City of Hope

Annual

Advances and Innovations in Endoscopic Oncology and Multidisciplinary Gastrointestinal Cancer Care

KEYNOTE LECTURE

Integrating Precision Medicine into Cancer Care: Promise and Progress

Stephen B. Gruber, MD, PhD

Eva and Ming Hsieh Family Director's Chair, Center for Precision Medicine

Vice President, COH National Medical Center

Professor, Medical Oncology

City of Hope



Disclosure

- This is a Non-CME Accredited session.

Outline

- Progress
  - Precision Medicine in Early-Stage Disease: **Colon Cancer**
  - Precision Medicine in Advanced-Disease: **Pancreatic Cancer**
- Promise
  - Precision Medicine in Prevention with Vaccine Clinical Trials: **Lynch Syndrome**

Progress – Early Stage Colon Cancer

- 70 y.o. healthy male with Lynch Syndrome due to *MSH6*…no history of cancer
- Diligent about annual colonoscopy
- March 2026 colonoscopy bx showed adenocarcinoma at hepatic flexure
- Clinical staging workup with conflicting interpretations of questionable prominent nodes by CT scan, no evidence of mets.
- Neoadjuvant immunotherapy? To treat, or not to treat…that is the question.

NICHE-2: Neoadjuvant Immune Checkpoint Inhibition and Novel IO Combinations in Early-Stage Colon Cancer 2


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 6, 2024 VOL. 390 NO. 21

Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair–Deficient Colon Cancer

Myriam Chalabi, M.D., Ph.D., Yara L. Verschoor, M.D., Pedro Batista Tan, M.Sc., Sara Balduzzi, Ph.D., Anja U. Van Lent, M.D., Ph.D., Cecile Grootscholten, M.D., Ph.D., Simone Dokter, M.Sc., Nikè V. Büller, M.D., Ph.D., Brechtje A. Grotenhuis, M.D., Ph.D., Koert Kuhlmann, M.D., Ph.D., Jacobus W. Burger, M.D., Ph.D., Inge L. Huibregtse, M.D., Ph.D., Tjeerd S. Aukema, M.D., Ph.D., Eduard R. Hendriks, M.D., Steven J. Oosterling, M.D., Ph.D., Petur Snaebjornsson, M.D., Ph.D., Emile E. Voest, M.D., Ph.D., Lodewyk F. Wessels, Ph.D., Regina G. Beets-Tan, M.D., Ph.D., Monique E. Van Leerdam, M.D., Ph.D., Ton N. Schumacher, Ph.D., José G. van den Berg, M.D., Ph.D., Geerard L. Beets, M.D., Ph.D., and John B. Haanen, M.D., Ph.D.

- Phase 2 single arm, locally advanced colon cancer
- Neoadjuvant ipilumimab + nivolumab
- N=111
- Primary outcomes: Safety and 3-yr disease-free survival
- “data on 3-year disease-free survival are not mature,” but no recurrences observed

Chalabi M et al, NEJM, 2024

NICHE-2: Neoadjuvant Immune Checkpoint Inhibition and Novel IO Combinations in Early-Stage Colon Cancer 2

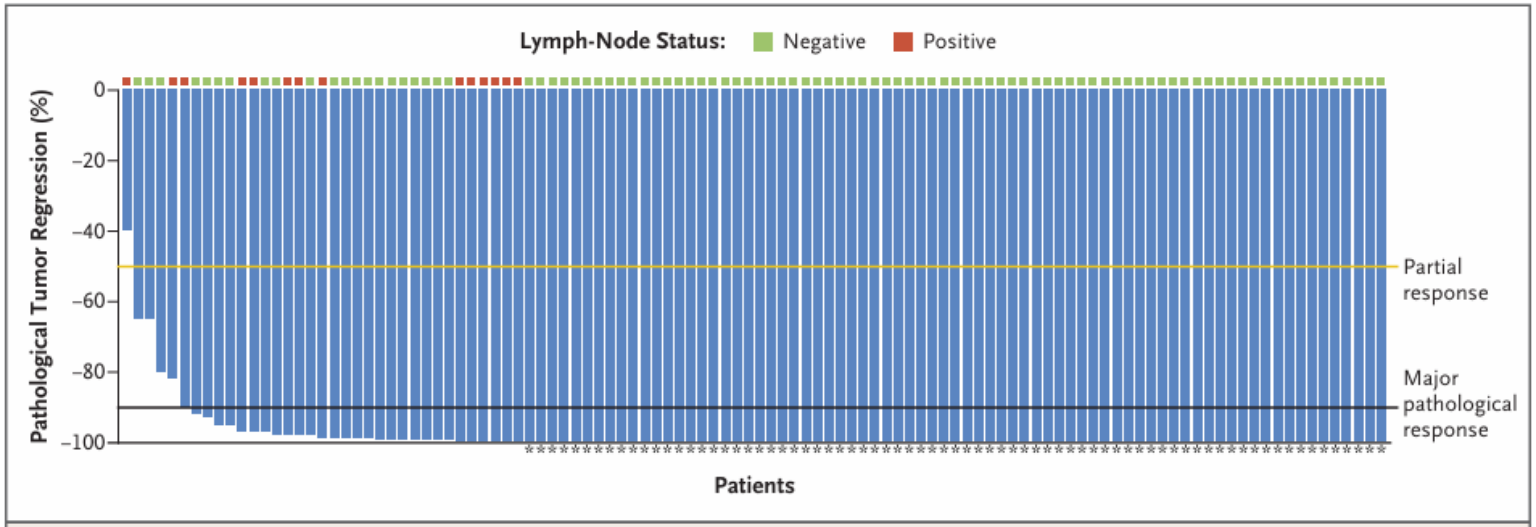


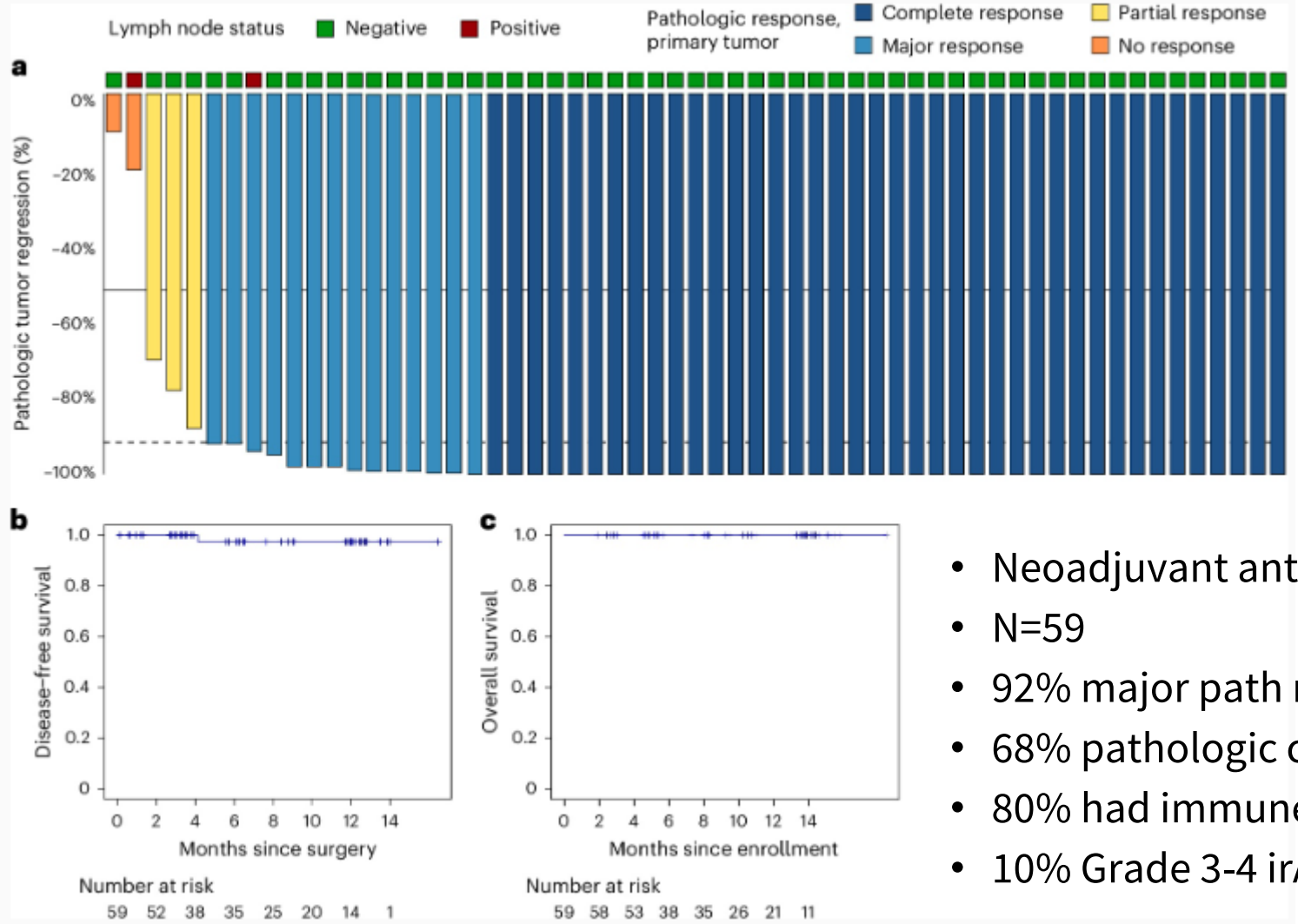
Figure 2. Pathological Responses among Patients in the Efficacy Analysis.

The waterfall plot shows the percentage of pathological tumor regression per tumor among the 110 tumors that could be evaluated for a pathological response. Boxes above each bar indicate the corresponding pathological lymph-node status. Patients with a pathological complete response in both the primary tumor and the lymph nodes are indicated by an asterisk. The black horizontal line indicates the threshold for a major pathological response, specified as at least 90% tumor regression. The yellow line indicates the threshold for a partial response, specified as at least a 50% regression.

- Acceptable safety profile and led to a pathological response in a high proportion of patients
- 4% Grade 3-4 immune related Adverse Events (irAEs)
- “One of the major limitations of our study is the often inaccurate radiographic staging of colon cancers, which can lead to possible over treatment.”

Chalabi M et al, NEJM, 2024

NICHE-3: Neoadjuvant nivolumab and relatlimab in locally advanced MMR-deficient colon cancer: a phase 2 trial



