The changing landscape of pancreatic cancer therapy.

2026 Debates and Didactics

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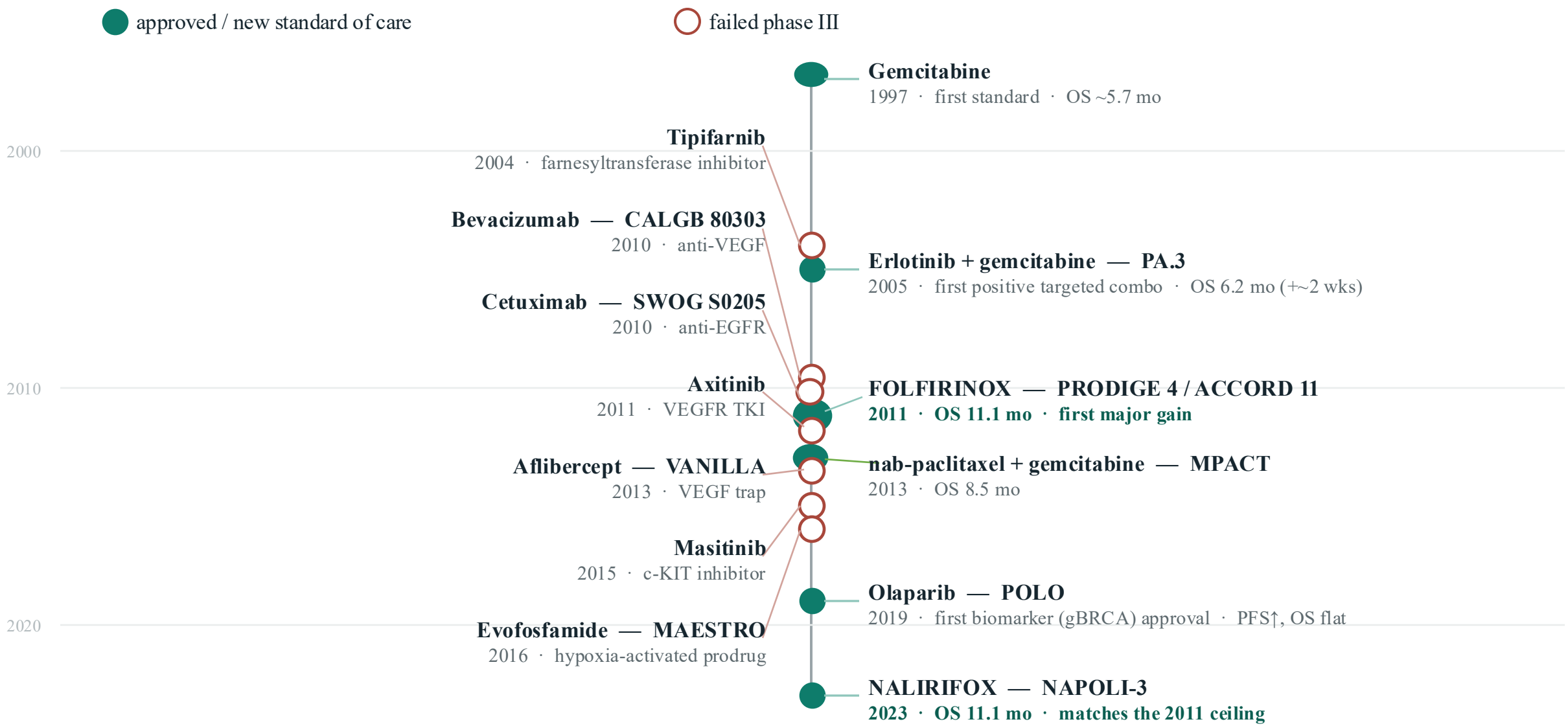
Disclosures and Disclaimers

Advisory role: Revolution Medicine, Natera, Jazz Pharma, Exilixis, AstraZeneca.
Research Support: NIH/NCI, Jazz Pharma, Alynam, Servier, AstraZeneca, Pfizer, Roche
No off- label uses of drugs will be presented.

