

Ducreux et al. J Clin Oncol 2025.

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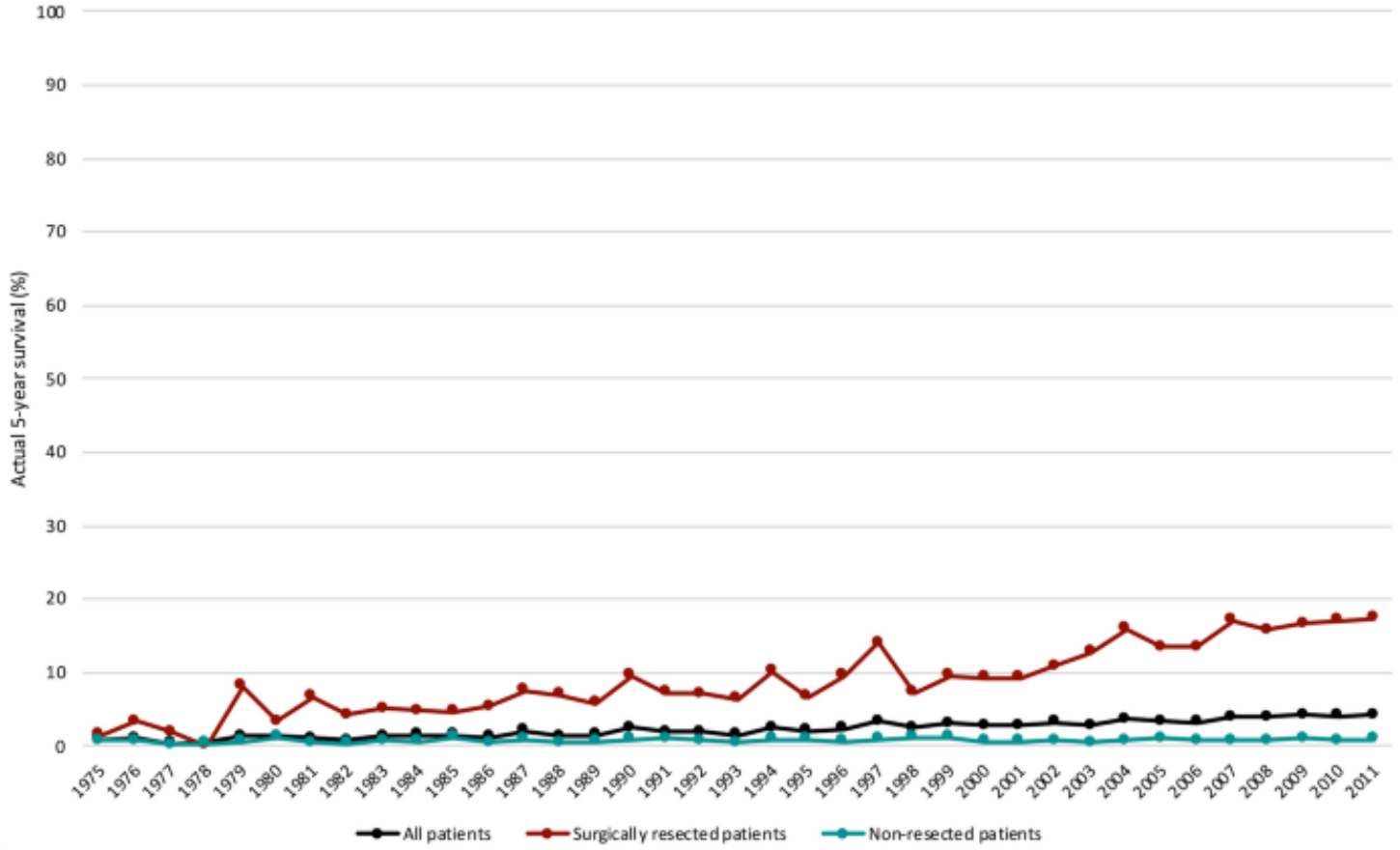
# Current Unmet Needs

- **Limited durable responses**

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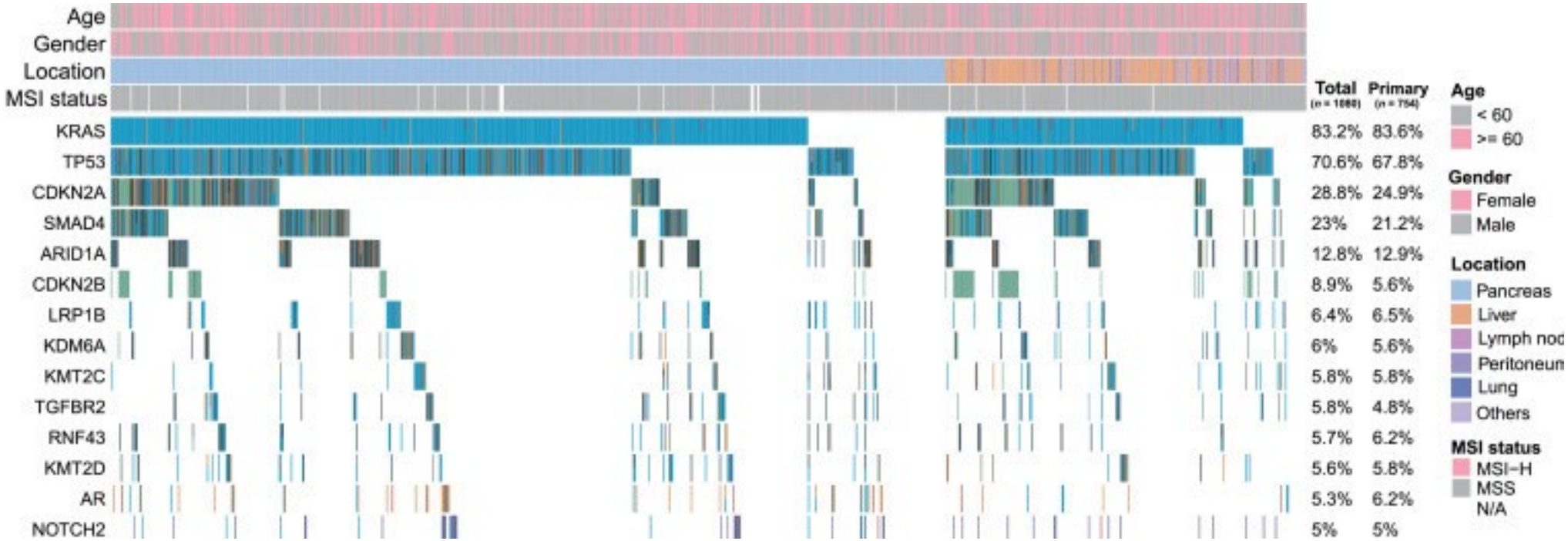
Bengtsson et al. Scientific Reports 2020.

# Current Unmet Needs

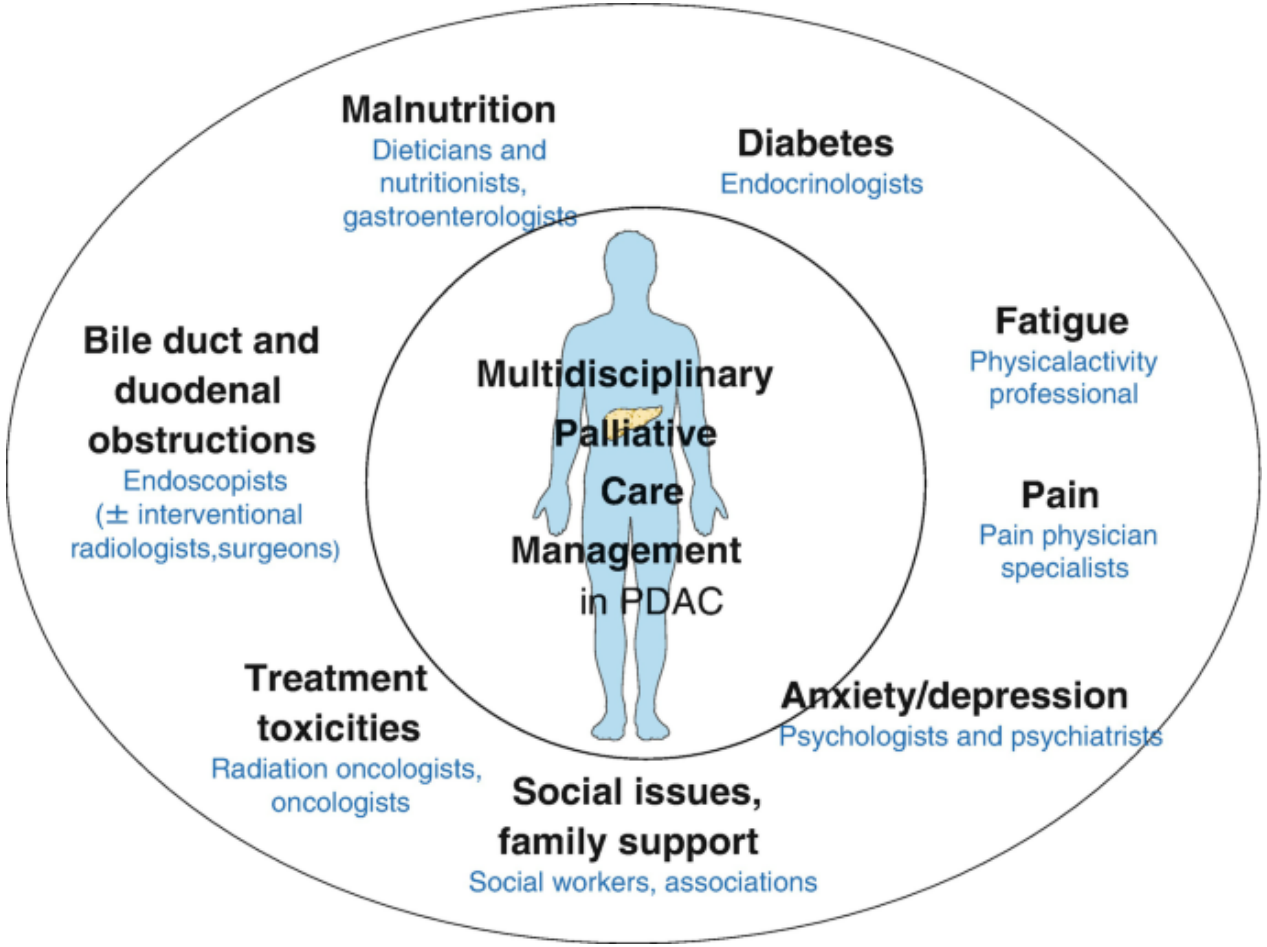
- **Few targeted therapies**




Zhang et al. eBioMedicine 2022.

# Current Unmet Needs

- **High symptom burden**

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# What's New in Pancreatic Cancer?

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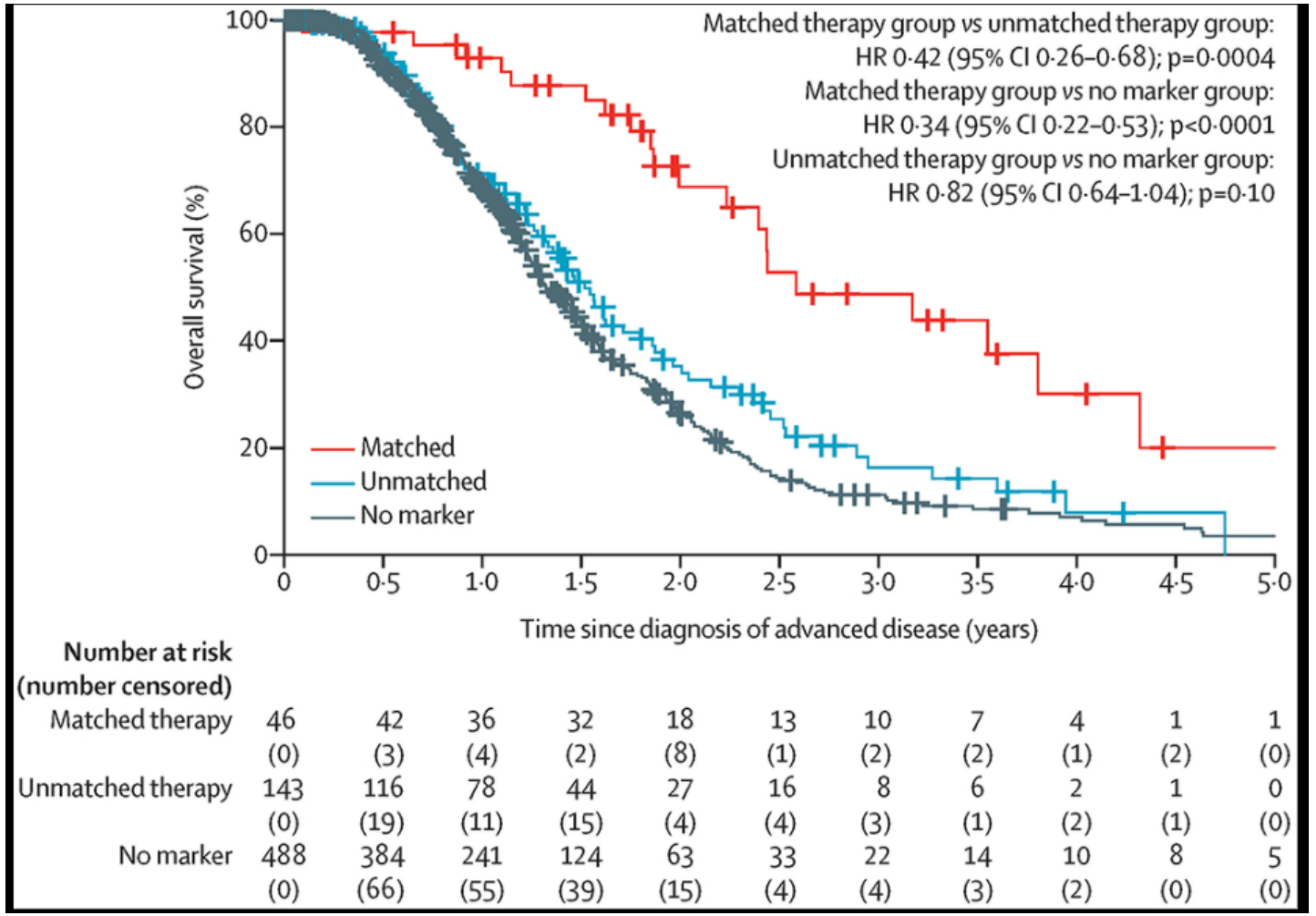
# Targeted Therapies in Pancreatic Cancer




| Number at risk (number censored) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Matched therapy | 46 | 42 | 36 | 32 | 18 | 13 | 10 | 7 | 4 | 1 | 1 |
| | (0) | (3) | (4) | (2) | (8) | (1) | (2) | (2) | (1) | (2) | (0) |
| Unmatched therapy | 143 | 116 | 78 | 44 | 27 | 16 | 8 | 6 | 2 | 1 | 0 |
| | (0) | (19) | (11) | (15) | (4) | (4) | (3) | (1) | (2) | (1) | (0) |
| No marker | 488 | 384 | 241 | 124 | 63 | 33 | 22 | 14 | 10 | 8 | 5 |
| | (0) | (66) | (55) | (39) | (15) | (4) | (4) | (3) | (2) | (0) | (0) |