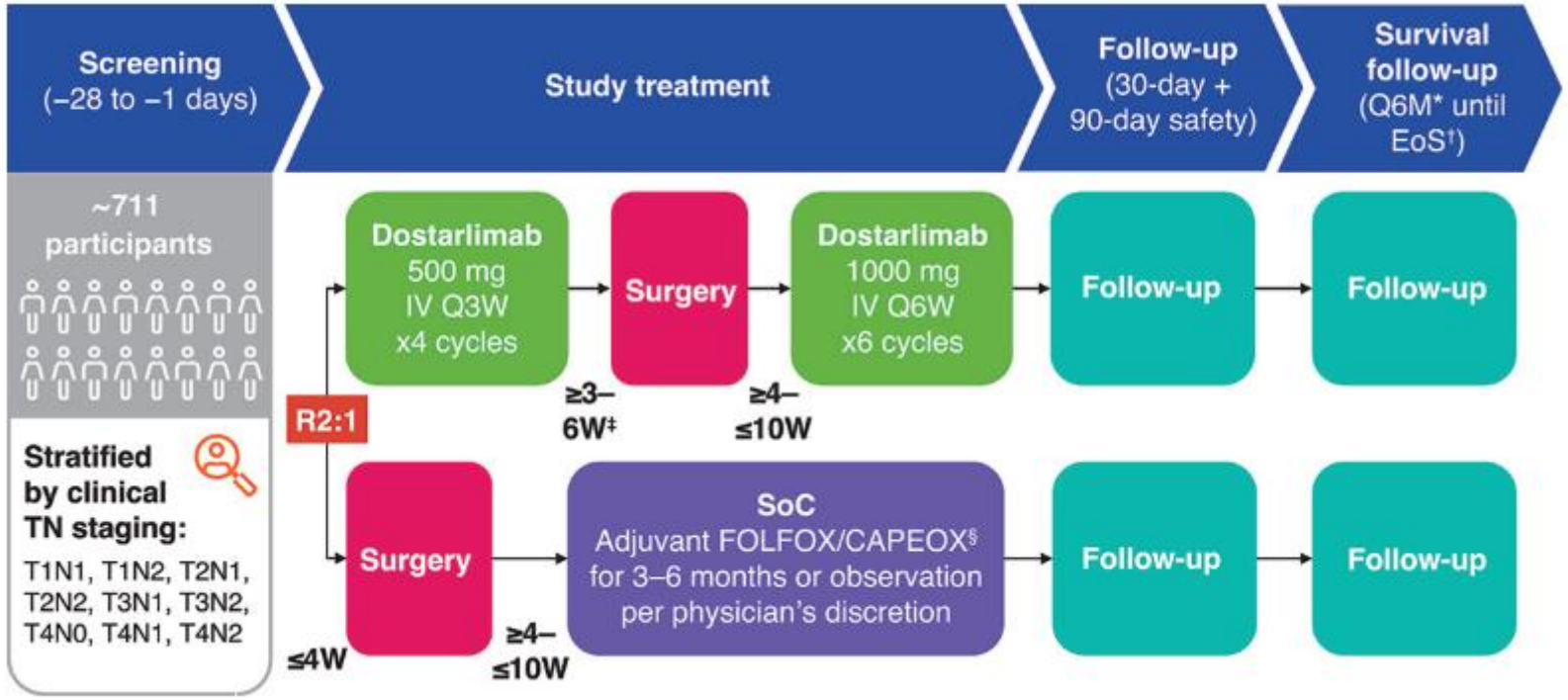
- Neoadjuvant anti PD-1 + anti-LAG-3
- N=59
- 92% major path response (<10% residual viable tumor)
- 68% pathologic complete response
- 80% had immune-related adverse events (irAEs)
- 10% Grade 3-4 irAEs

De Gooyer et al, Nat Med. 2024

Progress – Important caveats

- **No overall survival (OS) data have been reported** endpoint is 3-year DFS, not OS; with zero DFS events, OS is necessarily immature
- **Single-arm design limits causal inference.** NICHE-2 single-group study with selected cohort, low event rate, and well-recognized challenges with accurate radiographic staging—dMMR tumors frequently have enlarged regional nodes, creating risk of overstaging and overtreatment.
- **Confirmatory randomized data are pending.** The ongoing phase 3 AZUR-2 trial compares neoadjuvant dostarlimab followed by surgery plus adjuvant dostarlimab against upfront surgery and standard chemotherapy.

AZUR-2: A Phase III study of perioperative dostarlimab in patients with dMMR/MSI-H resectable colon cancer: AZUR-2 study design



- Only randomized trial comparing perioperative immunotherapy directly with standard surgery-first management
- Previously untreated T4N0 or Stage III dMMR/MSI-H resectable colon cancer
- n~711, randomized 2:1 to neoadjuvant therapy vs. upfront surgery and SOC

Starling et al, Future Oncology. 2026

To treat or not to treat?

- **Declined** neoadjuvant immunotherapy after consulting with multiple oncologists
- **Robotic assisted right hemicolectomy** April 2028
- **pT2N0M0 Stage I** moderately differentiated colon adenocarcinoma (0/29 LN+, no lymphovascular or perineural invasion)
- **Ascending Colon Adenocarcinoma (Stage I)** - following Signatera q3 months and imaging Q6.
- ***MSH6* associated Lynch syndrome** - Started ASA 81mg for primary prevention of a second primary CRC based on data from the CAPP3 study (PI3KCA negative)

FINAL RESULTS SUMMARY

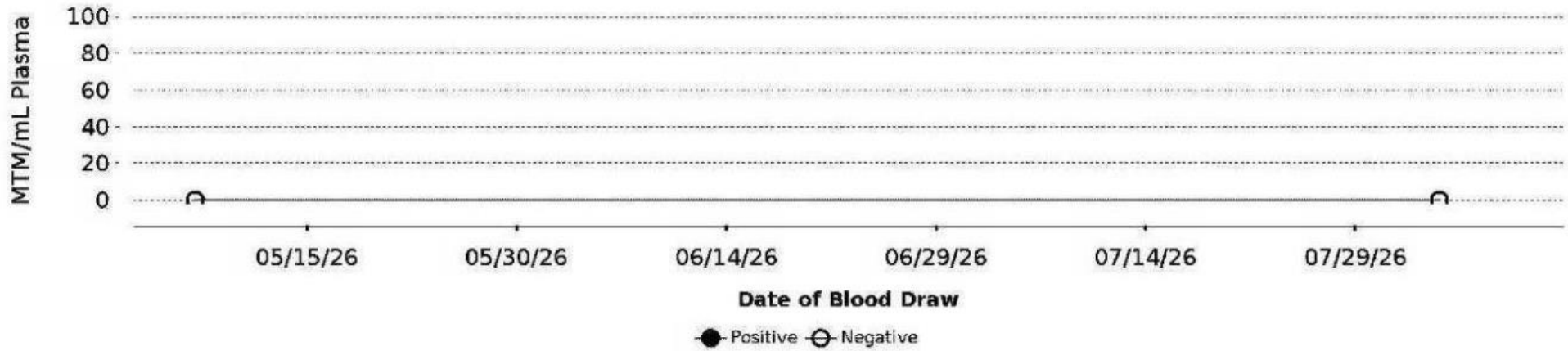
Signatera Negative

⊖

MTM/mL: Not Detected

Mean tumor molecules per mL is calculated based on the mean of ctDNA molecules detected per mL of the patient's plasma. ***See Limitations section below.***

Historical Results



Date	Reported MTM/mL
Aug 04, 2026	0.00
May 07, 2026	0.00

Progress – Pancreatic Cancer

- 61 yo male with metastatic pancreatic ductal adenocarcinoma
- Abdominal pain November 2024
- CT 4 cm x 3 cm mass in neck/body involving splenic vessels, suspicious 1.3 cm liver lesion
- Biopsy March 2025 confirmed moderately differentiated adenoca with liver met

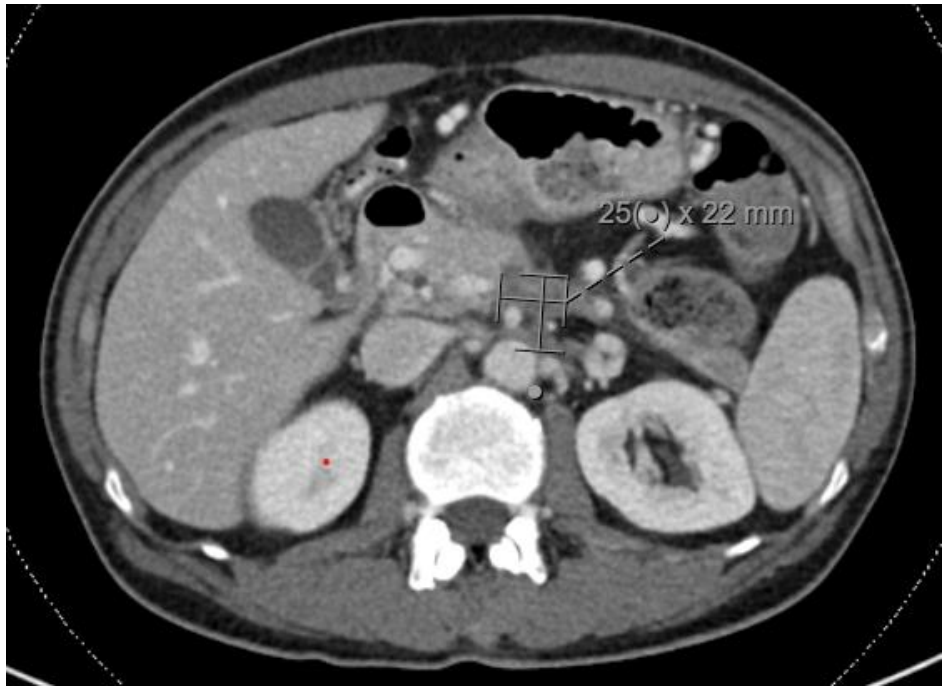
Pancreatic Cancer – Rx History

- 1st line Rx with NALIRIFOX started April 2025, d/c'd due to progression
- 2nd line gemcitabine plus nab-paclitaxel July 2025, CA19-9 reduced from >11,000 to nadir of 126 U/ml
- Nab-paclitaxel d/c'd early 2026 due to neuropathy, cont. gemcitabine maintaining stable disease
- Molecular profiling: **KRAS G12V**, SMAD4, TP53 & CDKN2A, low TMB, MSS
- Germline testing negative.
- June 2026: Recurrent disease 3.0 cm x 2.9 cm pancreatic body mass
- Daraxonrasib initiated for Palliative Rx on IRB Expanded Access 8/17/2026, cTX, cNX, cM1

Pancreatic Cancer – Response to Daraxonrasib



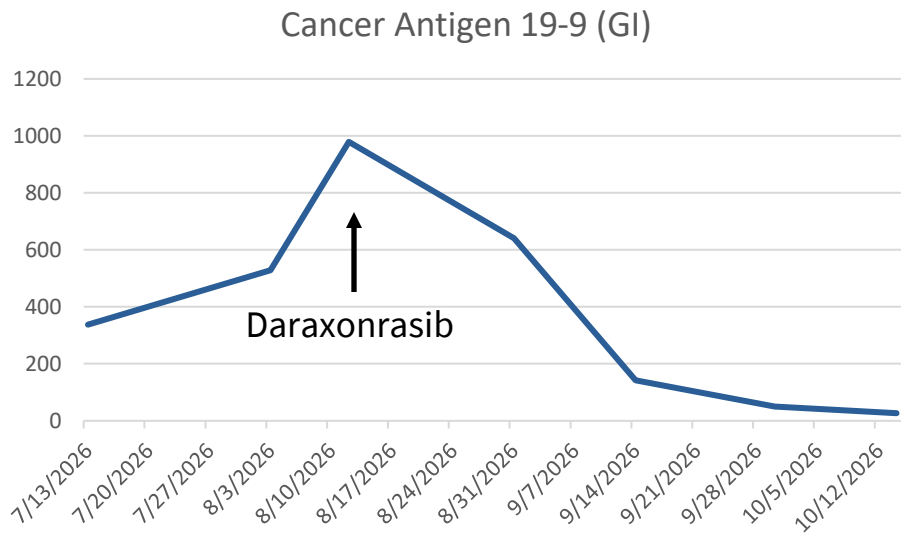
7/24/2026 3.8 x 2.6 cm



10/7/2026 2.5 x 2.2 cm

Pancreatic Cancer – Response

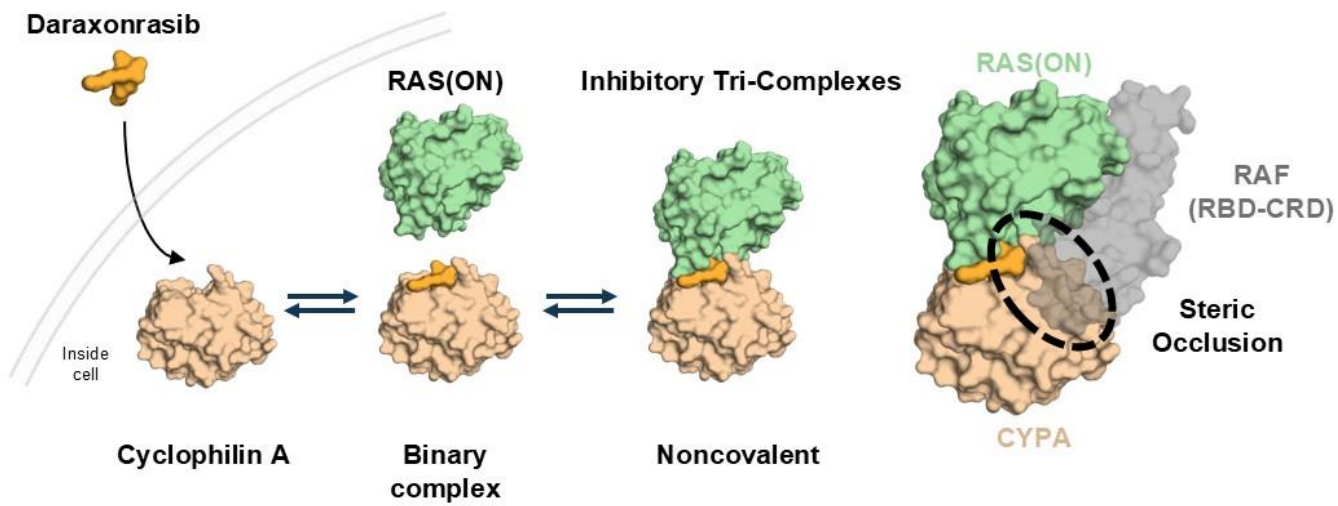
- Decrease in size of hypoenhancing adenocarcinoma pancreatic body in Oct 2026
- Mass now (10/26) 2.5 x 2.2 cm, previously 3.3 x 2.4 cm on 7/24/2026
- Pre-existing 7mm hypodense nodule in segment 6 of liver not seen
- Decrease in size of hypodense nodule in superior segment 2 of liver.
- 6mm ill-defined hypodense nodule in segment 2/3 is stable
- No new sites of metastases