Key Takeaway Points

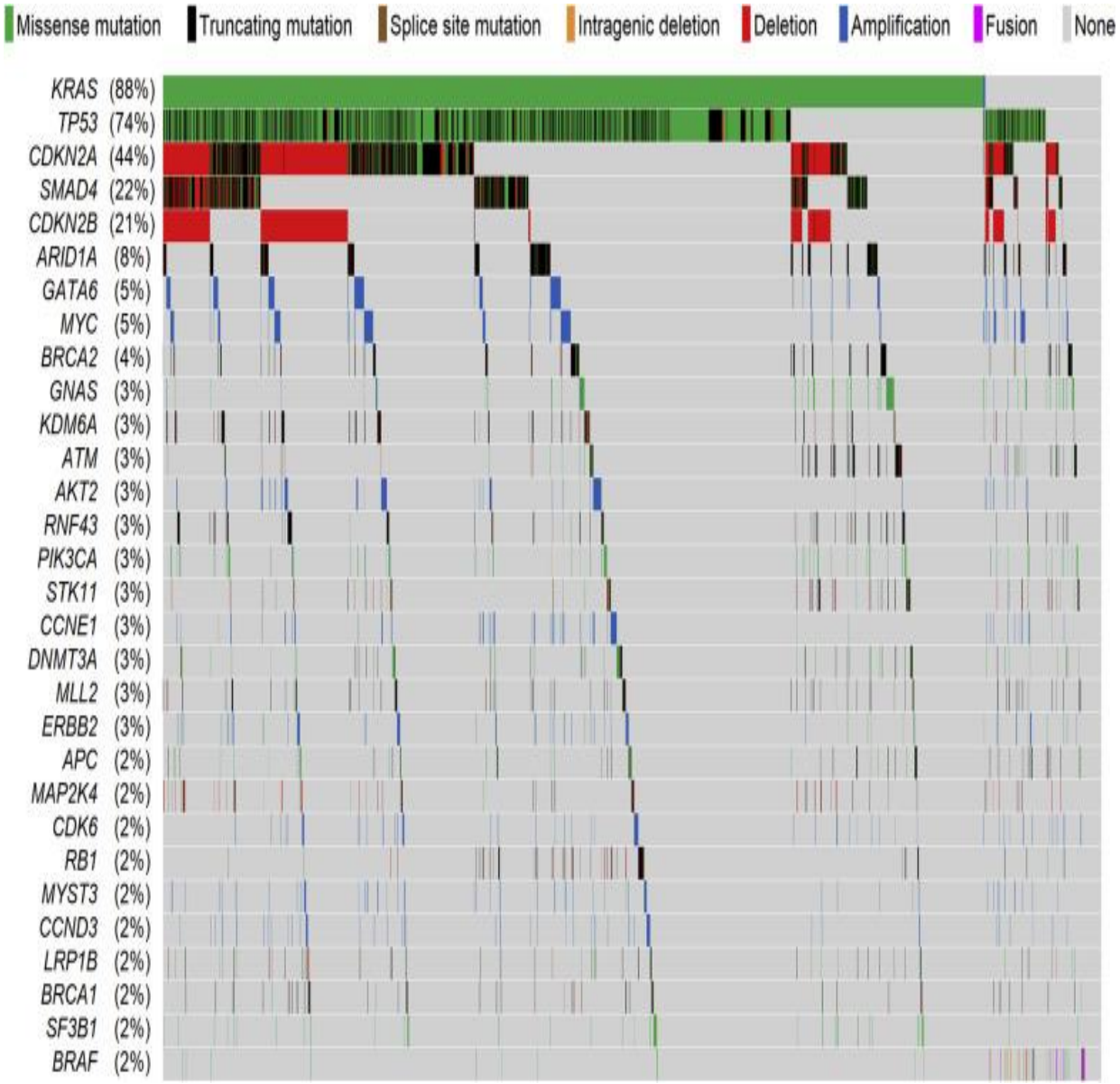
- **All patients** with pancreatic cancer should undergo comprehensive tumor genome testing. *NCCN, 03/2026.*
- Multiple RAS-targeting strategies, including mutant specific (G12C, G12D), pan-KRAS and multi-RAS ON inhibitors, have now shown clinical activity in pancreatic cancer.
- The next frontier is overcoming resistance through rational combination strategies.