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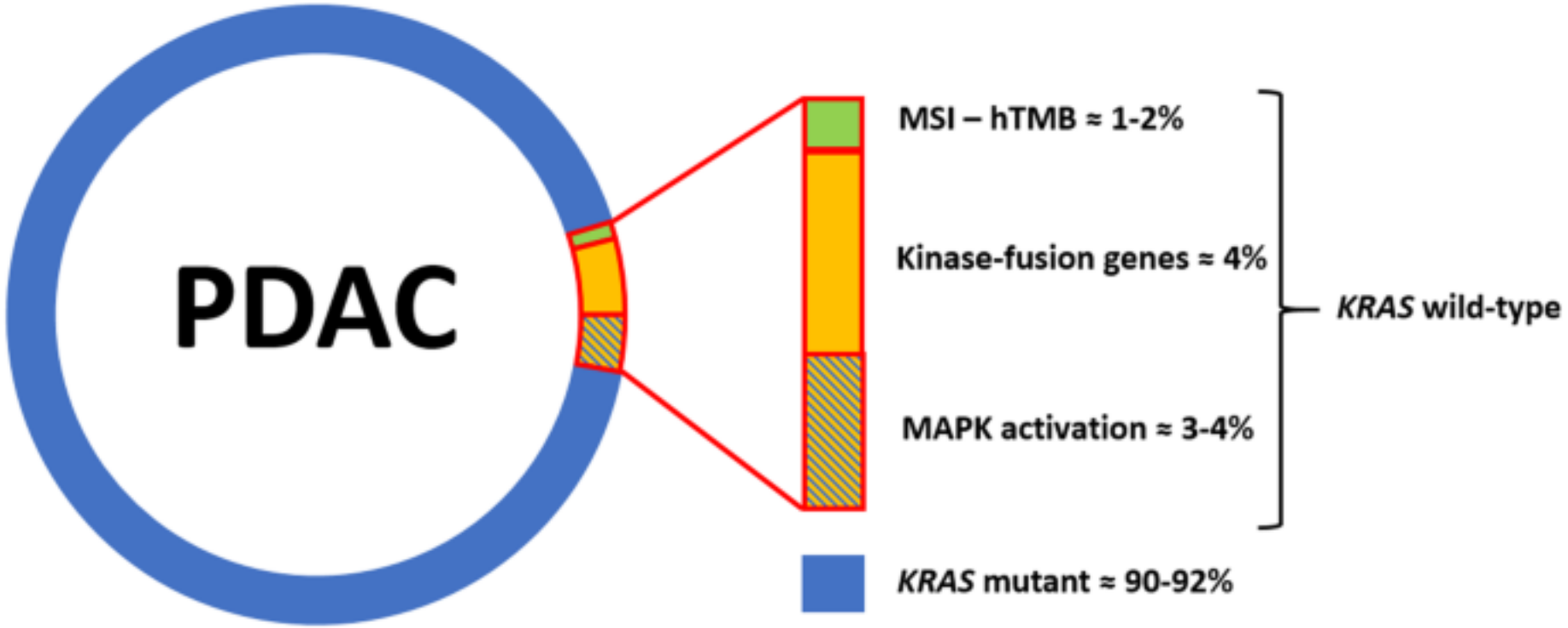
Pishvaian et al. Lancet Oncol. 2020.

# Targeted Therapies in Pancreatic Cancer

- Potential Targets are enriched in **KRAS wildtype** tumors

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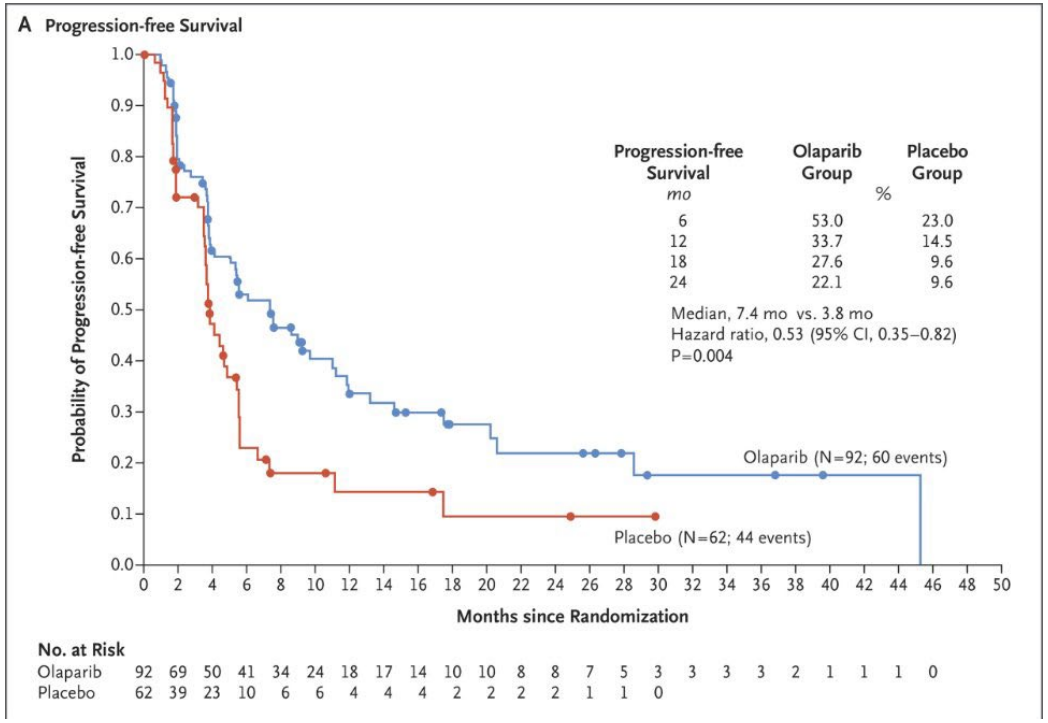
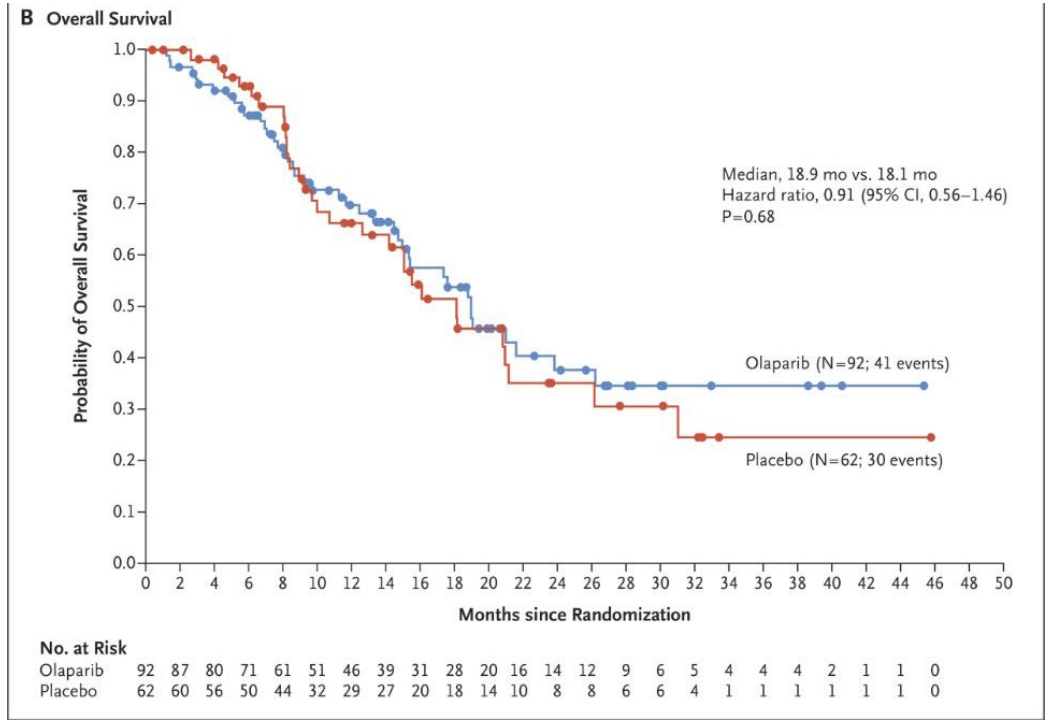
Luchini et al. J of Experimental & Clin Cancer Research. 2020.

# PARP Inhibition in gBRCA/PALB2

- POLO trial: **Olaparib** maintenance improved PFS in patients with metastatic PDAC after 4+ months of platinum-based chemotherapy

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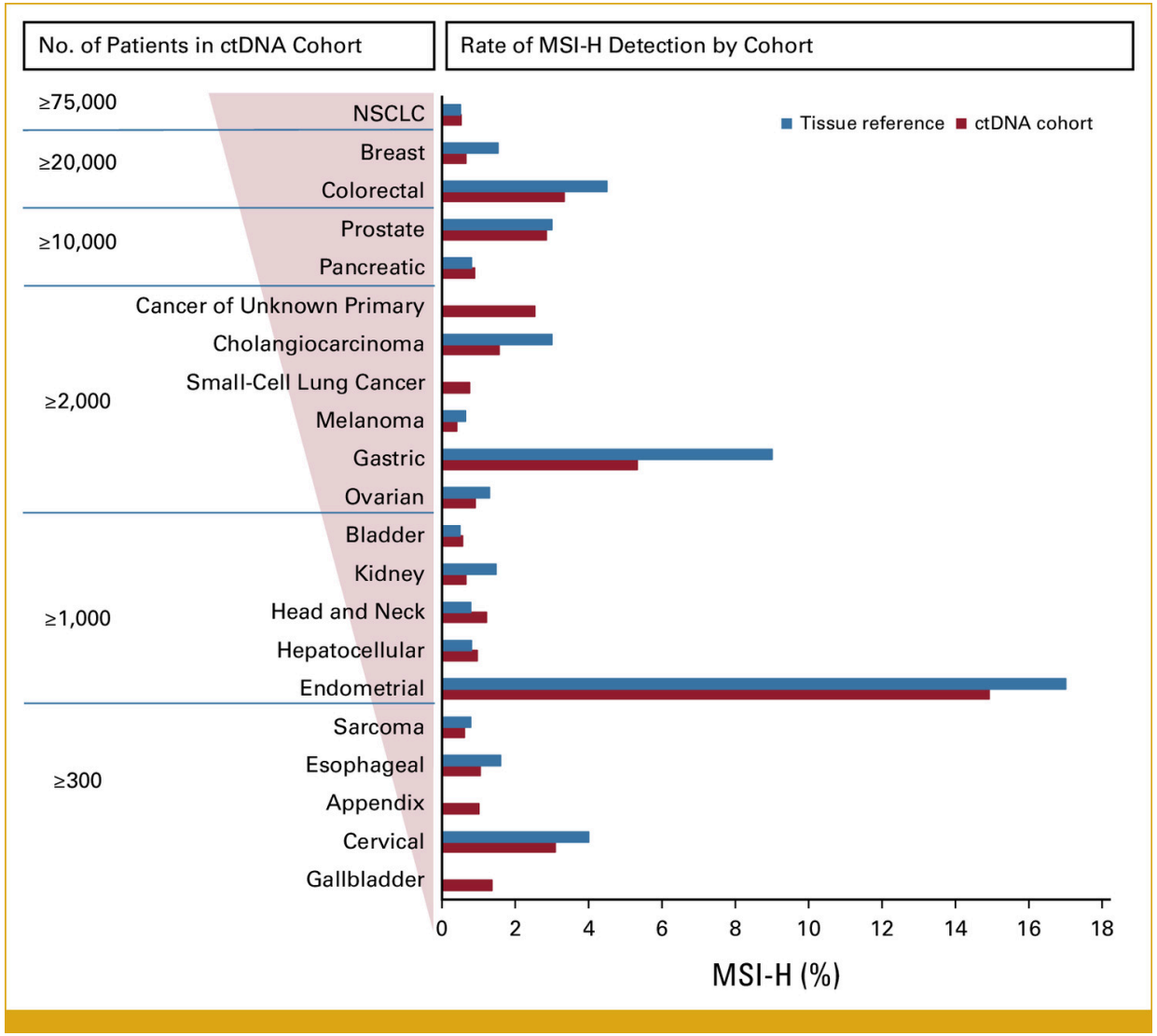
Golan et al. NEJM 2019.

# MSI-High/dMMR Pancreatic Cancer

- Rare but critical (~1%)
- Tumor agnostic approvals for dMMR/MSI-H tumors:
  - Pembrolizumab
  - Dostarlimab




Kasi et al. JCO Precision Oncol 2023.