Daraxonrasib Mechanism of Action

Daraxonrasib is an oral RAS(ON) multi-selective inhibitor

- Daraxonrasib is an oral, potent, RAS(ON), multi-selective, tri-complex inhibitor of GTP-bound mutant RAS (including variants with G12, G13, and Q61 mutations) and wild-type RAS[1-4]
- In a prior Phase 1/2 trial, daraxonrasib showed clinical activity with a manageable safety profile in patients with previously treated advanced PDAC[5]



Daraxonrasib binds to intracellular cyclophilin A to form a binary complex that engages RAS(ON) and suppresses downstream signaling[1-4]

CRD, cysteine rich domain; GTP, guanosine triphosphate; PDAC, pancreatic adenocarcinoma; RBD, RAS-binding domain.

1. Holderfield M, et al. Nature. 2024;629:919-26; 2. Cregg J, et al. J Med Chem. 2025;68:6064-83; 3. Lokhandwala J, et al. Front Oncol. 2024;14:1394702; 4. Jiang J, et al. Cancer Discov. 2024;14:994-1017; 5. Wolpin B, et al. N Engl J Med. 2026;394:1790-1802.

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Study Design

Key eligibility criteria:

- Adults with mPDAC
- One prior fluoropyrimidine- or gemcitabine-based regimen in the metastatic setting
- ECOG PS 0-1
- Documented tumor RAS mutational status[a] by local testing

R 1:1

Daraxonrasib
300 mg, PO QD

Investigator's choice chemotherapy (1 of 4)
GnP, mFOLFIRINOX, Nal-IRI + 5-FU/LV, FOLFOX

Dual primary endpoints

- OS and PFS[b] (RAS G12 population)

Key secondary endpoints

- OS and PFS[b] (overall population[c])
- ORR[b] (RAS G12 and overall populations)
- TTD in PROs[d] (RAS G12 and overall populations)

Stratification factors

- ECOG PS (0 vs 1)
- Metastatic disease at diagnosis (yes vs no)
- Liver metastases at baseline (yes vs no)
- Tumor RAS mutational status (RAS G12D/V vs other RAS G12 vs RAS G13 or Q61 mutation or no RAS mutation identified)

Global enrollment: 59 sites across 6 countries

NCT06625320.

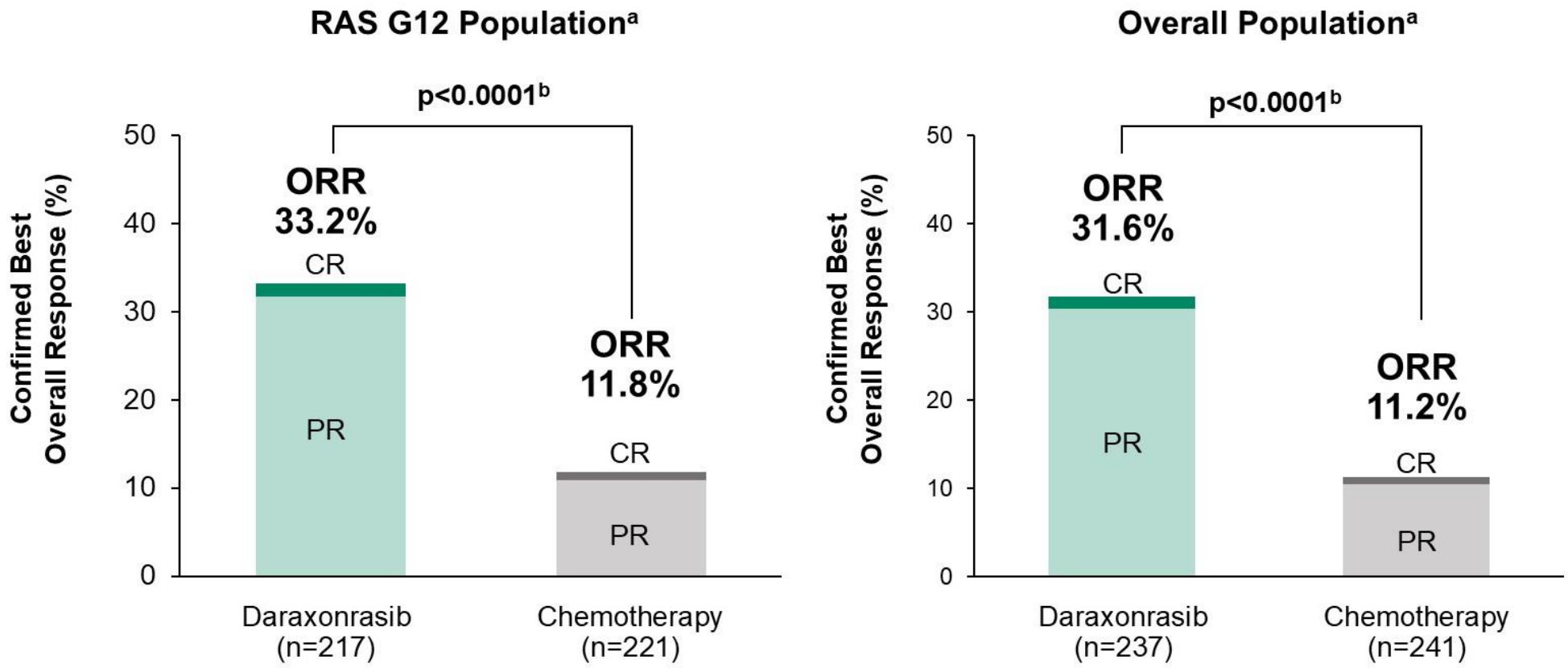
5-FU, 5-fluorouracil; BICR, blinded independent central review; ECOG Eastern Cooperative Oncology Group; FOLFOX, leucovorin, 5-FU, and oxaliplatin; GnP, gemcitabine and nab-paclitaxel; LV, leucovorin; mFOLFIRINOX, modified 5-FU, irinotecan, leucovorin, and oxaliplatin; mPDAC, metastatic pancreatic adenocarcinoma; Nal-IRI, nanoliposomal irinotecan; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral administration; PRO, patient-reported outcome; PS, performance status; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TTD, time to deterioration.

[a]Either mutant, defined as nonsynonymous mutations in KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61), or no RAS mutation identified. [b]By BICR per RECIST 1.1. [c]Including patients whose tumors harbor RAS G12, G13, or Q61 mutations, or had no RAS mutation identified. [d]TTD in symptom of pain and in global health status/quality of life.

PRESENTED BY: Brian M. Wolpin, MD, MPH

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Confirmed Objective Response Rate by BICR



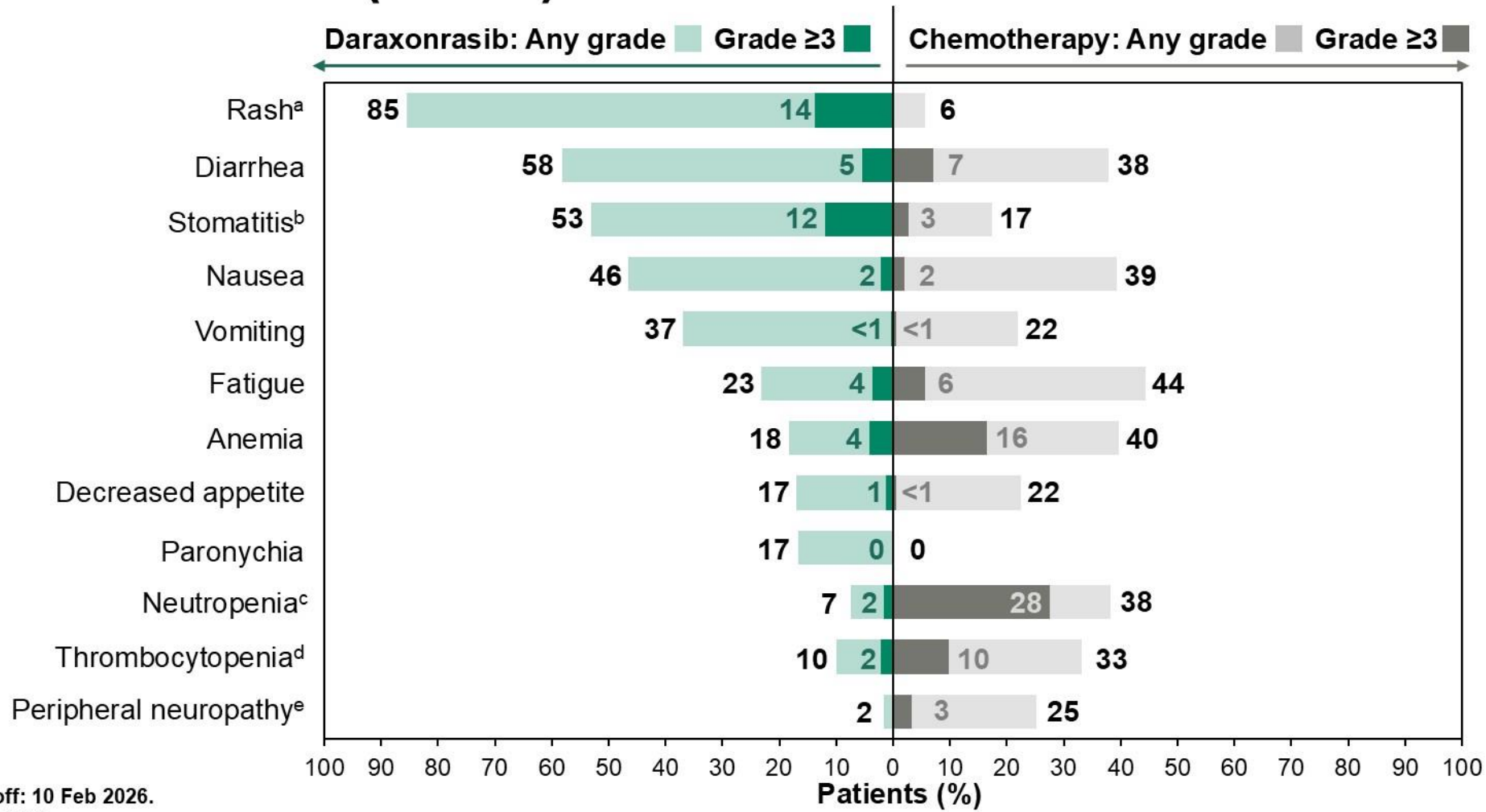
Data cutoff: 10 Feb 2026.

BICR, blinded independent central review; CR, complete response; ORR, objective response rate; PR, partial response.