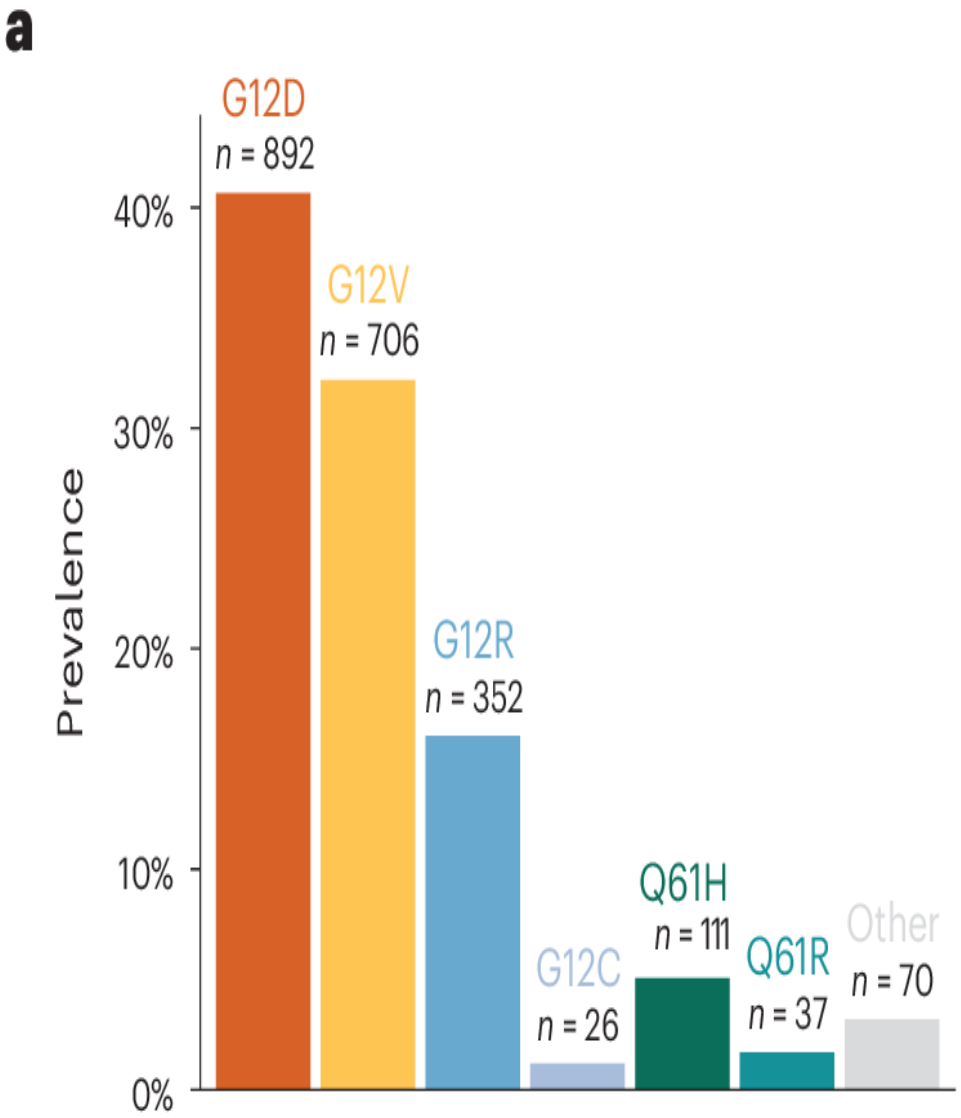
The Old Road: Ponderous Progress in PDAC Drug Development



Failures shown are landmark phase III trials (+ sorafenib, sunitinib, marimastat, ganitumab, trametinib and others). Wins: PA.3 (2007), PRODIGE 4/ACCORD 11 (2011), MPACT (2013), POLO (2019), NAPOLI-3 (2023).