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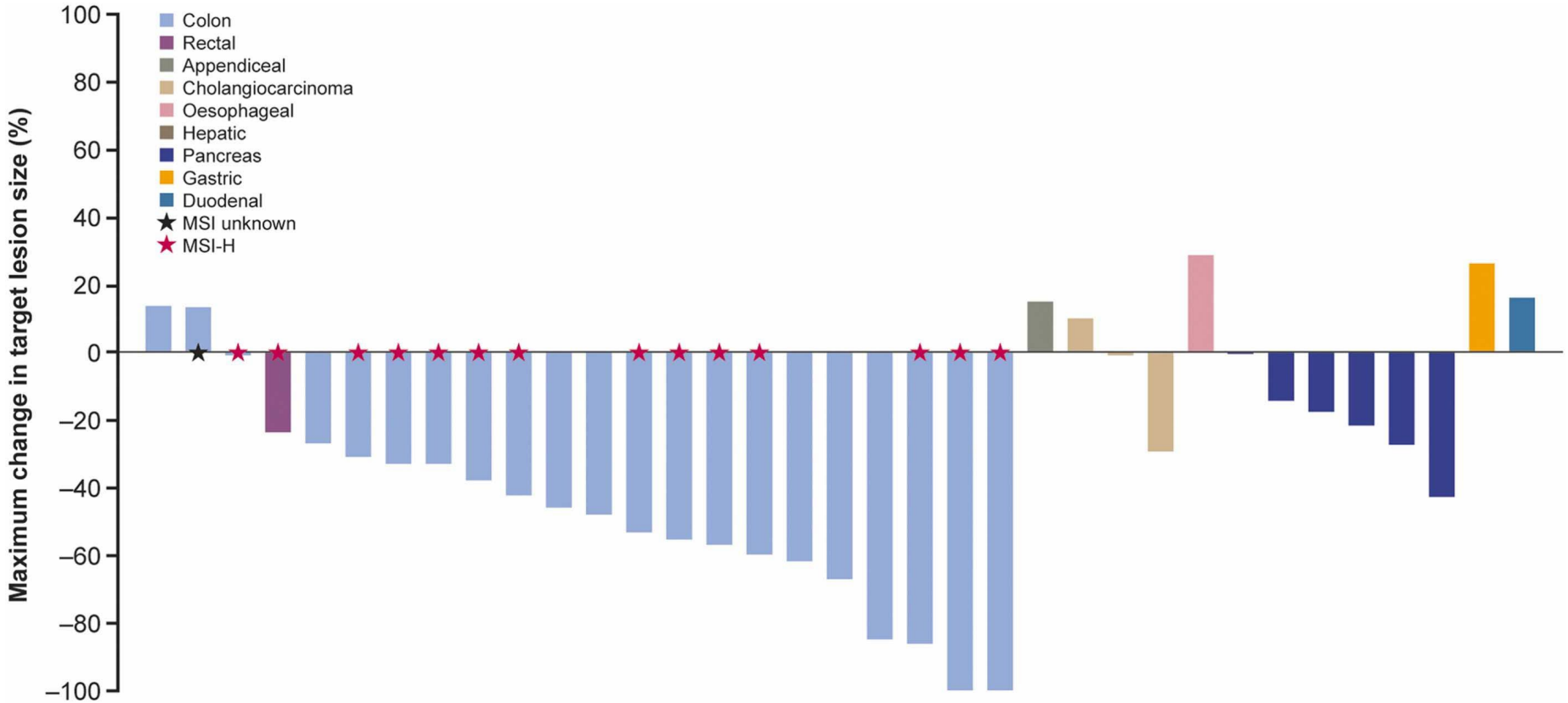
# NTRK Fusions

- Rare (< 1%) but targetable

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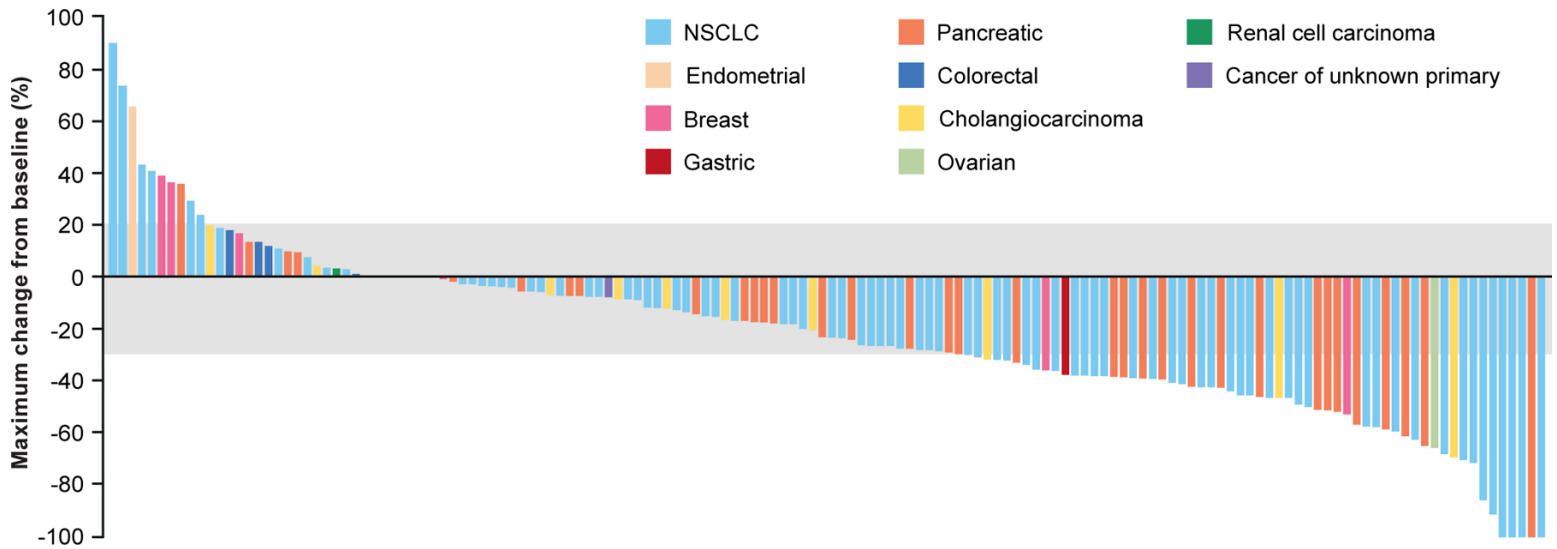
Qi et al. European J of Cancer 2025.

# NRG1 Fusions

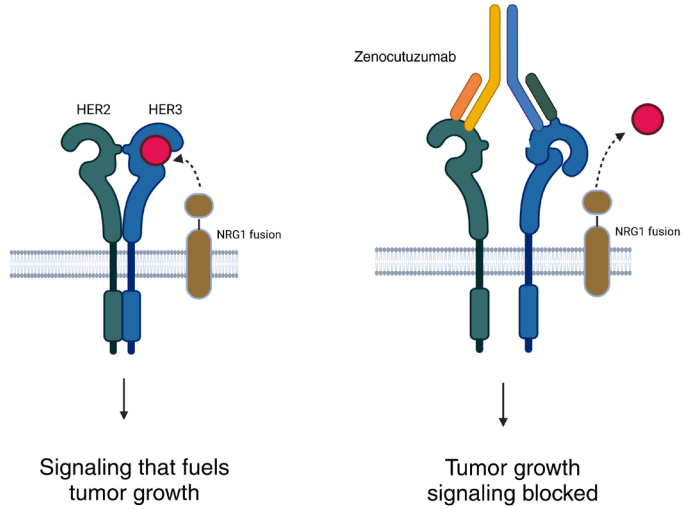
- Zenocutuzumab




## FDA grants accelerated approval to zenocutuzumab-zbco for non-small cell lung cancer and pancreatic adenocarcinoma

On December 4, 2024, the Food and Drug Administration granted accelerated approval to zenocutuzumab-zbco (Bizengri, Merus N.V.) for adults with the following:

- advanced, unresectable, or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy, or
- advanced, unresectable, or metastatic pancreatic adenocarcinoma harboring a *NRG1* gene fusion with disease progression on or after prior systemic therapy.

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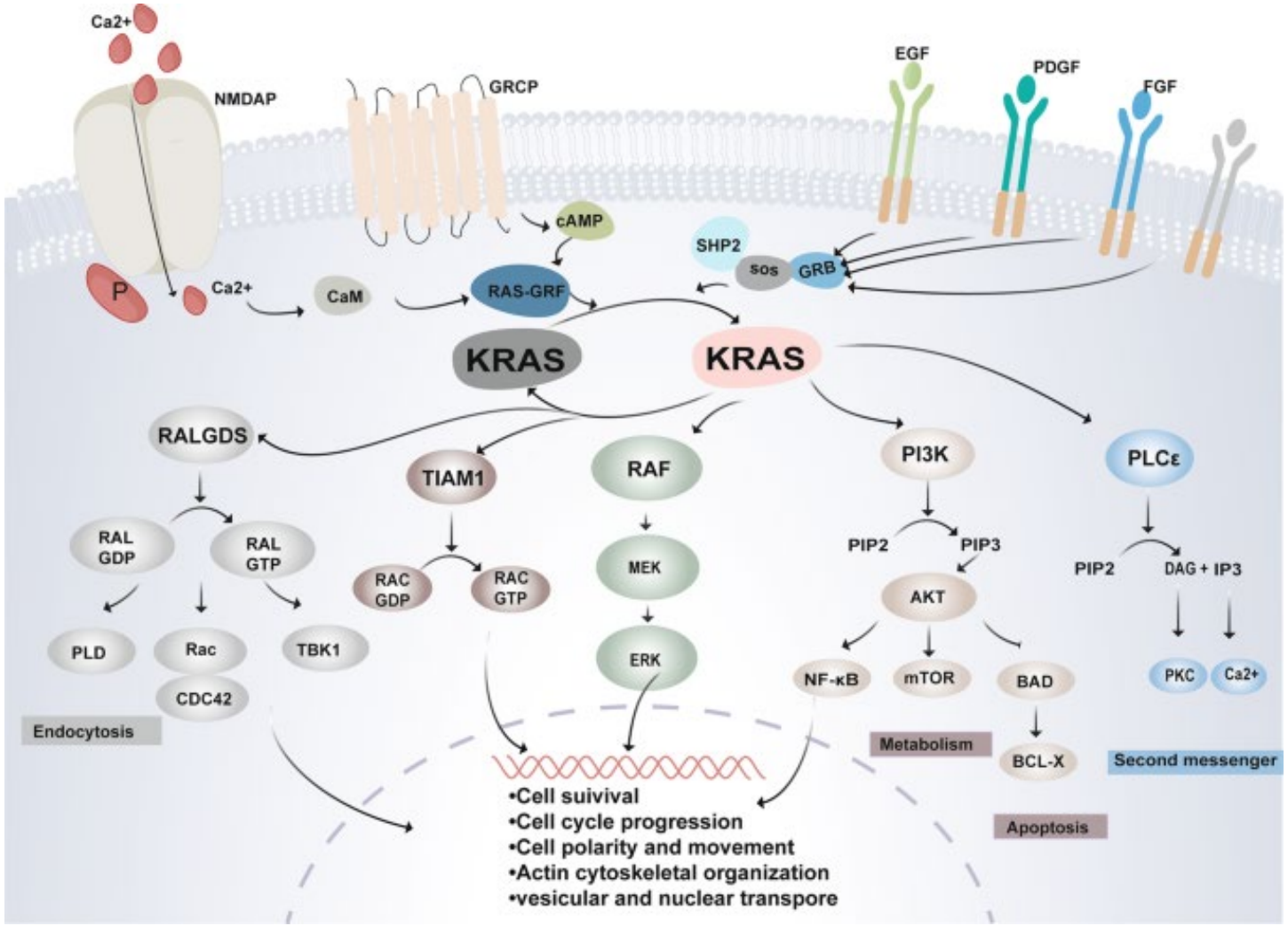
Schram et al. N Engl J of Med 2025.

# Once Undruggable



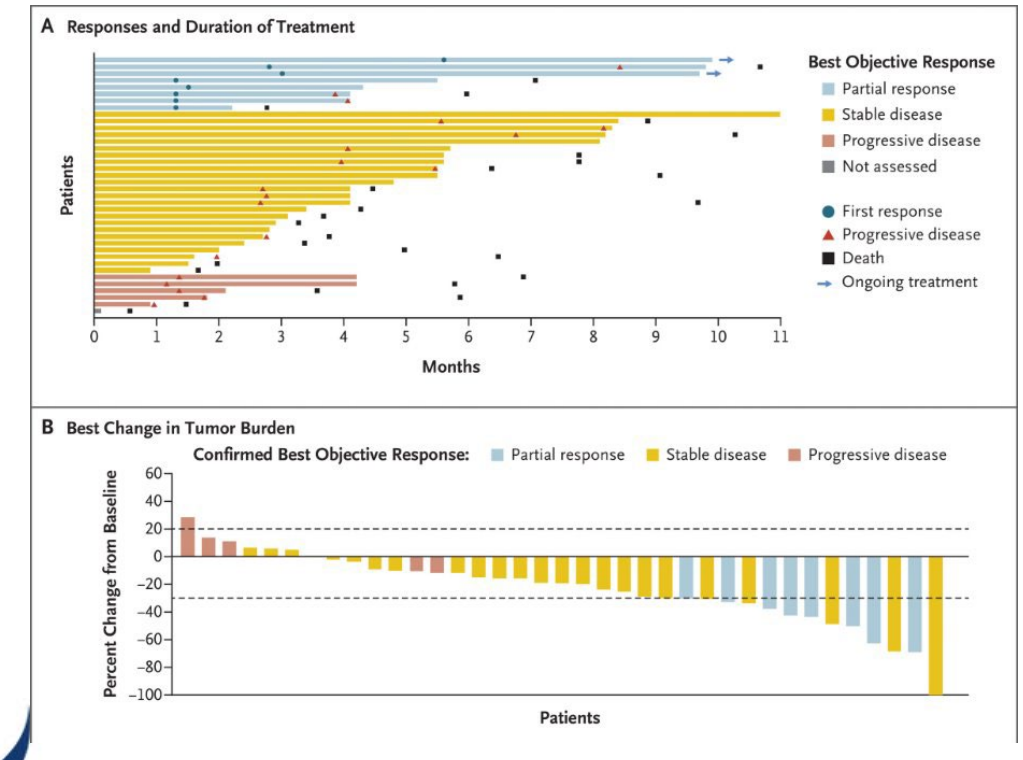

Huang et al. Signal Transduction and Targeted Therapy 2021.