[a]Only patients with measurable disease at baseline per BICR were included in the ORR analysis. [b]P-values were calculated using stratified Cochran-Mantel-Haenszel chi-square test.

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Most Common (>15%) Treatment-Related Adverse Events



Data cutoff: 10 Feb 2026.

PT, preferred term.

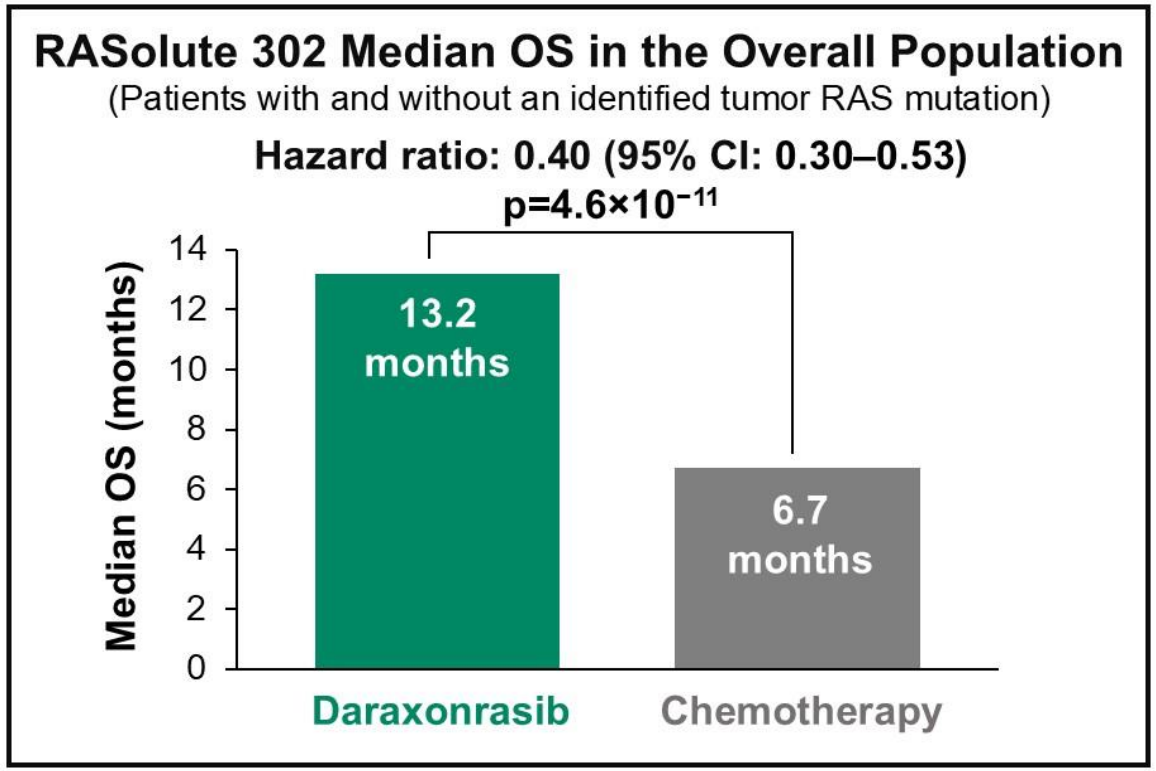
[a]Includes PTs of acne, butterfly rash, dermatitis, dermatitis acneiform, eczema, hand dermatitis, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and skin ulcer. [b]Includes PTs of aphthous ulcer, mucosal inflammation, mucosal ulceration, and stomatitis. [c]Includes PTs of febrile neutropenia, leukopenia, neutropenia, neutrophil count decreased, and white blood cell count decreased. [d]Includes PTs of platelet count decreased and thrombocytopenia. [e]Includes PTs of neuralgia, neuropathy peripheral, peripheral motor neuropathy, peripheral sensory neuropathy, and polyneuropathy.

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Conclusions

Daraxonrasib (300 mg PO QD):

- Demonstrated statistically significant and clinically meaningful improvements in OS, PFS, and ORR vs standard cytotoxic chemotherapy
- Showed a consistent treatment effect in patients with and without an identified tumor RAS mutation
- Exhibited a manageable safety profile with no unexpected safety findings[1,2]
- Significantly delayed time to deterioration for the symptom of pain and global health status/quality of life



ORR, objective response rate; OS, overall survival; PDAC, pancreatic adenocarcinoma; PFS, progression-free survival; PO, oral administration; QD, once daily.

1. Garrido-Laguna I, et al. J Clin Oncol. 2025;43:722; 2. Wolpin B, et al. N Engl J Med. 2026;394:1790-1802.

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ORIGINAL ARTICLE

Daraxonrasib in Previously Treated Advanced *RAS*-Mutated Pancreatic Cancer

Brian M. Wolpin, M.D., M.P.H.,[1] Wungki Park, M.D.,[2] Ignacio Garrido-Laguna, M.D., Ph.D.,[3] Alexander Spira, M.D., Ph.D.,[4] Alexander Starodub, M.D., Ph.D.,[5]* David Sommerhalder, M.D.,[6] Salman R. Punekar, M.D.,[7] Minal Barve, M.D.,[8] Meredith Pelster, M.D.,[9] Benjamin Herzberg, M.D.,[10] Nilofer S. Azad, M.D.,[11] Joel Randolph Hecht, M.D.,[12] Sai Hong Ignatius Ou, M.D., Ph.D.,[13] Tong Lin, Ph.D.,[14] Sumit Kar, Ph.D.,[14] Lin Tao, M.S.,[14] Rashmi Vora, M.B., B.S.,[14] Aparna Hegde, M.D.,[14] Kyaw Aung, M.B., B.S., Ph.D.,[15] and David S. Hong, M.D.,[16] for the RMC-6236-001 Investigators†

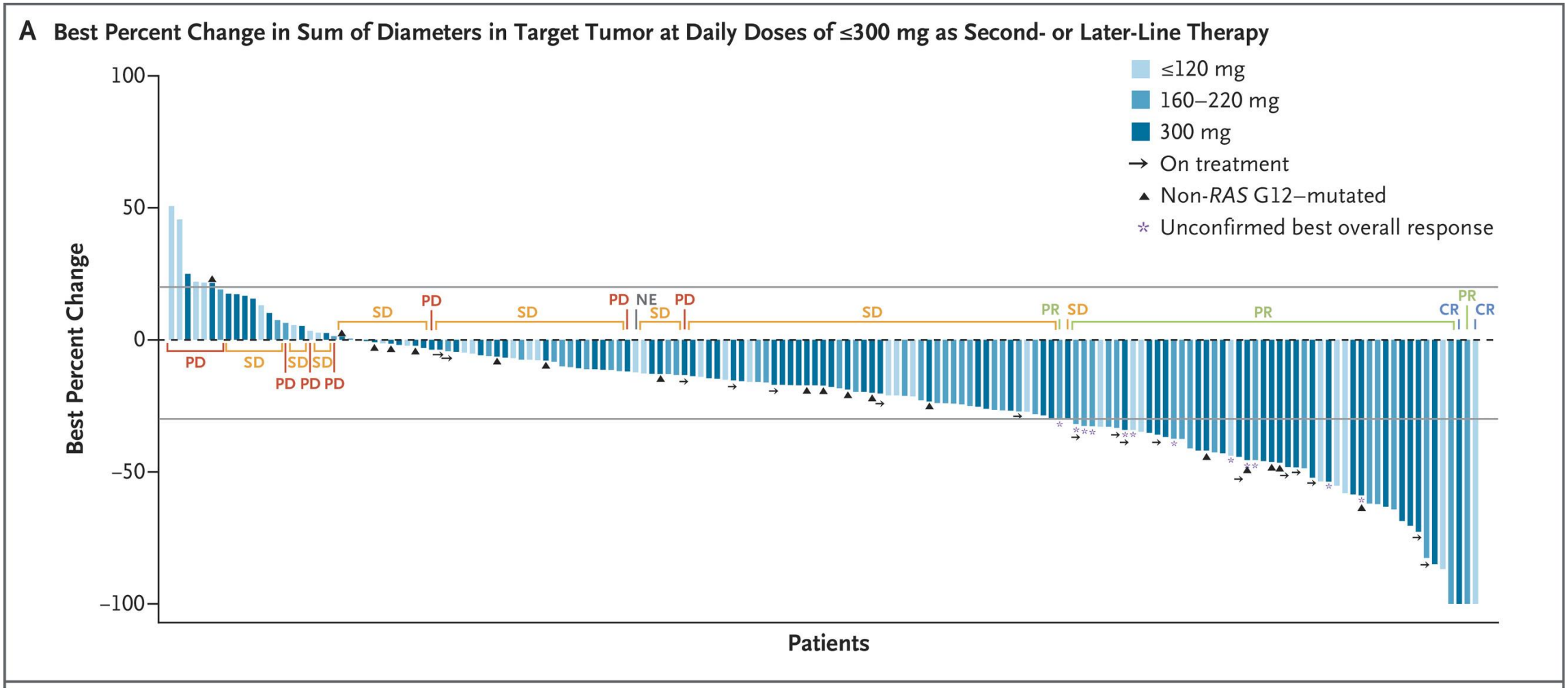
BACKGROUND

Current therapies for patients with pancreatic ductal adenocarcinoma (PDAC) provide modest benefit. Activating *RAS* mutations occur in more than 90% of PDAC tumors. Daraxonrasib (RMC-6236) is an oral RAS(ON) multiselective inhibitor that targets guanosine triphosphate–bound mutant and wild-type RAS.

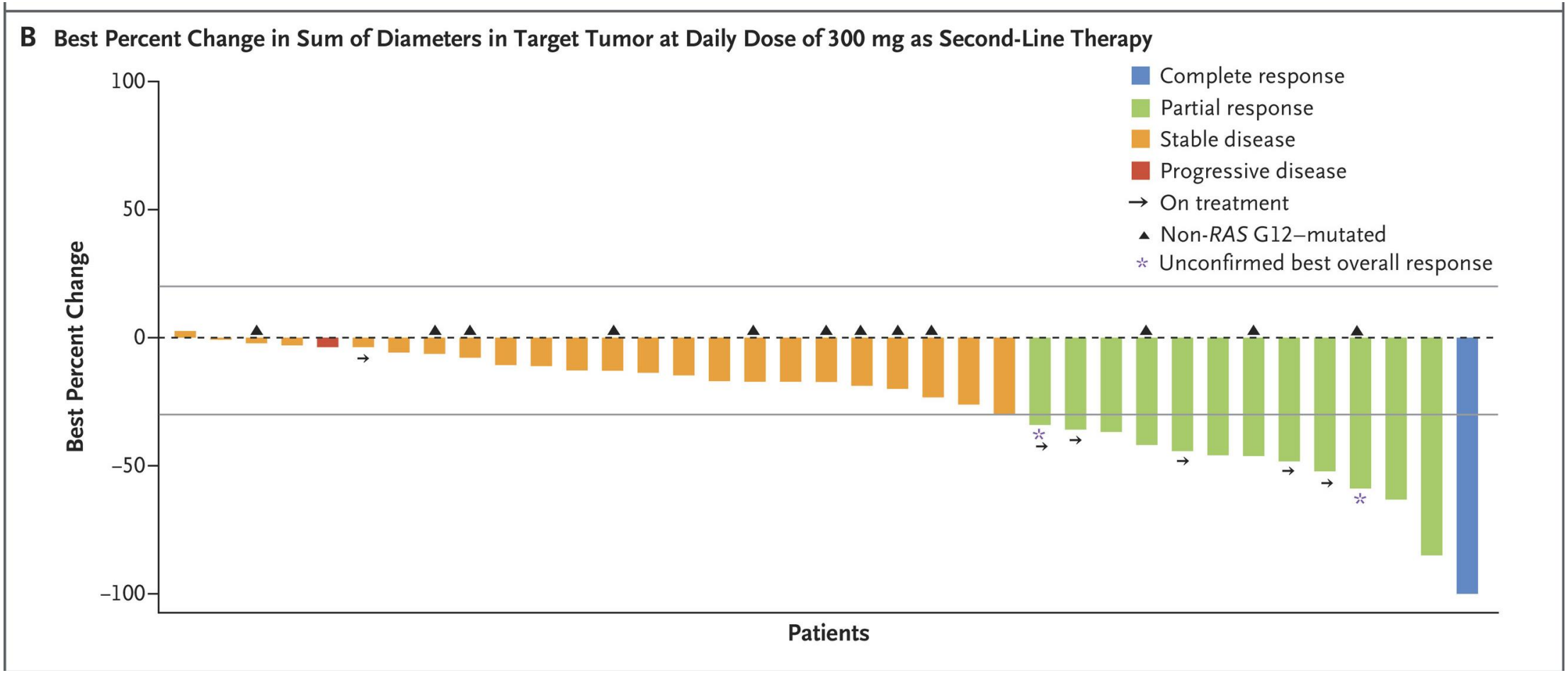
CONCLUSIONS

Daraxonrasib was associated with treatment-related adverse events of grade 3 or higher in one third of patients with previously treated *RAS*-mutated PDAC; antitumor activity was also reported. (Funded by Revolution Medicines; RMC-6236-001 ClinicalTrials.gov number, NCT05379985.)