The most common alterations in pancreatic cancer are ‘undruggable’



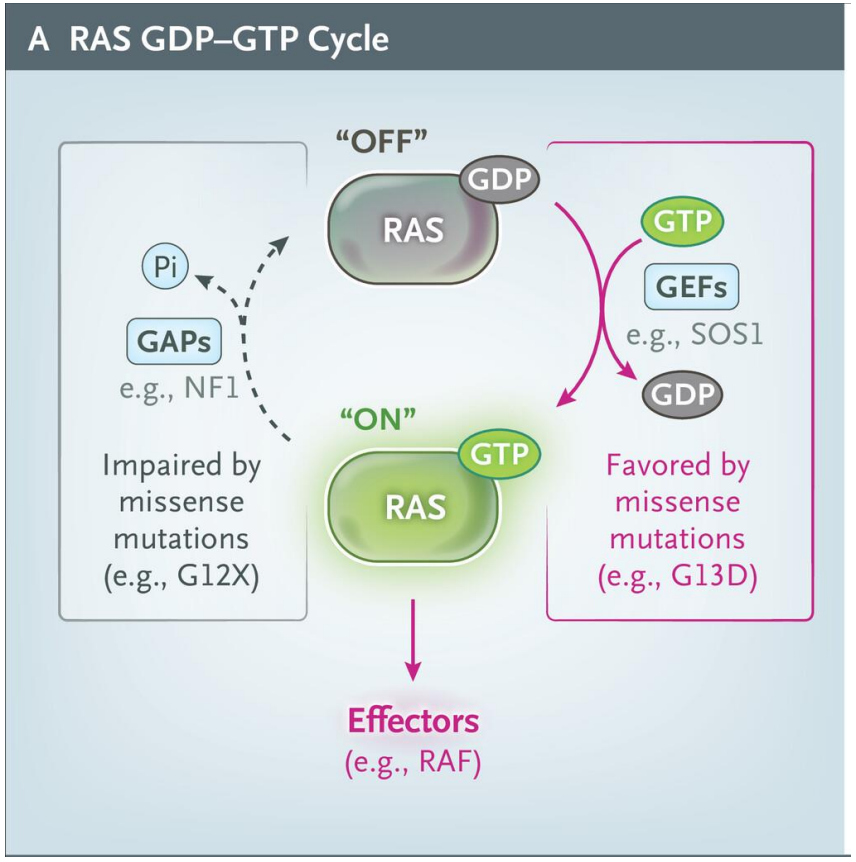


Singhi AD et al. Gastroenterology 2019;156:2242–2253.

Varghese AM et al. *Nature Medicine* **volume 31**, pages 466–477 (2025)