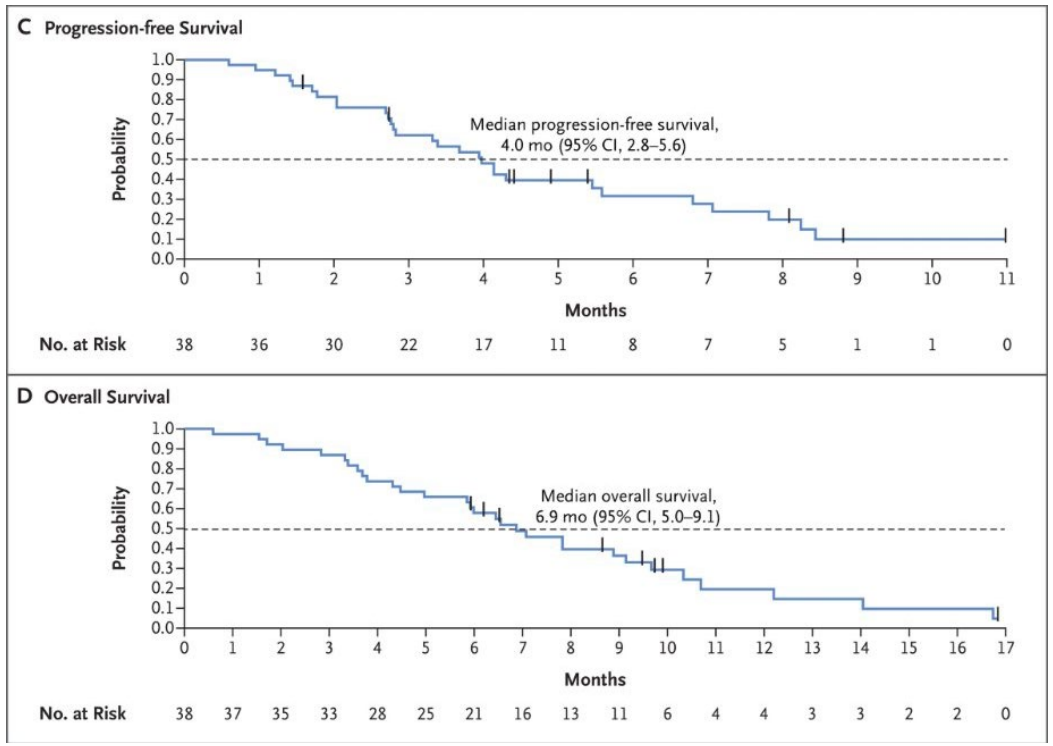
The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

# Sotorasib in *KRAS* p.G12C–Mutated Advanced Pancreatic Cancer

Strickler JH et al. DOI: 10.1056/NEJMoa2208470

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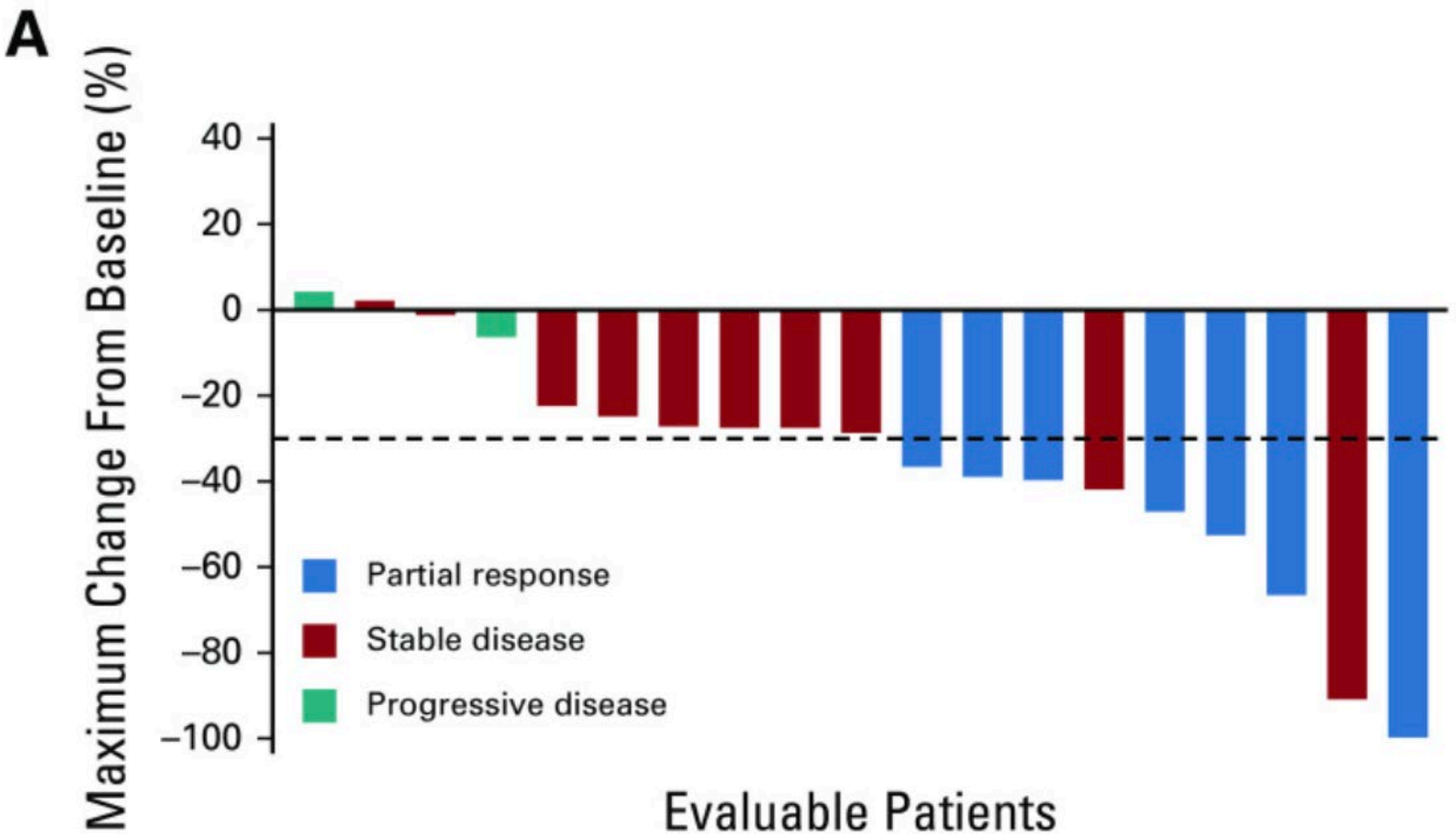
# Adagrasib in Advanced Solid Tumors Harboring a *KRAS*$^{G12C}$ Mutation

Tanios S. Bekaii-Saab, MD[1]; Rona Yaeger, MD[2]; Alexander I. Spira, MD[3,4,5]; Meredith S. Pelster, MD[6]; Joshua K. Sabari, MD[7]; Navid Hafez, MD[8]; Minal Barve, MD[9]; Karen Velastegui, BSc[10]; Xiaohong Yan, PhD[10]; Aditya Shetty, MD[10]; Hirak Der-Torossian, MD[10]; and Shubham Pant, MBBS[11]

KRYSTAL-1

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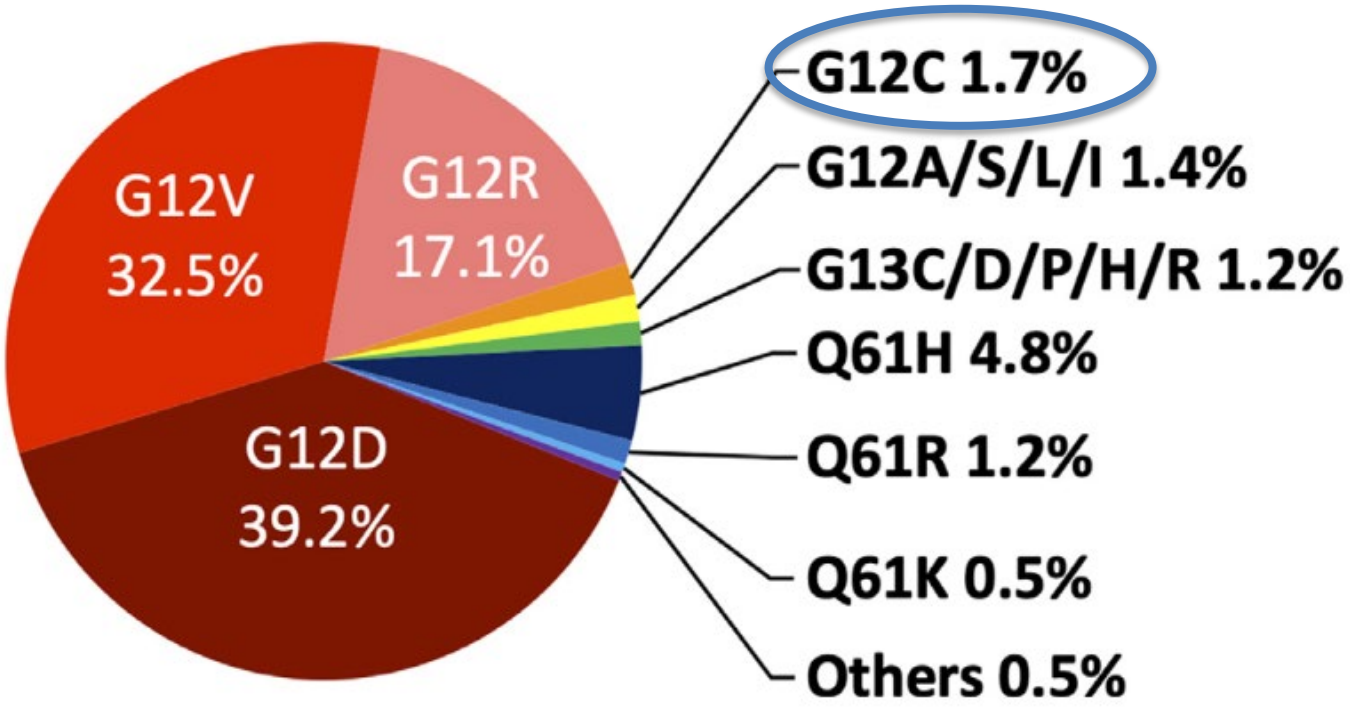
# KRAS Mutation Landscape in PDAC

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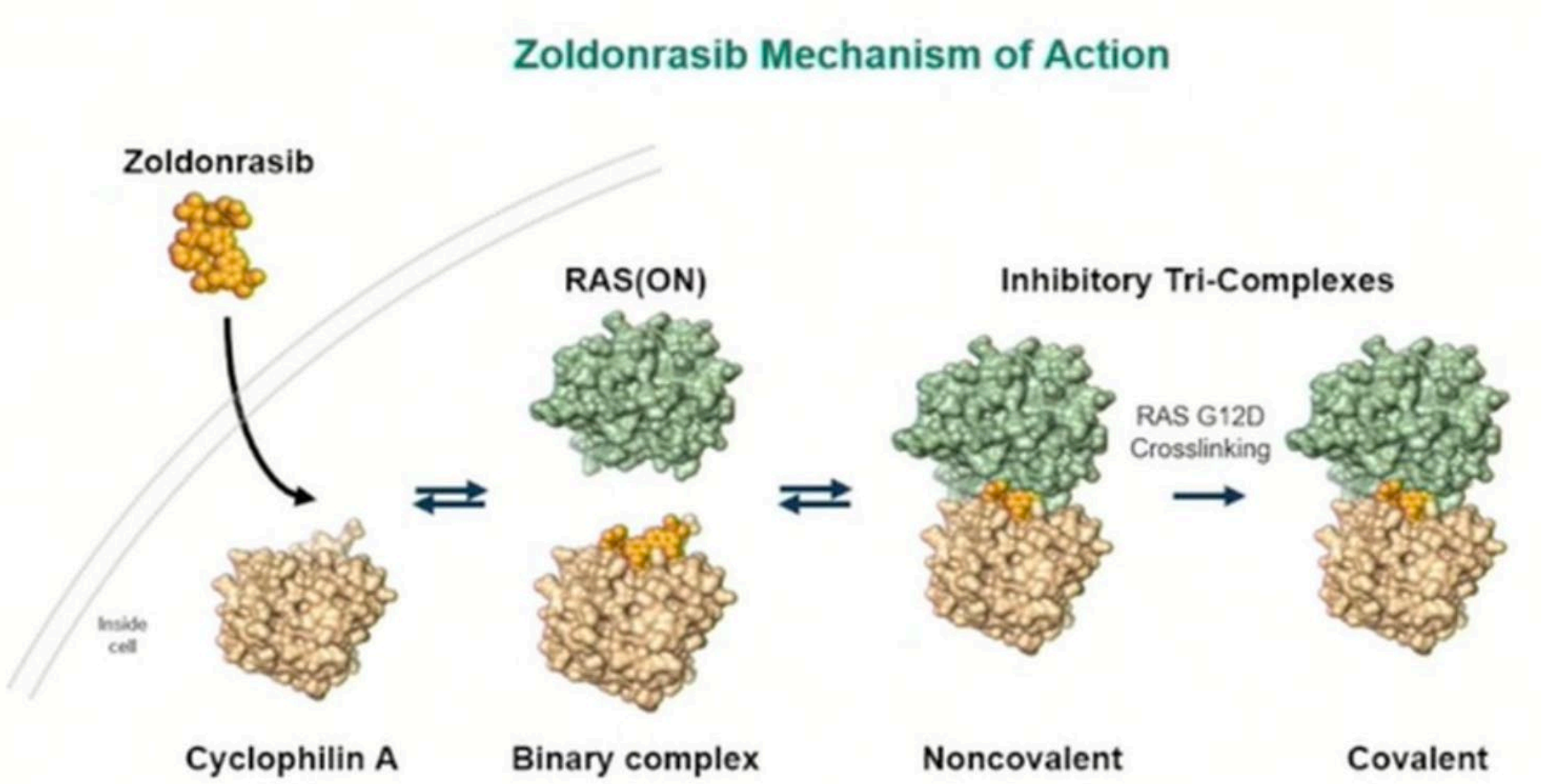
Luo. Seminars in Oncology. 2021