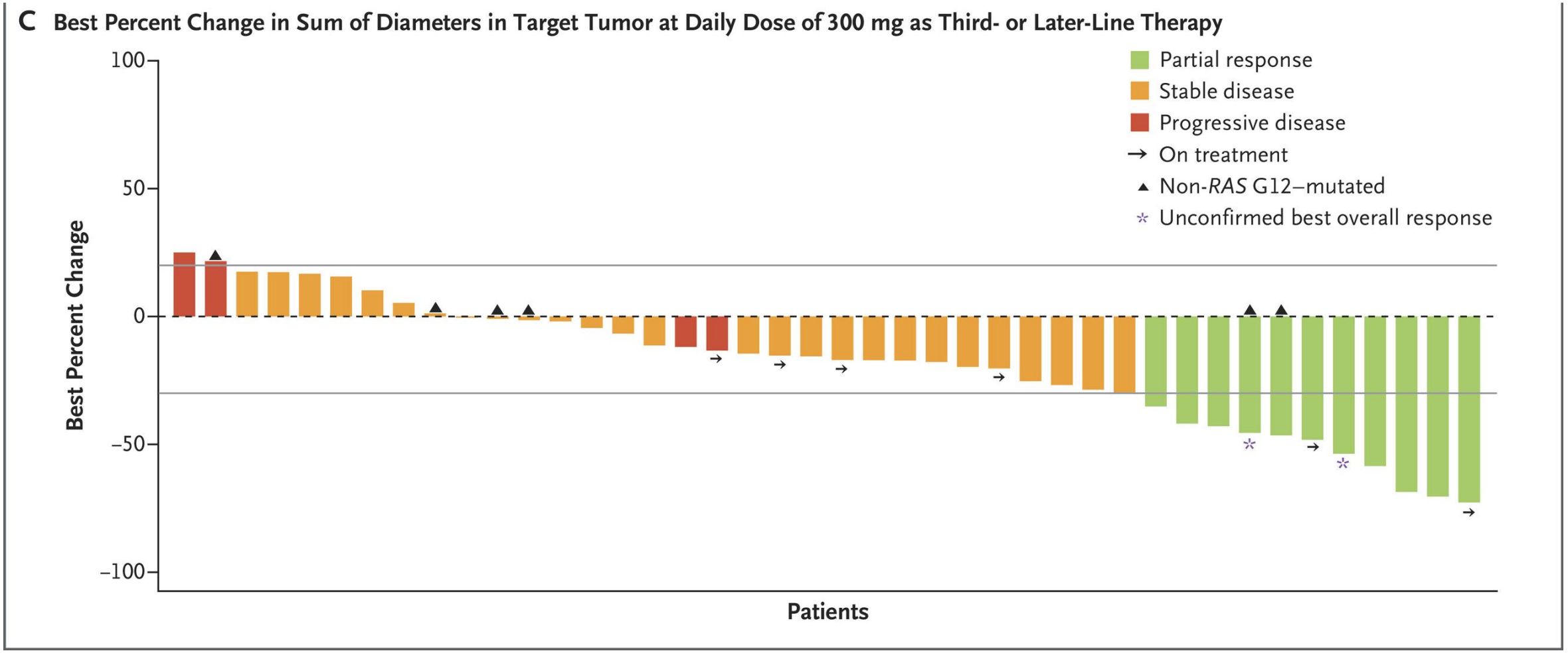
Wolpin BM et al, N Engl J Med. 2026



Wolpin BM et al, N Engl J Med. 2026



Wolpin BM et al, N Engl J Med. 2026



Wolpin BM et al, N Engl J Med. 2026

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Daraxonrasib or Chemotherapy in Previously Treated Metastatic Pancreatic Cancer

E.M. O'Reilly,[1] Z.A. Wainberg,[2] A.E. Hendifar,[3] M.J. Borad,[4] F. Pietrantonio,[5] S. Pant,[6] P. Hammel,[7] C. Cremolini,[8] G.A. Manji,[9] P.E. Oberstein,[10] I. Garrido-Laguna,[11] C. Springfeld,[12] N.S. Azad,[13] M. Ueno,[14] S.Y. Chui,[15] Y. Zhang,[15] H. Patel,[15] Y. Lee,[15] Z. Salman,[15] and B.M. Wolpin,[16] for the RASolute 302 Trial Investigators*

CONCLUSIONS

Among patients with previously treated mPDAC, treatment with daraxonrasib led to significantly longer overall survival and progression-free survival than chemotherapy. (Funded by Revolution Medicines; RASolute 302 ClinicalTrials.gov number, NCT06625320.)

- "Once-daily treatment with oral daraxonrasib resulted in significantly longer overall survival and progression-free survival than standard cytotoxi chemotherapy among patients with previously treated mPDAC, more than 90% of whom had RAS G12 mutations."
- "The results of this trial support daraxonrasib as a clinically meaningful advance in the treatment of patients with previously treated mPDAC."

O'Reilly EM et al, N Engl J Med. 2026

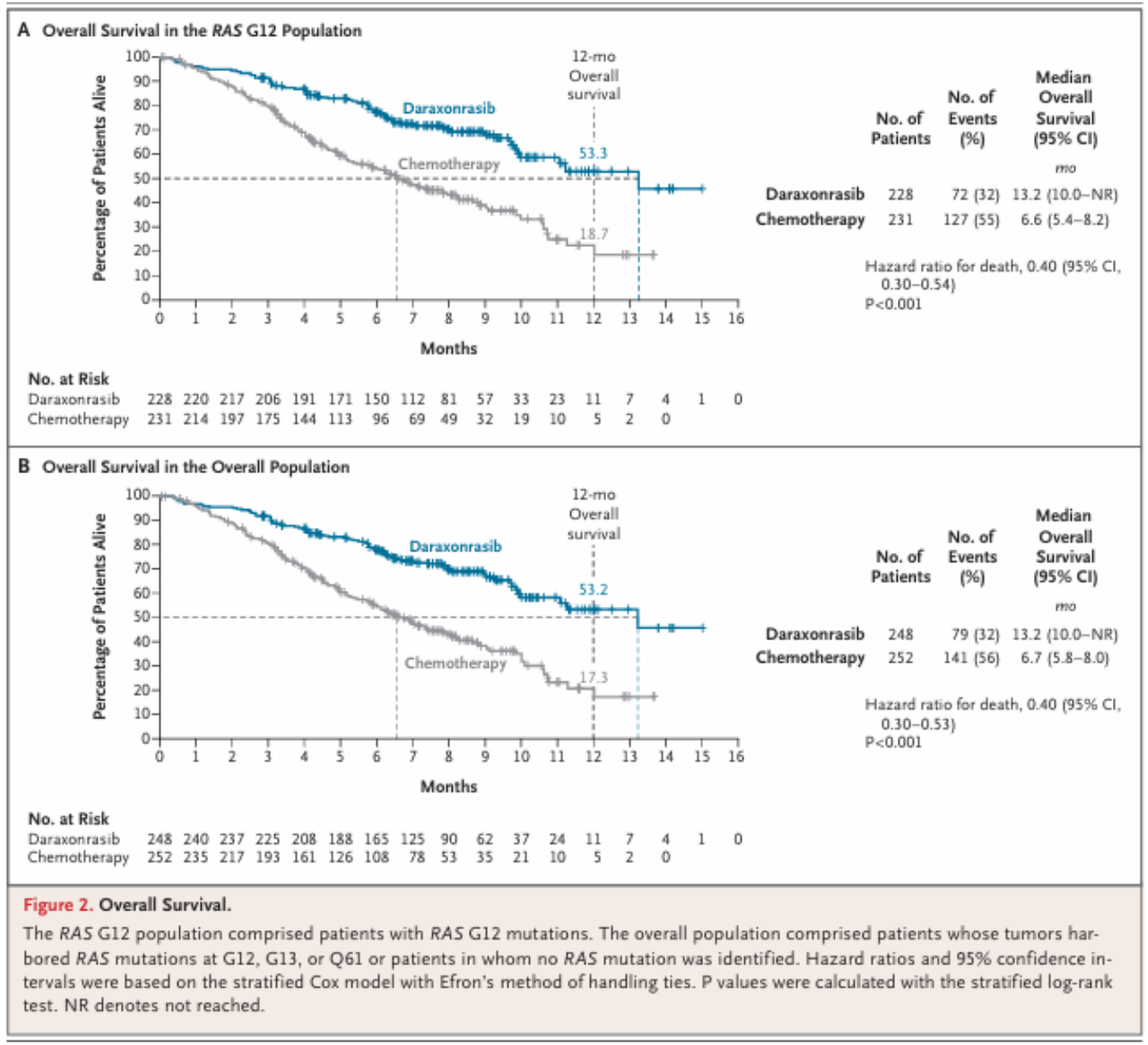


Figure 2. Overall Survival.

The *RAS* G12 population comprised patients with *RAS* G12 mutations. The overall population comprised patients whose tumors harbored *RAS* mutations at G12, G13, or Q61 or patients in whom no *RAS* mutation was identified. Hazard ratios and 95% confidence intervals were based on the stratified Cox model with Efron's method of handling ties. P values were calculated with the stratified log-rank test. NR denotes not reached.

O'Reilly EM et al, N Engl J Med. 2026

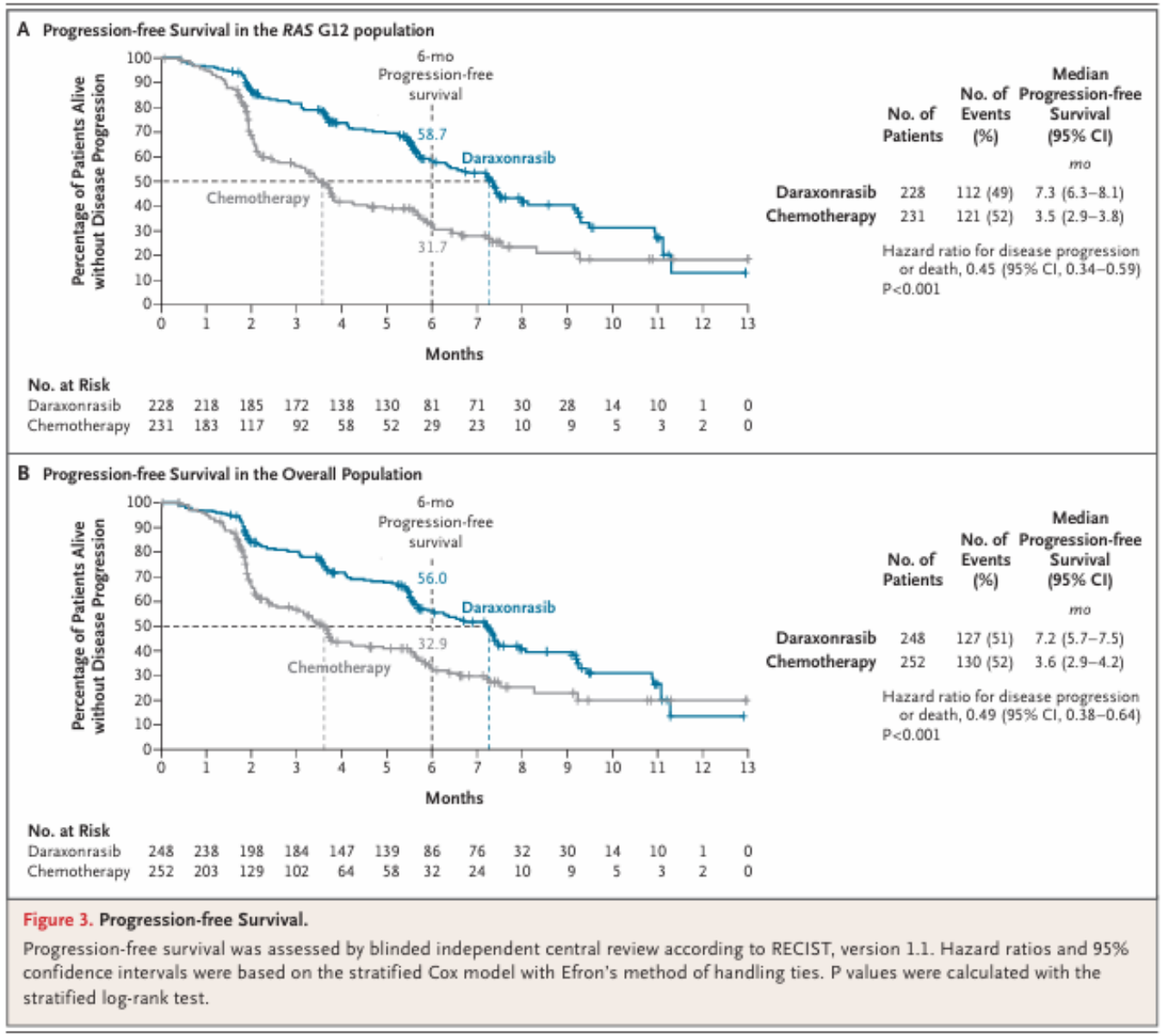


Figure 3. Progression-free Survival.

Progression-free survival was assessed by blinded independent central review according to RECIST, version 1.1. Hazard ratios and 95% confidence intervals were based on the stratified Cox model with Efron's method of handling ties. P values were calculated with the stratified log-rank test.

O'Reilly EM et al, N Engl J Med. 2026

Promise – Cancer Interception with Vaccine

- 42 y.o. healthy male with Lynch Syndrome due to *MSH2*
- Family history of early-onset CRC in father dx'd age 37
- Lynch surveillance with perfect adherence
- Interested in clinical trials for prevention
- Consents to Nous-209 Phase 1b/2 clinical trial
- Off-the-shelf viral vector cancer immunotherapy vaccine to intercept cancer in LS

nature medicine

Article

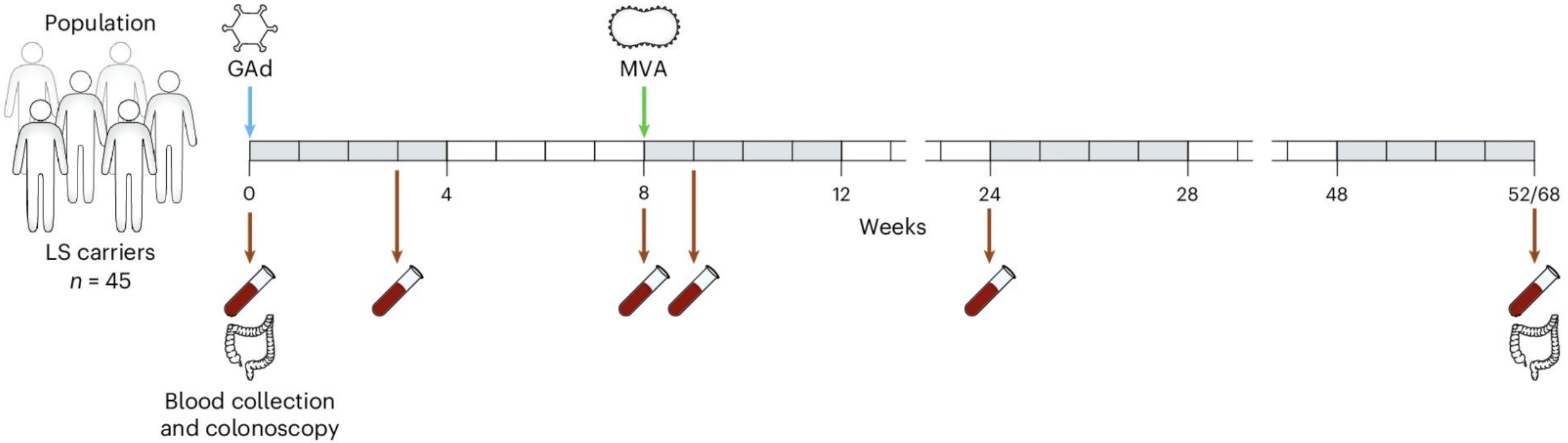
https://doi.org/10.1038/s41591-025-04182-9

Nous-209 neoantigen vaccine for cancer prevention in Lynch syndrome carriers: a phase 1b/2 trial

Anna Morena D'Alise[1,12], Jason Willis[2,12], Fahriye Duzagac[3], Michael J. Hall[4], Marcia Cruz-Correa[5], Gregory E. Idos[6], Selvi Thirumurthi[7], Veroushka Ballester[5], Guido Leoni[1], Irene Garzia[1], Laura Antonucci[1], Lorenzo De Marco[1], Elisa Micarelli[1], Nan Deng[3], Laura Secli[1], Sven Gogov[8], Wenli Dong[9], J. Jack Lee[9], Charles M. Bowen[3], Lana A. Vornik[3], Araceli Garcia-Gonzalez[3], Laura Reyes-Uribe[3], Ellen Richmond[10], Asad Umar[10], Powel H. Brown[3], Krishna M. Sinha[3], Luz Maria Rodriguez[10,11], Elisa Scarselli[1] ✉ & Eduardo Vilar[3] ✉

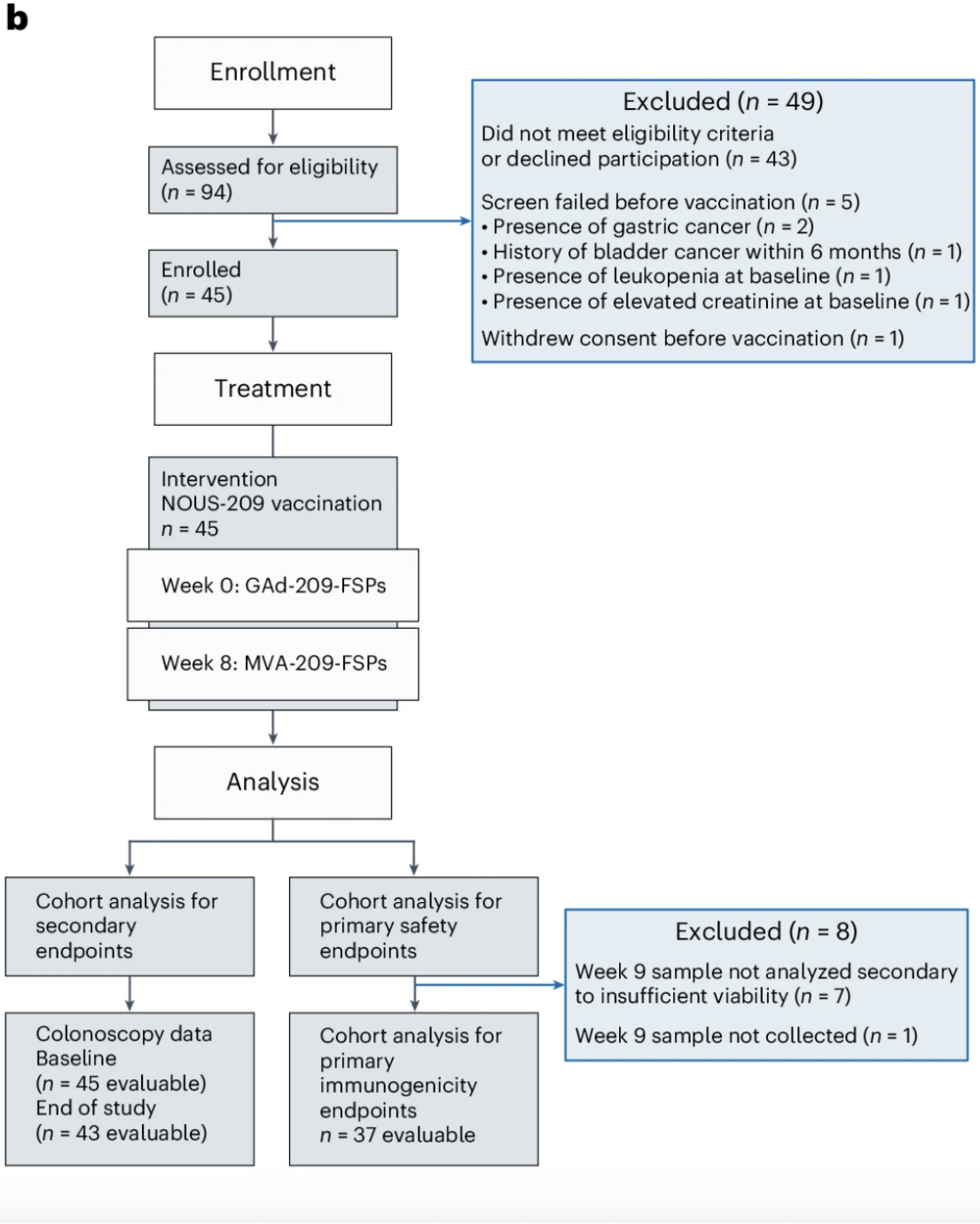
- Prime–boost viral vector vaccine approach encoding 209 shared frameshift-derived neoantigens identified from MSI tumors