# Expanding the Repertoire

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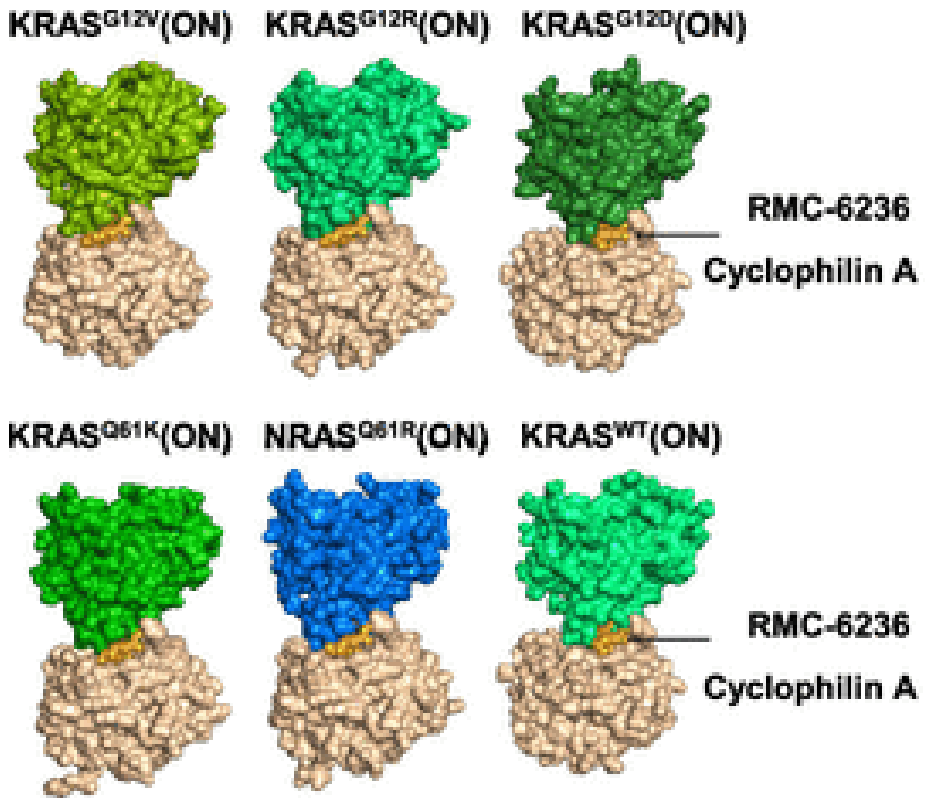
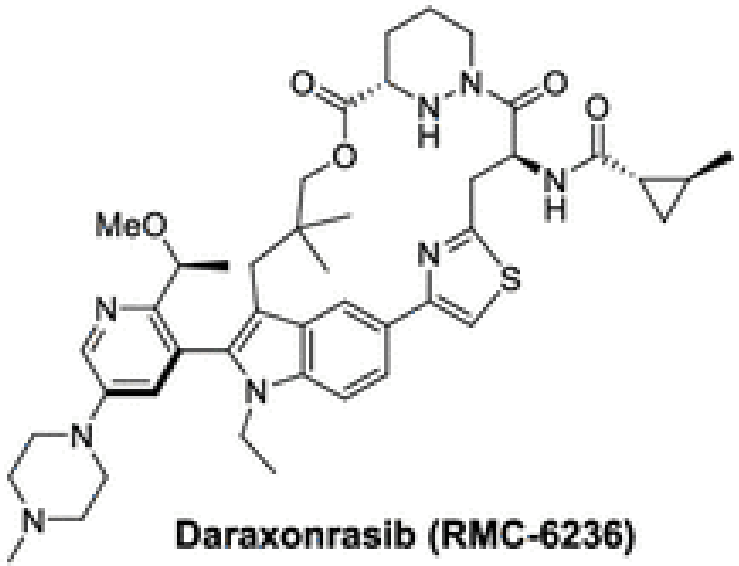
# Expanding the Repertoire




Daraxonrasib (RMC-6236)

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# Trial Design for RASolute 302: 2L Metastatic PDAC

## Key Eligibility Criteria

- Confirmed PDAC
- 1 prior line of therapy in the metastatic setting
- ECOG PS 0-1

N = 460

R
1:1

- RMC-6236 300 mg p.o. QD (N = 230)
- Investigator's Choice SOC Chemotherapy[1] (N = 230)

### Primary Endpoints (RAS G12X)

- PFS, OS

### Secondary Endpoints (All Patients)

- PFS, OS
- ORR, DOR
- QoL

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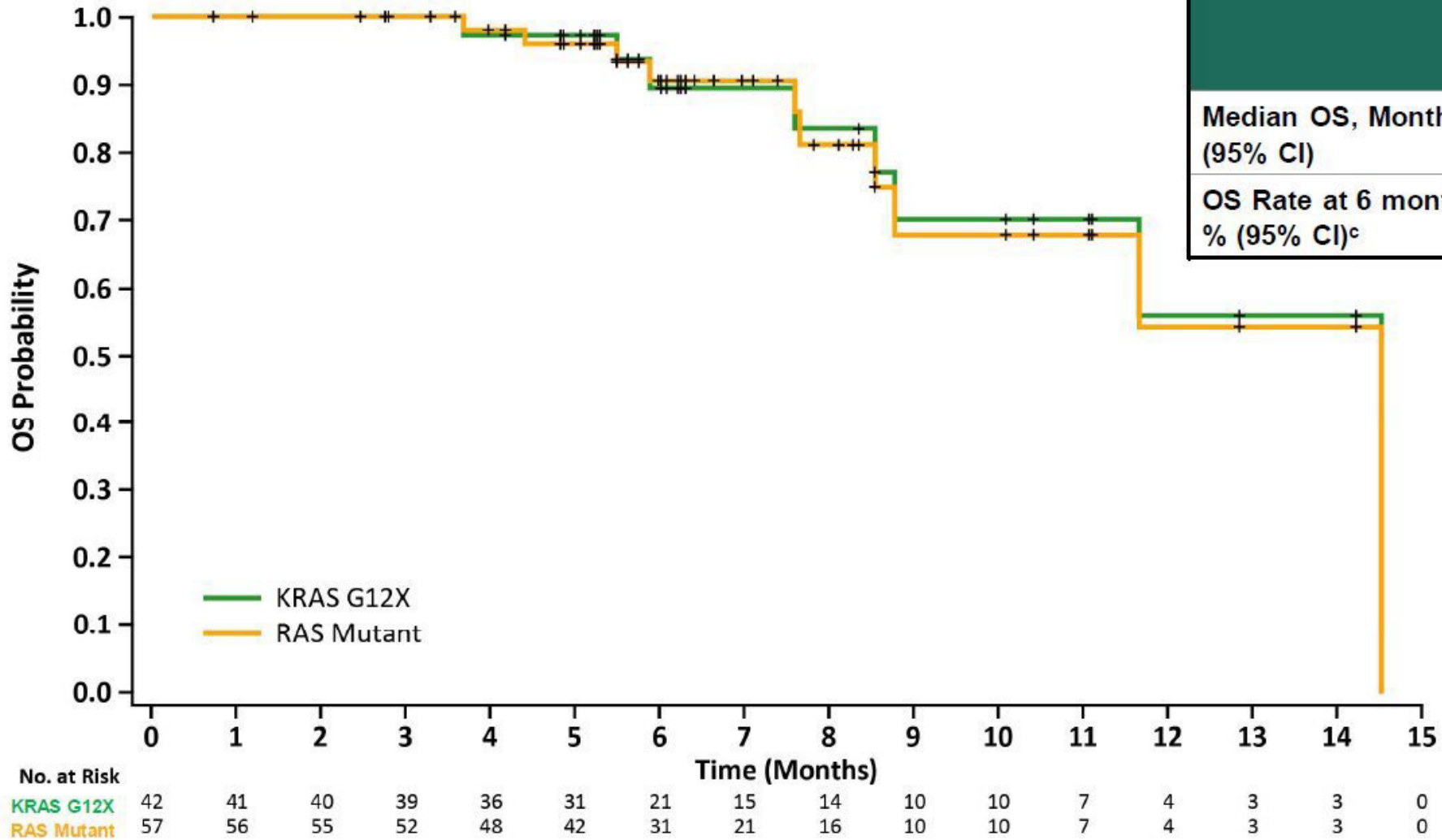
SOC, standard of care; WT, wild type; p.o., oral administration; QD, once daily, DOR, duration of response; QoL, quality of life.
Trial design and dose selection based on FDA meeting. Finalization of design details pending final protocol submission.
(1) SOC chemotherapy options: Gemcitabine + nab-paclitaxel, modified FOLFIRINOX, NAL-IRI+5-FU+LV, or FOLFOX

# RMC-6236 Overall Survival in Patients with 2L PDAC



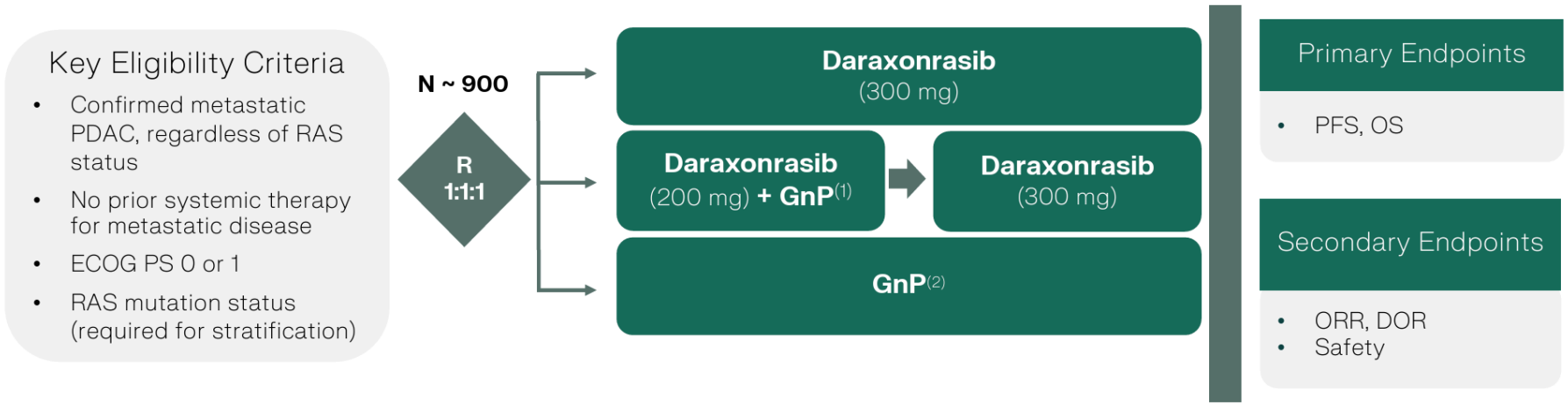

| | KRAS G12X[a] 160-300mg (N=42) | RAS Mutant[b] 160-300mg (N=57) |
|---|---|---|
| Median OS, Months (95% CI) | **14.5** (8.8, NE) | **14.5** (8.8, NE) |
| OS Rate at 6 months, % (95% CI)[c] | **89** (70, 97) | **91** (77, 96) |

Data cutoff 23 Jul 2024.
Median follow-up is 6 months for KRAS G12X and 6.2 months for RAS mutant.
[a]KRAS G12X mutations are defined as nonsynonymous mutations in KRAS codon 12 (G12).
[b]RAS mutant is defined as patients with G12, G13, or Q61 mutant metastatic PDAC.
[c]OS rate at 6 months and 95% CI are from Kaplan-Meier analysis.
2L, second line; PDAC, pancreatic ductal adenocarcinoma; NE, not evaluable; OS, overall survival.

# What about 1st Line?



## Daraxonrasib in 1L Metastatic PDAC: Proposed RASolute 303 Trial Design




Treatment until disease progression or intolerance for all three arms. (1) Daraxonrasib (200 mg) + GnP (1000 mg/m² and 125 mg/m²) given on Days 1, 15 in a 28-day cycle for up to 6 months, followed by daraxonrasib monotherapy (300 mg). (2) GnP (1000 mg/m² and 125 mg/m²) on Days 1, 8, and 15 in a 28-day cycle.
1L, first line; PDAC, pancreatic ductal adenocarcinoma; ECOG PS, Eastern Cooperative Oncology Group Performance Status; R, randomized; GnP, gemcitabine nab-paclitaxel; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; DOR, duration of response.

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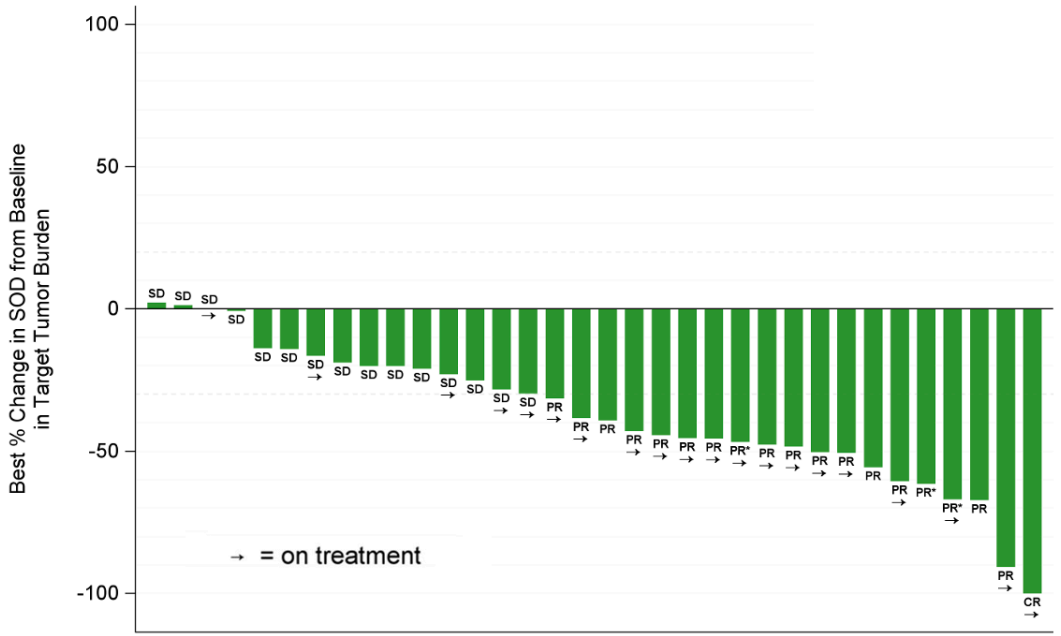
# What about 1st Line?