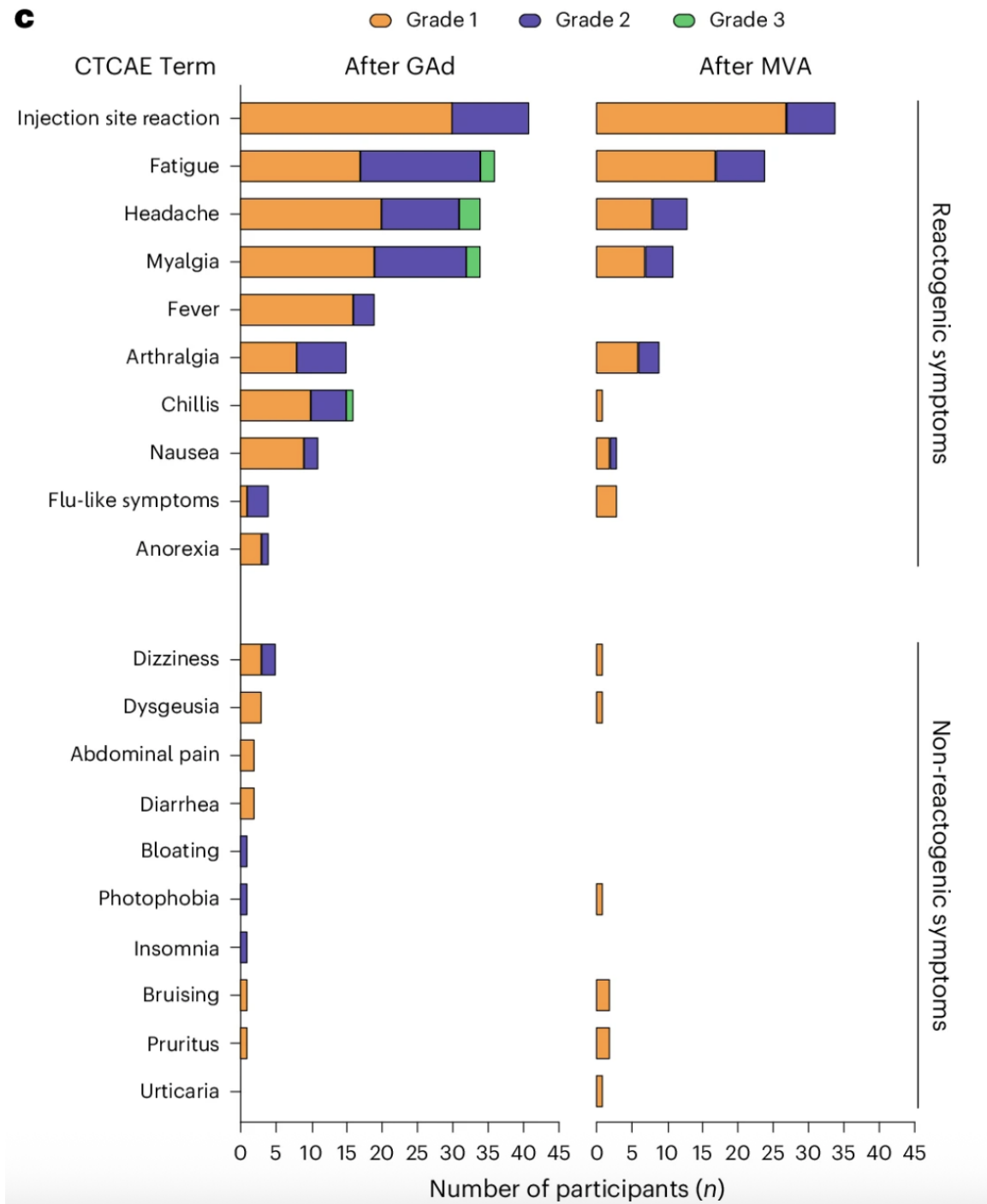
D'Alise AM et al. Nat Med. 2026

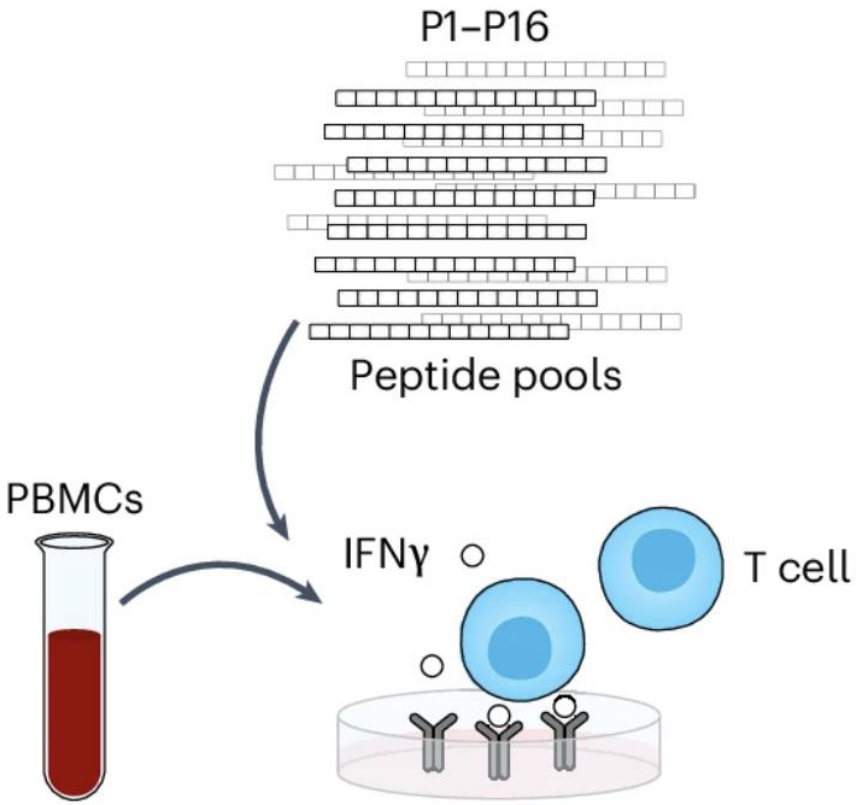


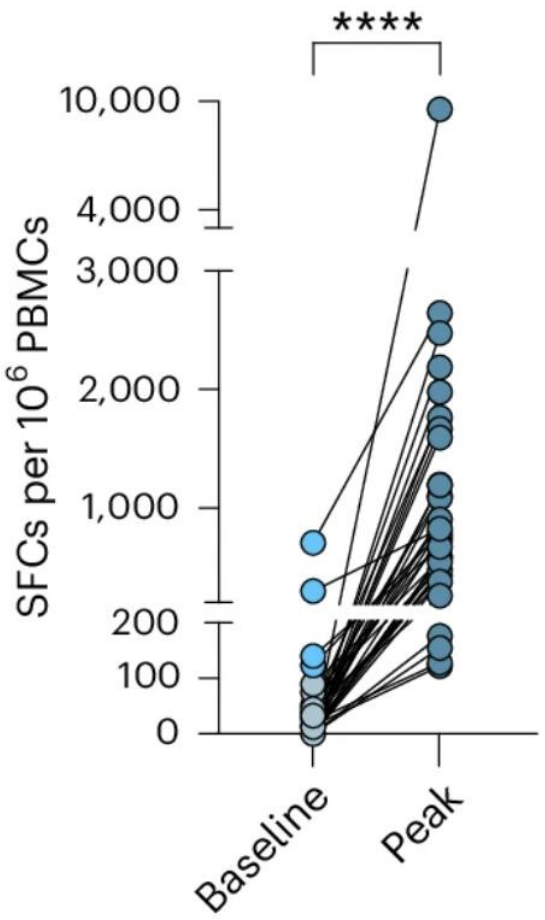
- Participants received a prime–boost regimen using two distinct viral vectors encoding the same cargo of 209 shared frameshift neoantigens

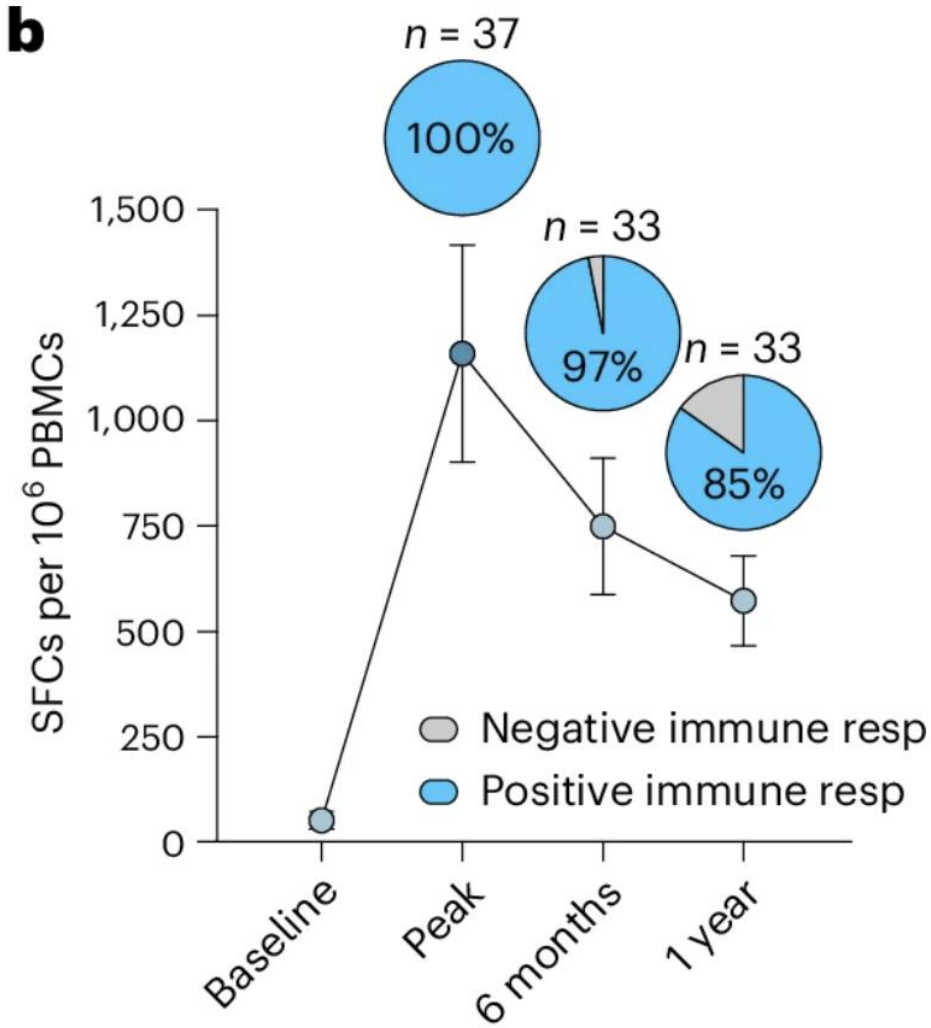
D'Alise AM et al. Nat Med. 2026


b
Enrollment
Assessed for eligibility (n = 94)
Enrolled (n = 45)
Treatment
Intervention NOUS-209 vaccination n = 45
Week 0: GAd-209-FSPs
Week 8: MVA-209-FSPs
Analysis
Cohort analysis for secondary endpoints
Cohort analysis for primary safety endpoints
Colonoscopy data Baseline (n = 45 evaluable) End of study (n = 43 evaluable)
Cohort analysis for primary immunogenicity endpoints n = 37 evaluable
Excluded (n = 49)
Did not meet eligibility criteria or declined participation (n = 43)
Screen failed before vaccination (n = 5)
• Presence of gastric cancer (n = 2)
• History of bladder cancer within 6 months (n = 1)
• Presence of leukopenia at baseline (n = 1)
• Presence of elevated creatinine at baseline (n = 1)
Withdrew consent before vaccination (n = 1)
Excluded (n = 8)
Week 9 sample not analyzed secondary to insufficient viability (n = 7)
Week 9 sample not collected (n = 1)