## 1L PDAC: Daraxonrasib (300 mg) Monotherapy Demonstrated Promising Initial Antitumor Activity in Patients with RAS Mutations




| | N=38[1,4] |
|---|---|
| **ORR[2], % (n)** | 47% (18) |
| **DCR[3], % (n)** | 89% (34) |

Two treatment-naïve patients who are included in the safety analysis are excluded from the waterfall and ORR/DCR analysis because they do not meet the definition of 1L metastatic PDAC: one patient had locally advanced disease and the other had a synchronous neuroendocrine tumor. Median (range) follow-up is 9.3 (4.8, 11.5) months. (1) All patients received a first dose 300 mg QD of daraxonrasib at least 14 weeks prior to data cutoff date. (2) Objective response rate (ORR) (per RECIST v 1.1) includes complete (CR) and partial responses (PR) that were confirmed or still had the potential to confirm. (3) Disease control rate (DCR) includes CR, PR and stable disease (SD). (4) Four patients included in the denominator for ORR and DCR calculations are not displayed on waterfall and treated as non-responders for purposes of the ORR and DCR calculations due to lack of post-baseline target lesion assessment. RAS mutations defined as patients with G12X, G13X or Q61X PDAC. 1L, first line; PDAC, pancreatic ductal adenocarcinoma; PR*, unconfirmed partial response; CI, confidence interval; QD, once daily; RECIST, response evaluation criteria in solid tumors, SOD, sum of diameters.

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Data cutoff: July 28, 2025

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# Immunotherapy in Pancreatic Cancer

- Up to this point, immune checkpoint inhibitors with or without chemotherapy have been largely ineffective in the treatment of pancreatic cancer
- Vaccines may be able to unlock benefits of immune activation

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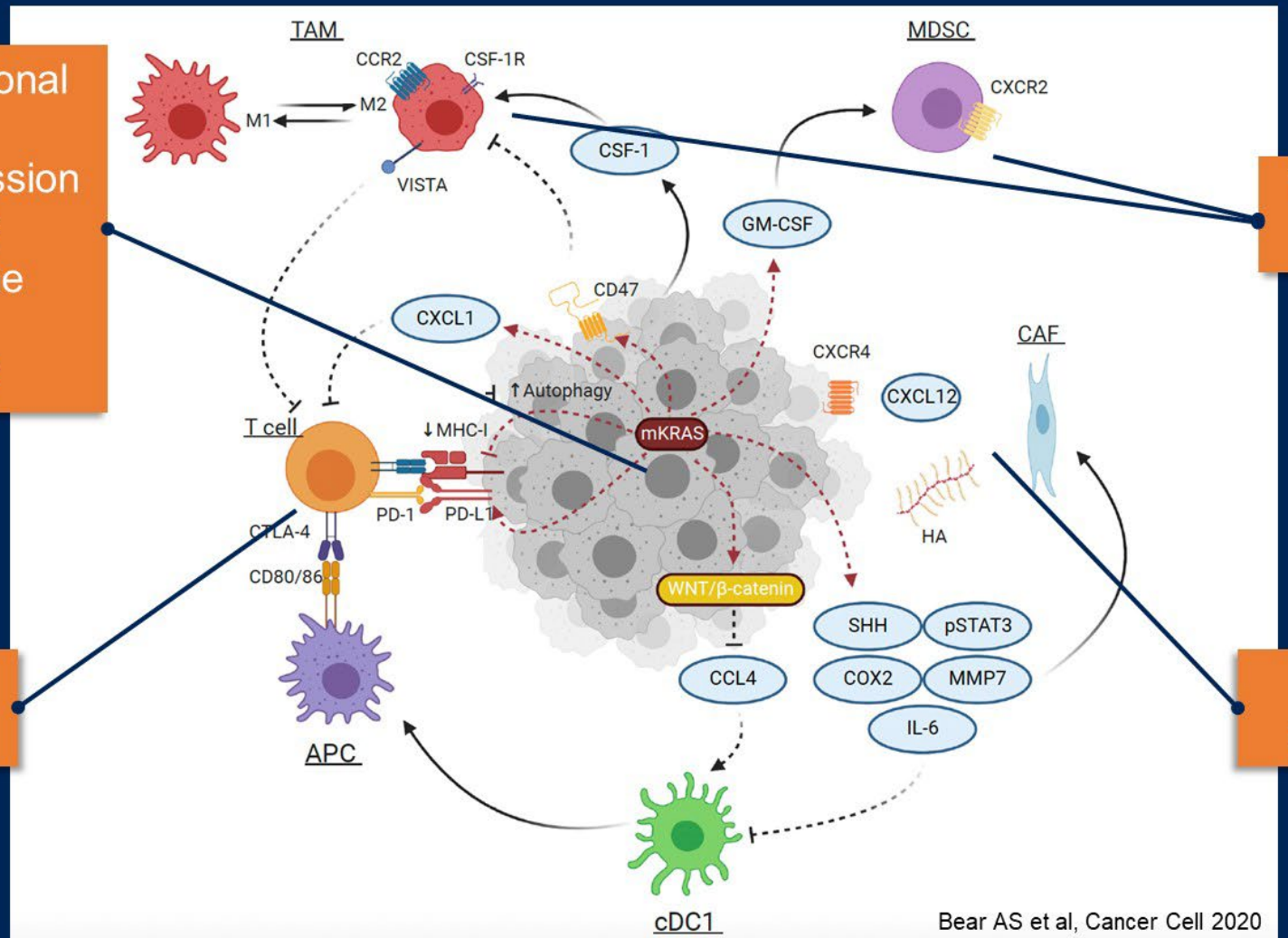
# Immune resistance mechanisms in PDAC



- Low tumor mutational burden
- Low MHC-I expression
- Low antigenic strength/immune privilege
- Mutant KRAS




Bear AS et al, Cancer Cell 2020

Immunosuppressive myeloid cells

Low T cell infiltration

Dense desmoplasia

# Vaccines for Pancreatic Cancer

nature medicine

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nature › nature medicine › brief communications › article

Brief Communication | Open access | Published: 11 August 2025

## Lymph node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: phase 1 AMPLIFY-201 trial final results

Zev A. Wainberg, Colin D. Weekes, Muhammad Furqan, Pashtoon M. Kasi, Craig E. Devoe, Alexis D. Leal, Vincent Chung, James R. Perry, Thian Kheoh, Lisa K. McNeil, Esther Welkowsky, Peter C. DeMuth, Christopher M. Haqq, Shubham Pant & Eileen M. O'Reilly

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### Associated content

**Lymph-node-targeted, mKRAS-specific amphiphile vaccine in pancreatic and colorectal cancer: the phase 1 AMPLIFY-201 trial**

Shubham Pant, Zev A. Wainberg ... Eileen M. O'Reilly

Nature Medicine | Article | Open Access

09 Jan 2024

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# Vaccines for Pancreatic Cancer

- ELI-002 2P
  - mKRAS G12D and G12R specific antigens
  - 25 patients (20 with PDAC, 5 with CRC) who were NED but had ctDNA+ or rising tumor markers (CA 19-9 or CEA)
  - Median OS for PDAC: 28.94 months; median RFS 15.31 months

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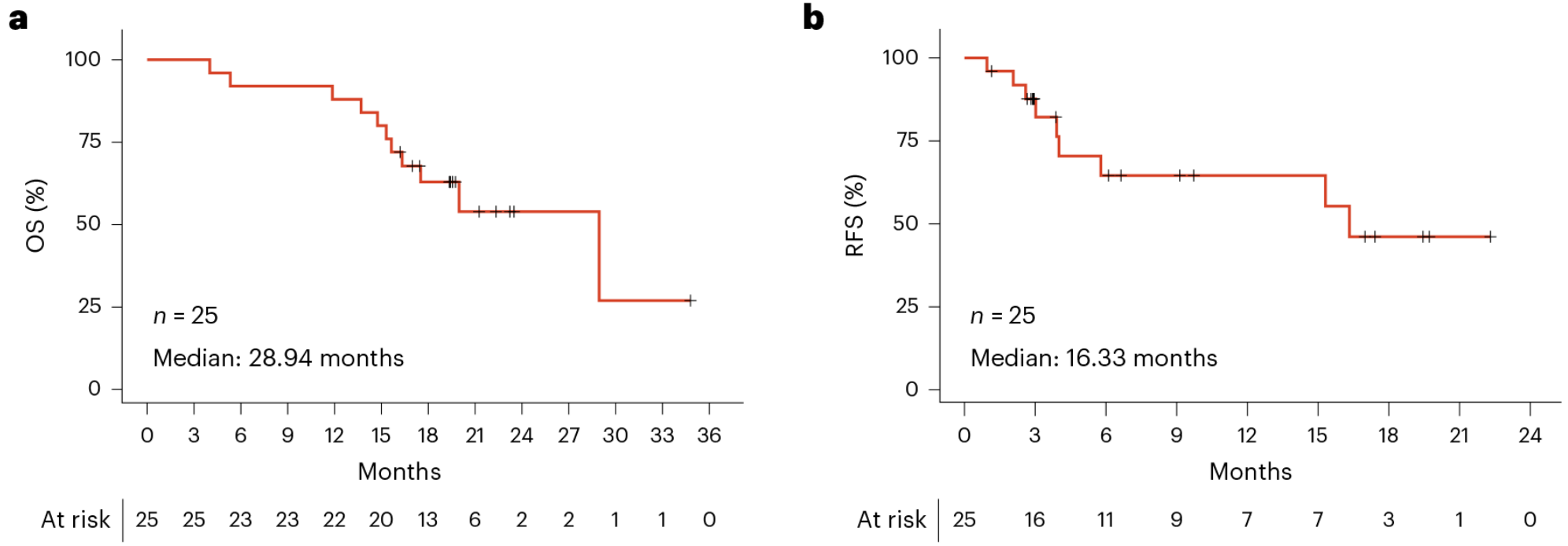
Wainberg et al. Nature Medicine. 2025

# Vaccines for Pancreatic Cancer

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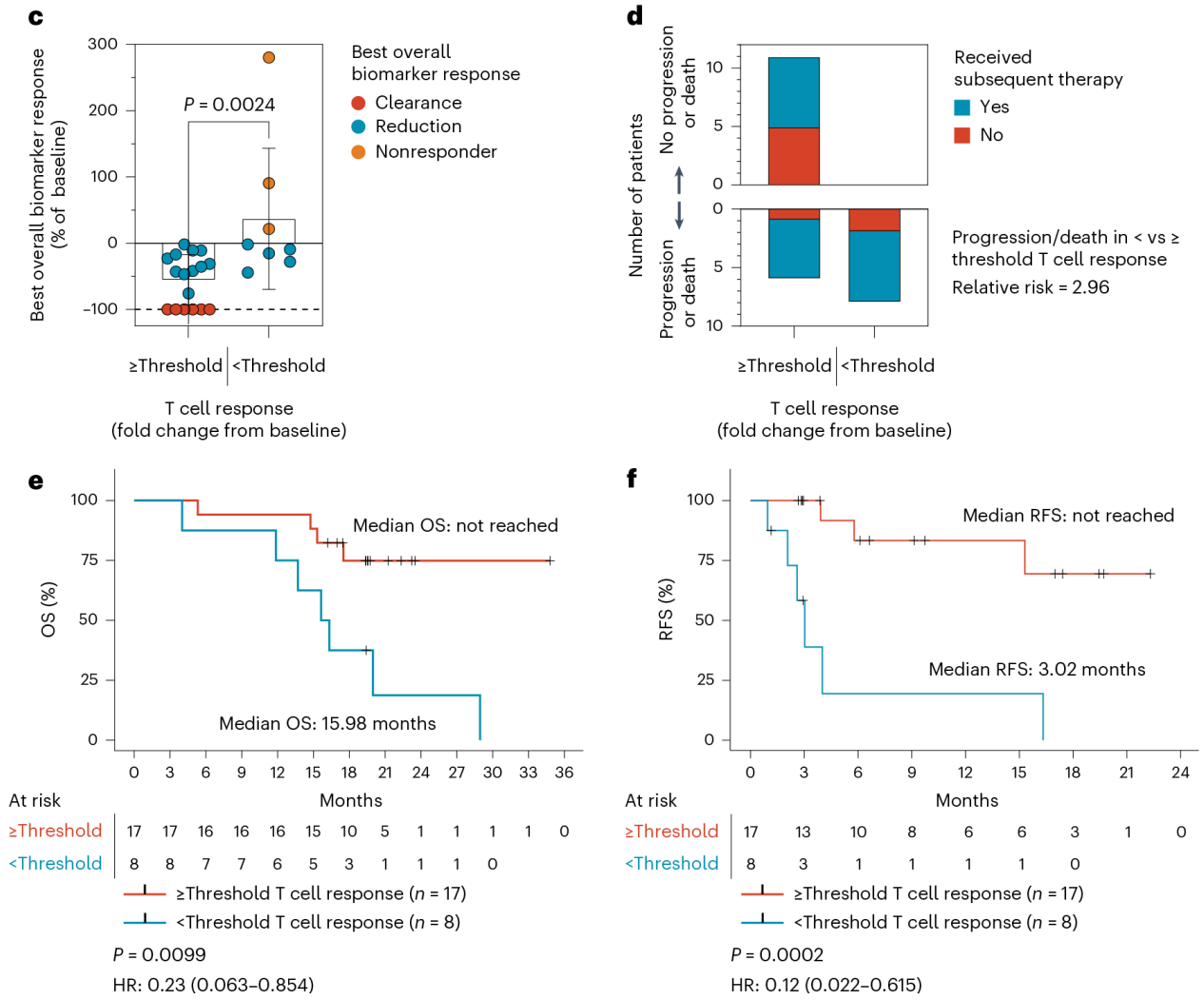


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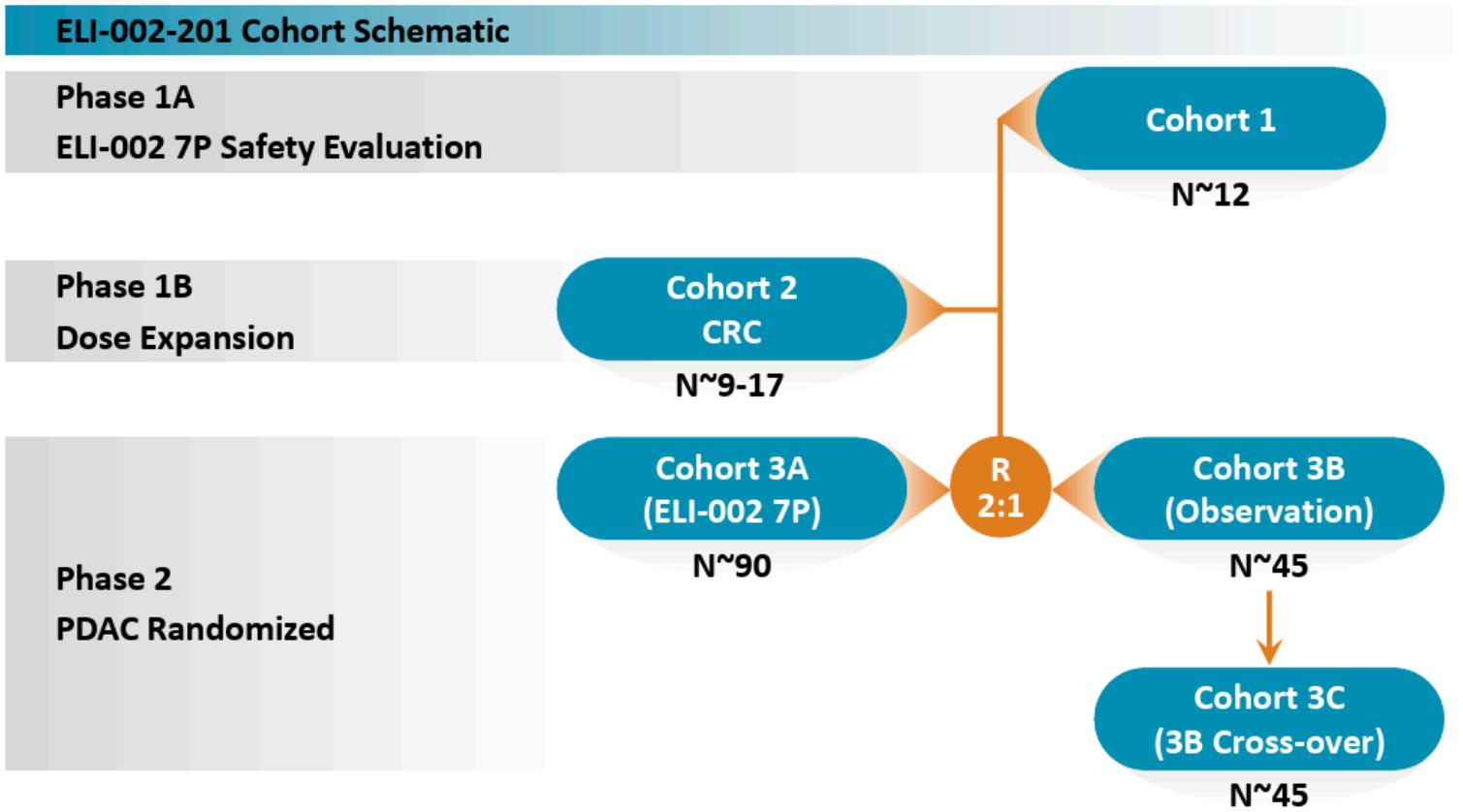
Wainberg et al. Nature Medicine. 2025

# The AMPLIFY 7P trial: Lymph node targeted vaccine ELI-002 7P in patients with RAS mutated pancreatic and colorectal tumors after locoregional treatment

## ELI-002-201 Cohort Schematic

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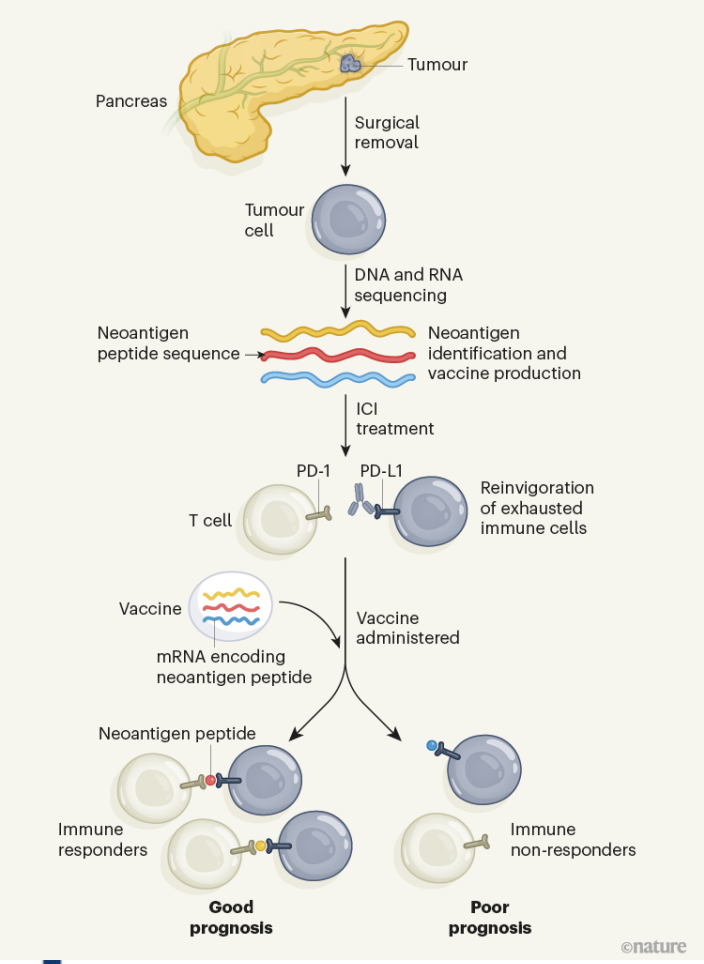
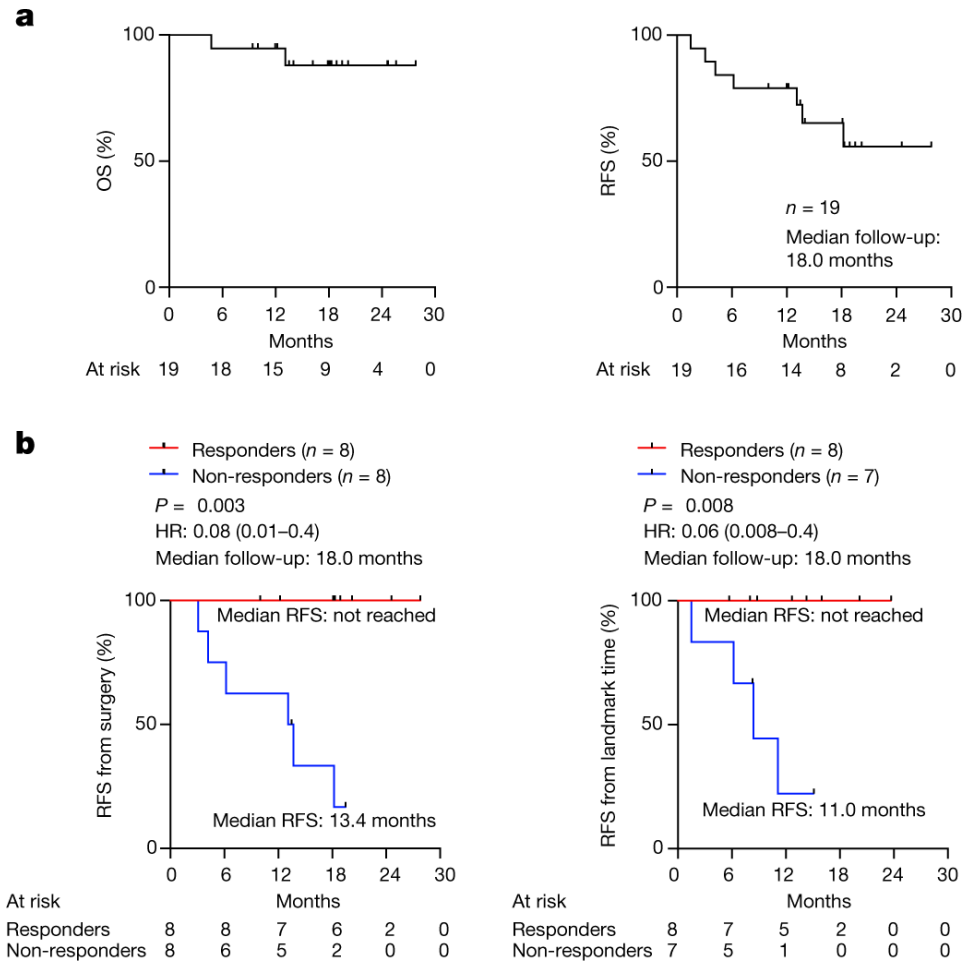
# Personalized Neoantigen Vaccine




Rojas et al. Nature. 2023

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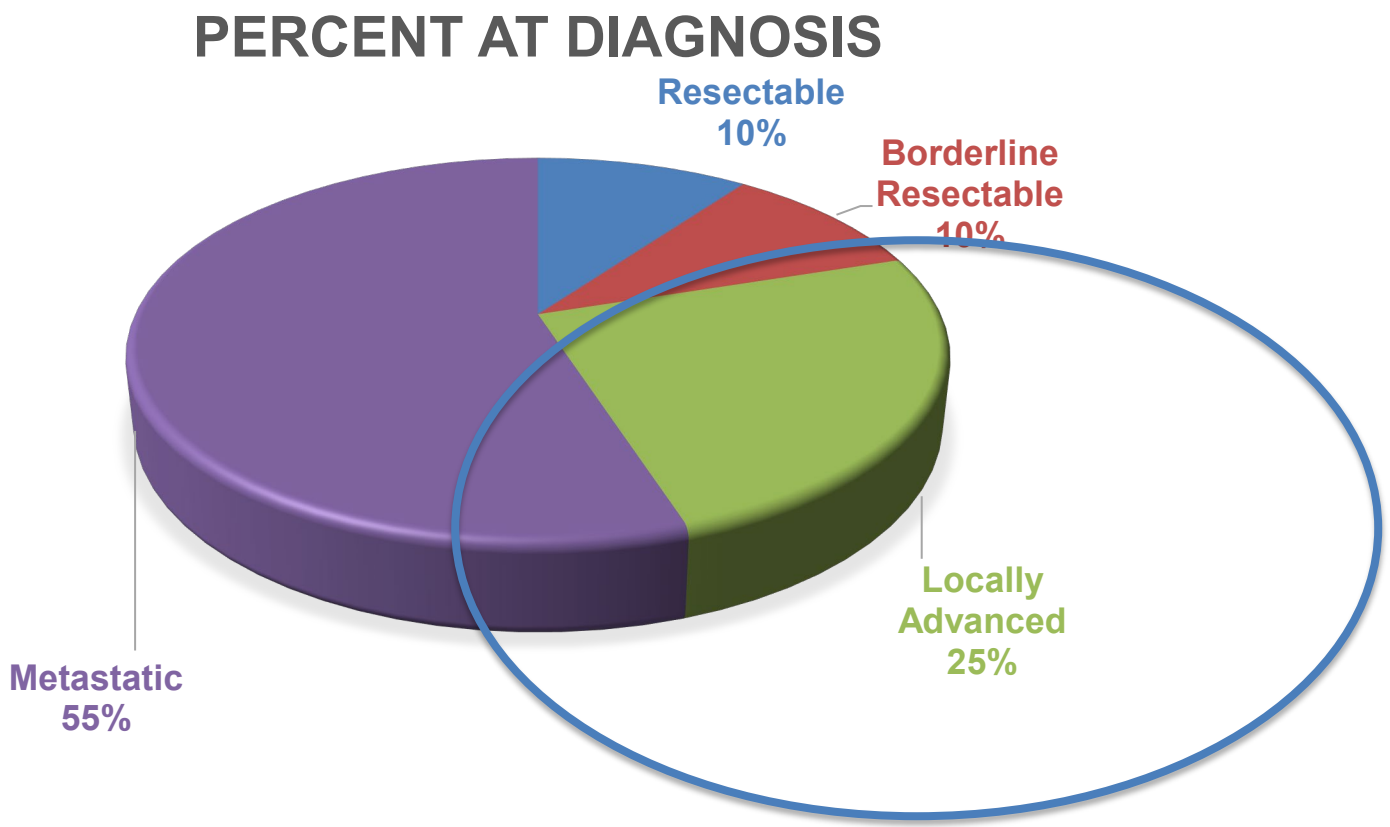
# What about locally advanced pancreatic cancer?