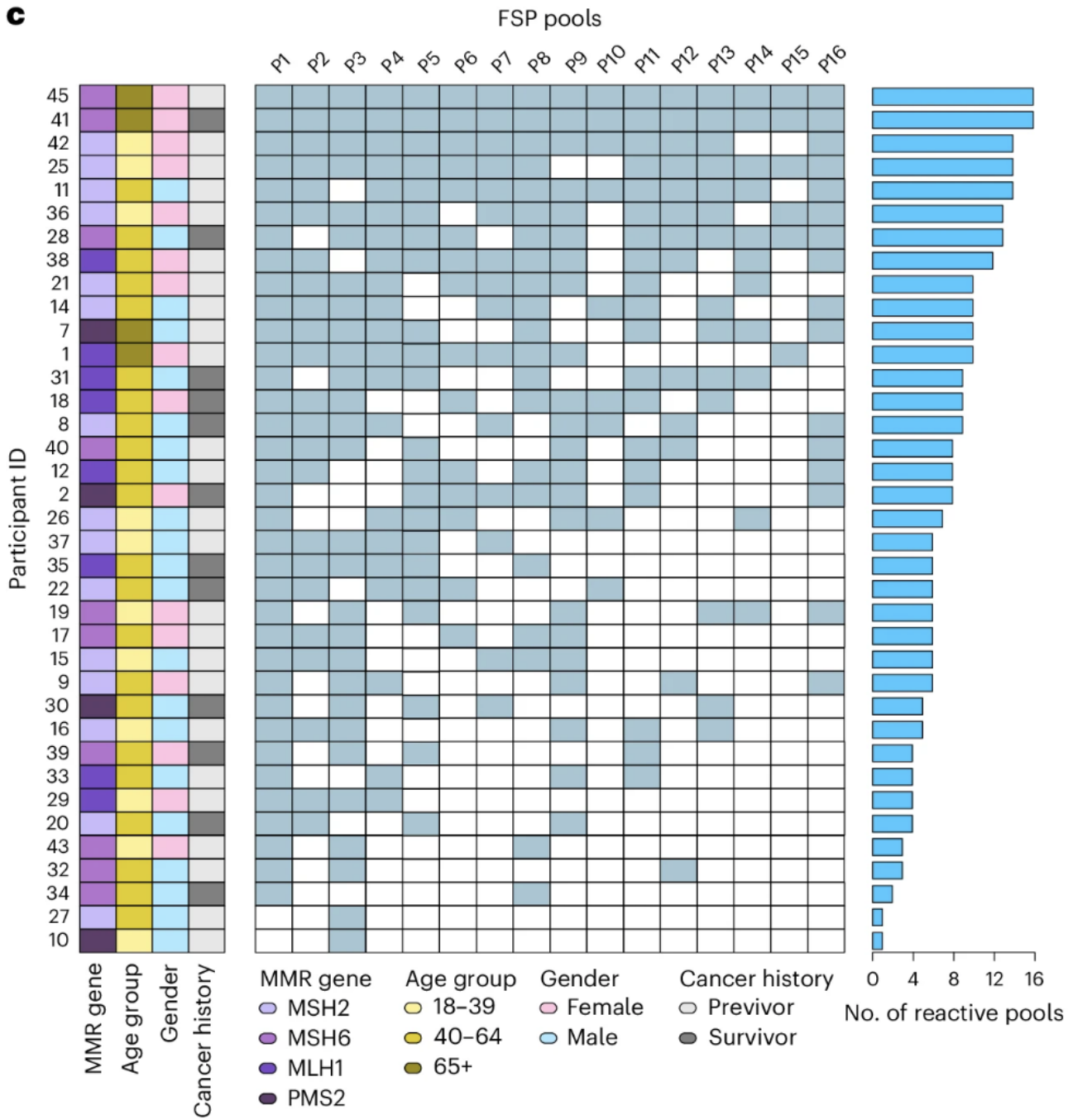

c
Grade 1
Grade 2
Grade 3
CTCAE Term
After GAd
After MVA
Injection site reaction
Fatigue
Headache
Myalgia
Fever
Arthralgia
Chillis
Nausea
Flu-like symptoms
Anorexia
Dizziness
Dysgeusia
Abdominal pain
Diarrhea
Bloating
Photophobia
Insomnia
Bruising
Pruritus
Urticaria
Reactogenic symptoms
Non-reactogenic symptoms
0 5 10 15 20 25 30 35 40 45
0 5 10 15 20 25 30 35 40 45
Number of participants (n)

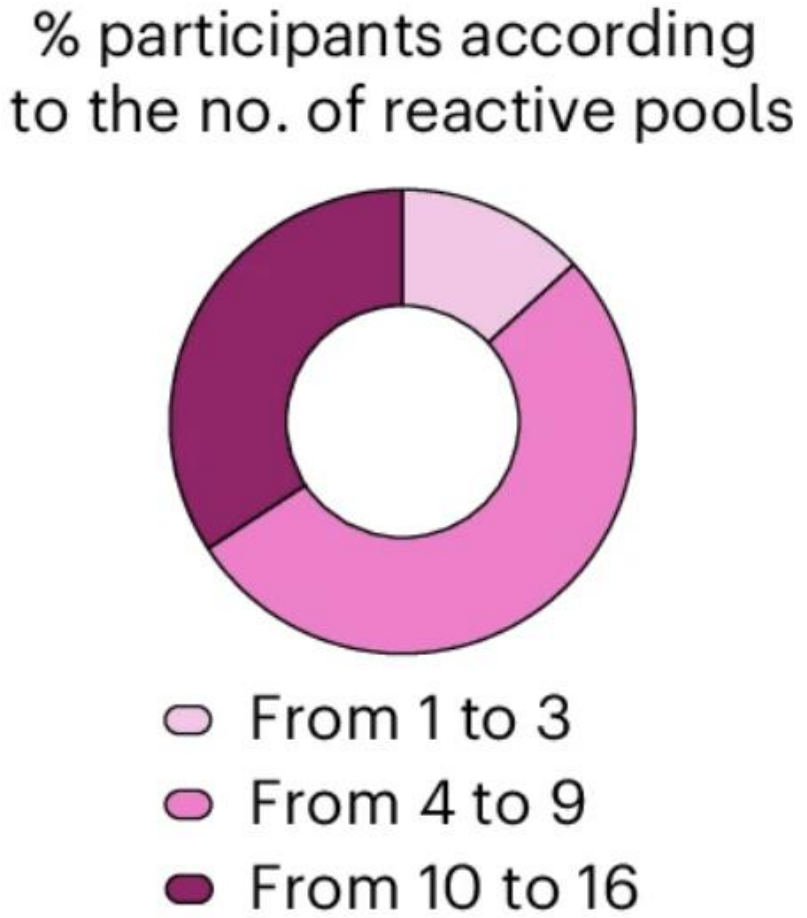




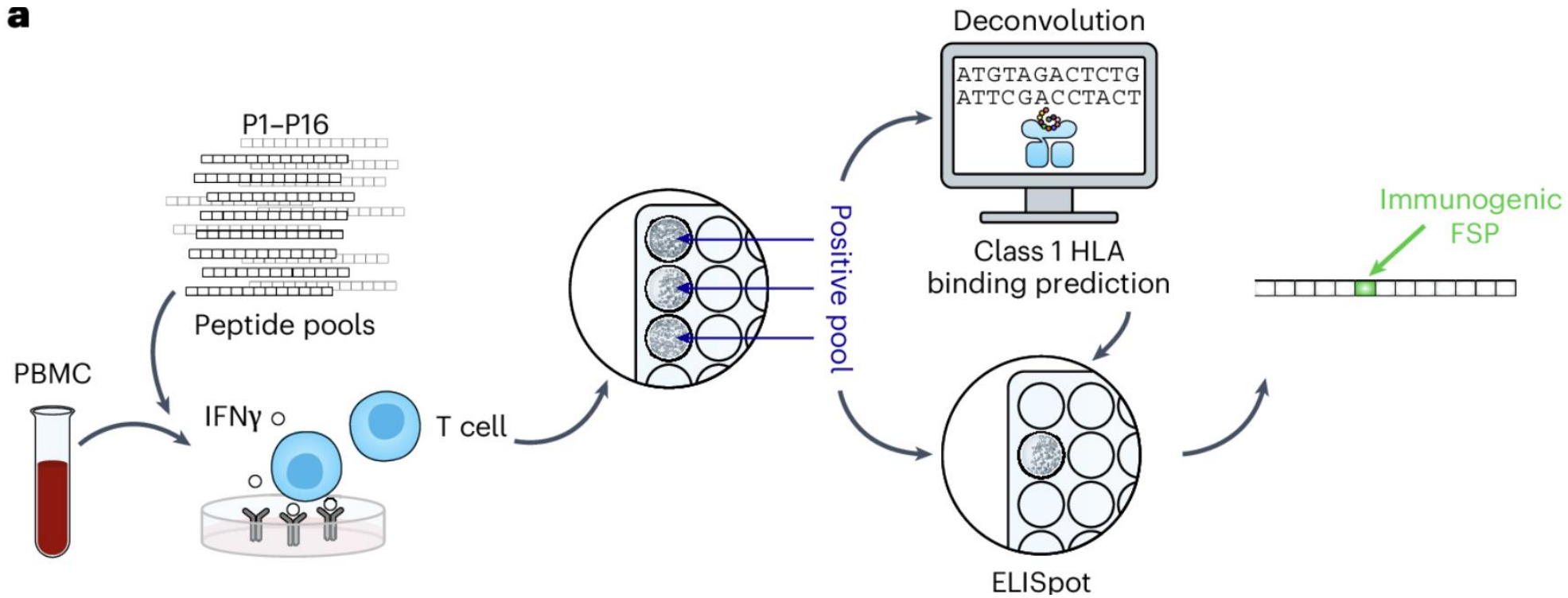


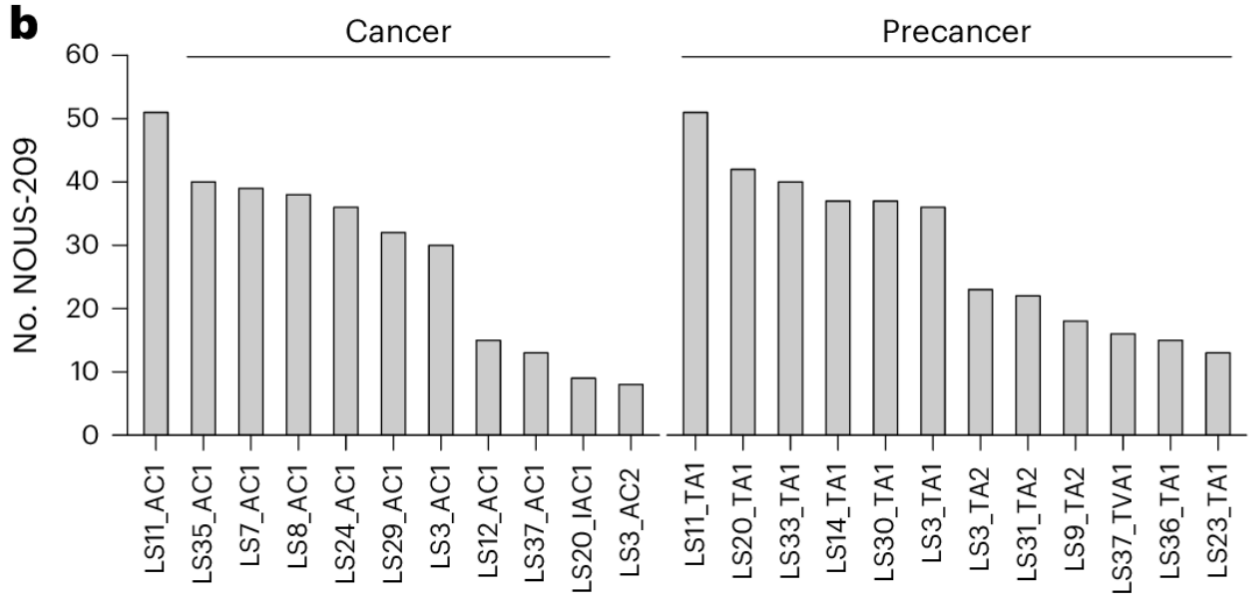
D'Alise AM et al. Nat Med. 2026

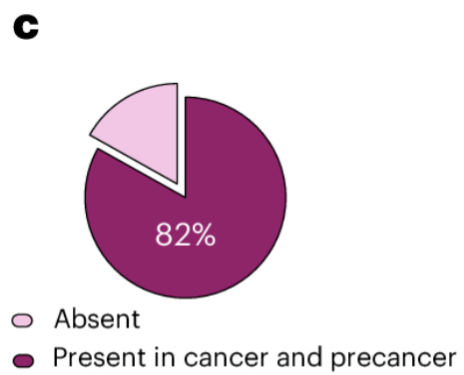




D'Alise AM et al. Nat Med. 2026







D'Alise AM et al. Nat Med. 2026

Promise – Cancer Interception with Vaccine

- MMR deficiency → **shared frameshift neoantigens (FSPs)**
- FSPs **arise early** and are **recurrently expressed**.
- Nous-209 induces:
  - **Broad, durable T-cell responses**
  - **$CD8^+$ and $CD4^+$ functional immunity**
  - Targeting of **disease-relevant epitopes**
- **Future Directions**
  - Larger **Phase II/III prevention trial - DEFIANT**
  - Long-term **clinical endpoints (adenoma/cancer incidence)**
  - Integration with **standard surveillance strategies**

Conclusions

- Precision medicine leveraging genetic testing and genomic profiling - changing the standard of care and outcomes for GI cancer.
- Immunotherapy in early stage colon cancer holds enormous potential, balancing risks with prognosis.
- Daraxonrasib is indicated for the treatment of adult patients with metastatic pancreatic adenocarcinoma who have received at least one prior systemic therapy or who are not candidates for multiagent systemic therapy.
- Vaccines hold promise to prevent cancer and cancer precursors in Lynch Syndrome taking advantage of shared frameshift peptides that function as neoantigens, inducing broad durable T-cell responses and functional immunity.

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