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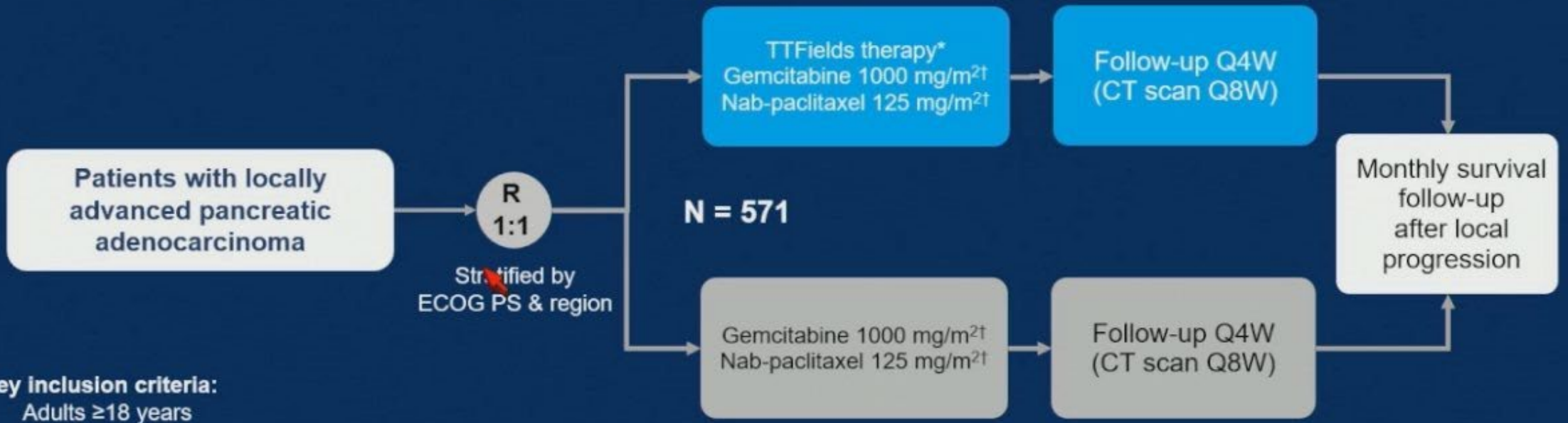
# PANOVA-3 study design




**Key inclusion criteria:**
- Adults ≥18 years
- Previously untreated, biopsy confirmed disease
- Life expectancy ≥3 months
- ECOG PS 0-2

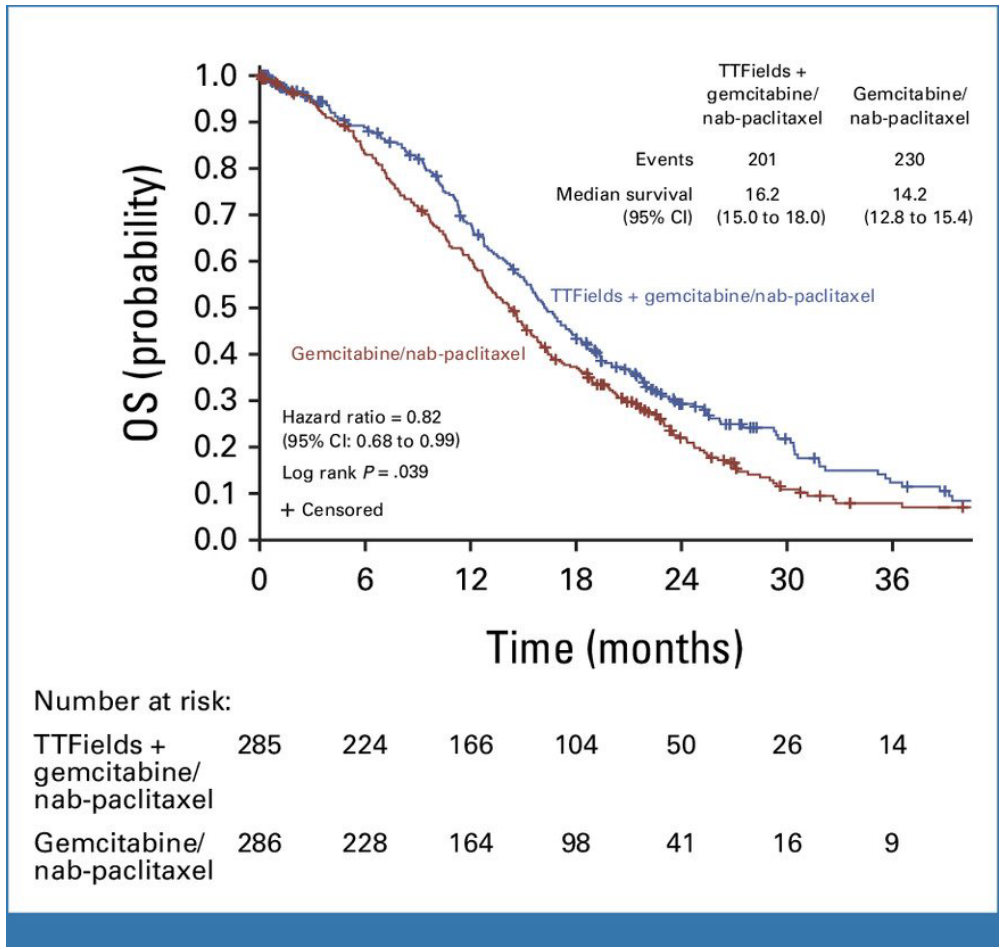
**Key exclusion criteria:**
- Prior palliative treatment to the tumor
- Implanted electronic medical device in torso
- Known allergies to medical adhesives, hydrogel or chemotherapies

**Study sites:** 198 across 20 countries (North and South America, Europe, Asia)‡
**Enrollment:** March 2018 – March 2023

**Data cut-off:** October 16, 2024
**Registration number:** NCT03377491

*150 kHz, 18h/day; †On days 1, 8, and 15 of each 28-day cycle; ‡ US, Mexico, Brazil, Canada; Spain, Hungary, Czech Republic, France, Poland, Germany, Austria, Switzerland, Italy, Israel, Belgium, Croatia; China, South Korea, Australia and Hong Kong;
CT, computer tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; R, randomization; TTFields, Tumor Treating Fields; Q4W, every 4 weeks; Q8W, every 8 weeks.

# PANOVA-3

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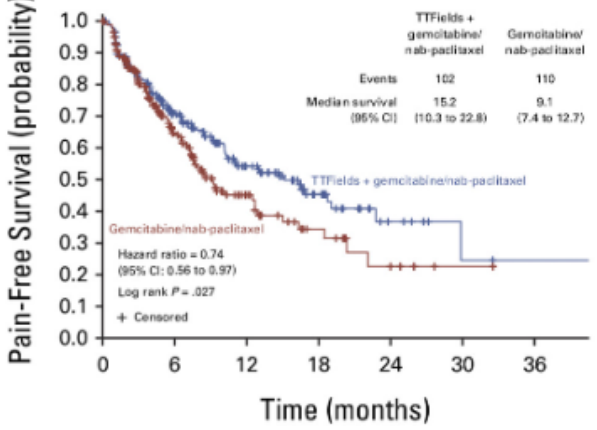
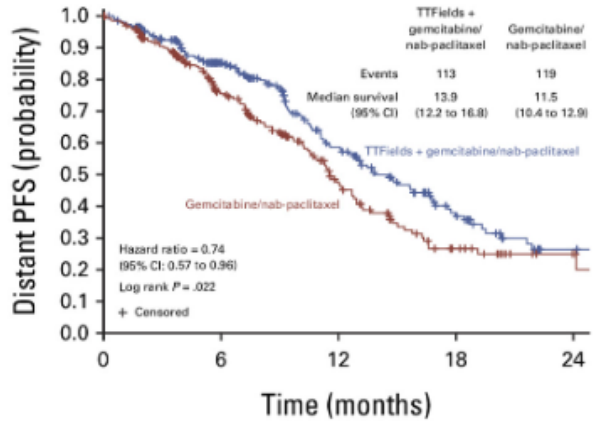



Number at risk:

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| TTFields + gemcitabine/ nab-paclitaxel | 285 | 122 | 58 | 25 | 7 | 2 | 1 |
| Gemcitabine/ nab-paclitaxel | 286 | 98 | 30 | 12 | 4 | 1 | 0 |

D




Number at risk:

| | | | | | |
|---|---|---|---|---|---|
| TTFields + gemcitabine/ nab-paclitaxel | 285 | 164 | 86 | 33 | 11 |
| Gemcitabine/ nab-paclitaxel | 286 | 138 | 55 | 19 | 6 |

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Babiker et al. Journal of Clin Oncol. 2025

# PANOVA-3

- Safety:
  - 8.4% of TTF arm discontinued TTF due to AEs
  - Rash in 25.9% of TTF arm (vs 8.4%); Gr 3-4 in 1.8%
  - Dermatitis in 29.9% (vs 2.9%); Gr 3-4 in 0%.

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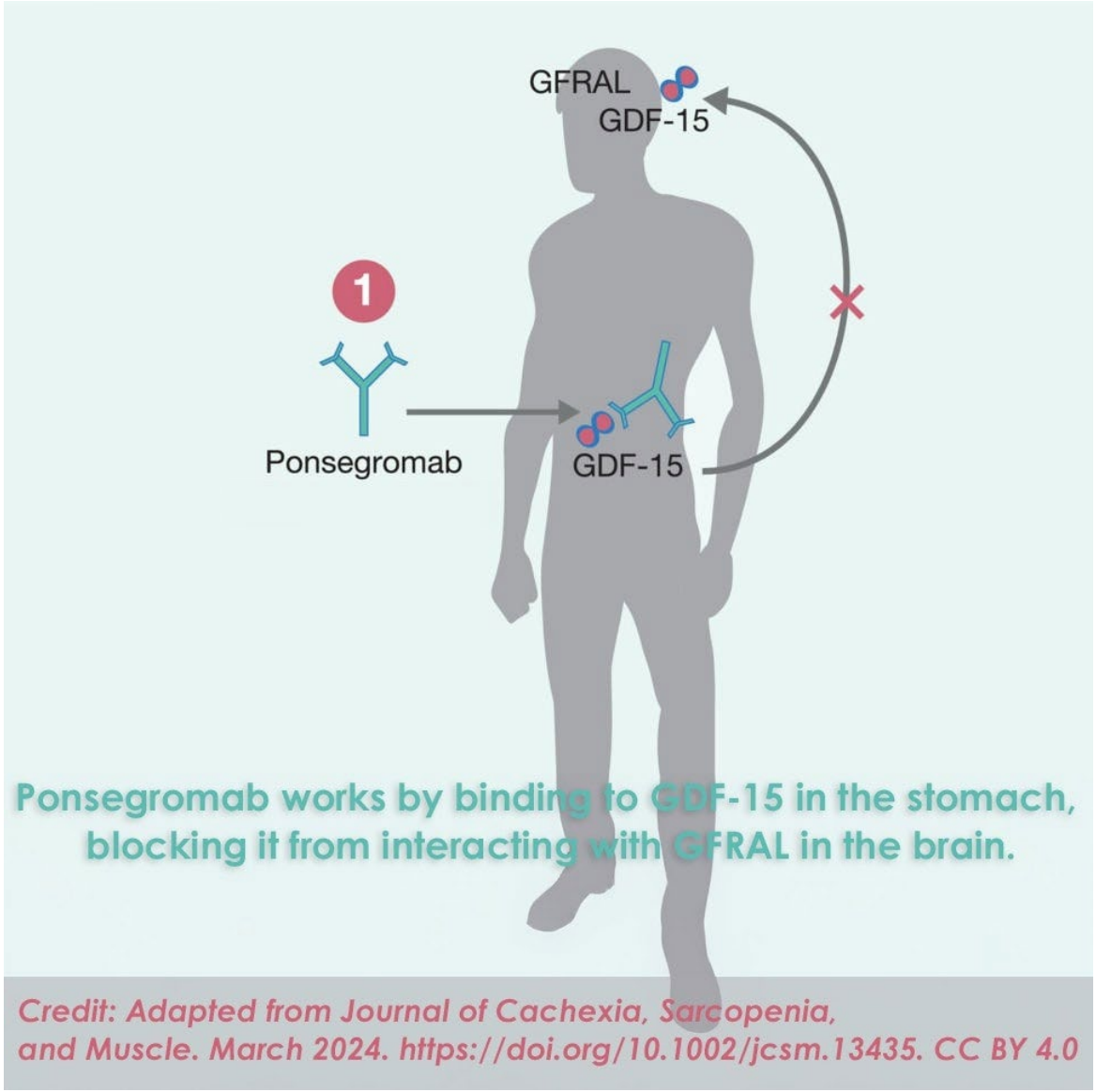
# Cancer Cachexia

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 19/26, 2024 VOL. 391 NO. 24

## Ponsegromab for the Treatment of Cancer Cachexia

John D. Groarke, M.B., B.Ch., M.P.H., Jeffrey Crawford, M.D., Susie M. Collins, M.Sc., Shannon Lubaczewski, Pharm.D., Eric J. Roeland, M.D., Tateaki Naito, M.D., Andrew E. Hendifar, M.D., Marie Fallon, M.D., Koichi Takayama, M.D., Timothy Asmis, M.D., Richard F. Dunne, M.D., Isik Karahanoglu, Ph.D., Carrie A. Northcott, Ph.D., Magdalena A. Harrington, Ph.D., Michelle Rossulek, M.A., Ruolun Qiu, Ph.D., and Aditi R. Saxena, M.D.




*Credit: Adapted from Journal of Cachexia, Sarcopenia, and Muscle. March 2024. https://doi.org/10.1002/jcsm.13435. CC BY 4.0*

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- 187 patients, 32% of whom had pancreatic cancer

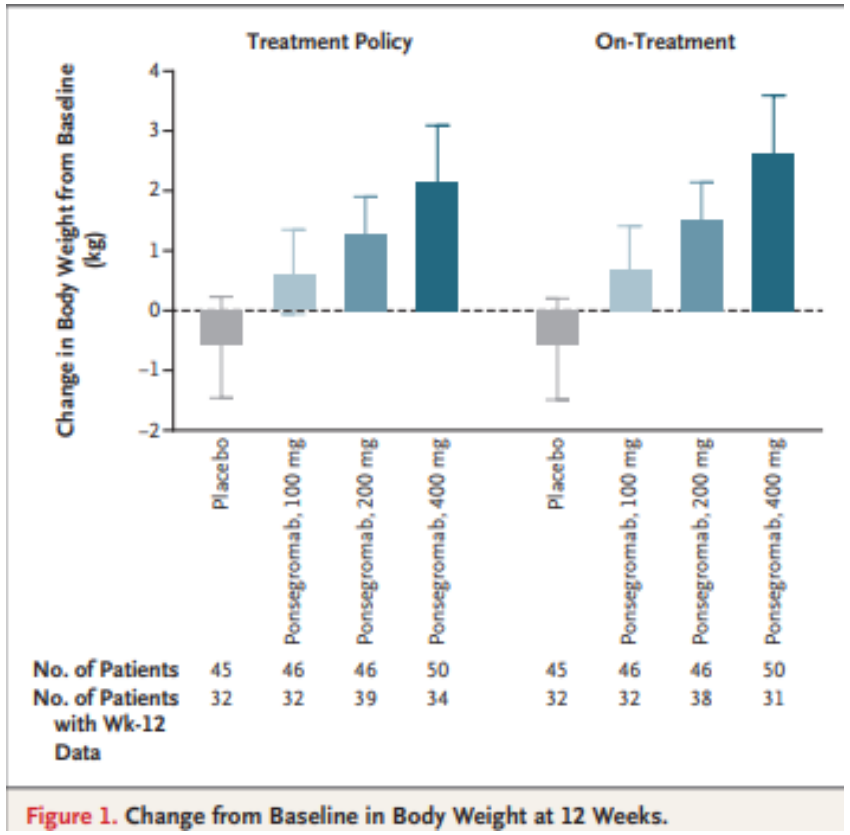


Figure 1. Change from Baseline in Body Weight at 12 Weeks.

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# Summary

- Chemo remains backbone
- 10–15% actionable alterations → test all patients
- IO limited but evolving
- Treating cachexia may provide clinical benefit
- Clinical trials essential


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Thanks!

E-mail me with questions.

Jonathan.Mizrahi@ochsner.org

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