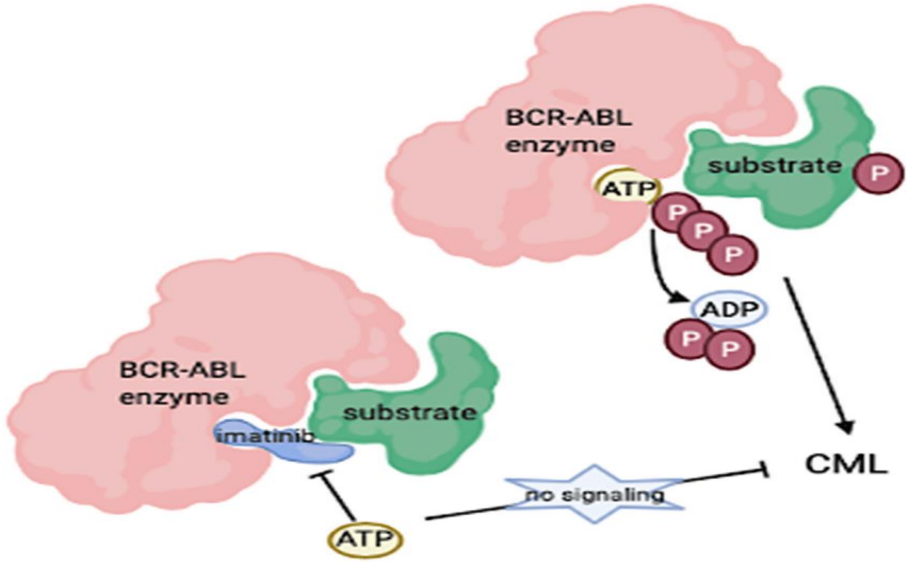
Ras Biology

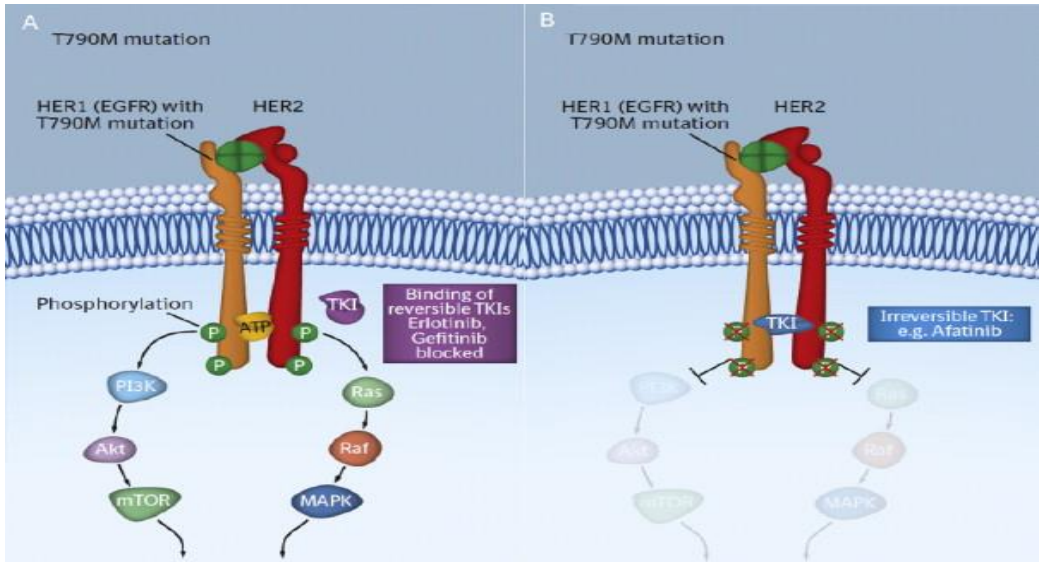
- Binary switch: Ras cycles between inactive GDP-bound and active GTP-bound states.
- Activation: GEFs (eg SOS) promote GDP→GTP exchange (On); GAPs + intrinsic GTPase trigger GTP→GDP hydrolysis (Off).
- Mutations: Oncogenic RAS impairs GAP binding and intrinsic GTPase activity, locking Ras in the active GTP (On) state
- This favors Ras-GTP accumulation and drives proliferation



Der CJ et al. N Engl J Med 2026;394:1857-1861

Targeting K-Ras in pancreatic cancer: in search of pockets

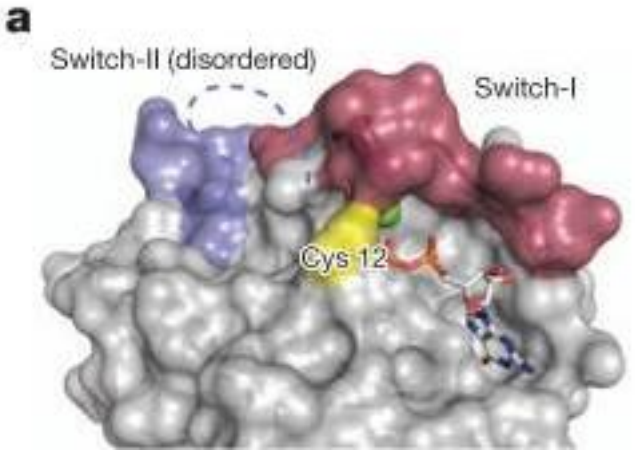


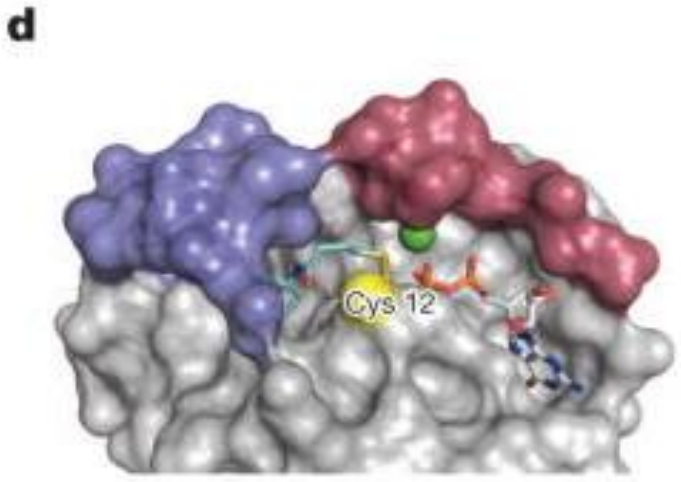


- GTP binding site is deep within the K-Ras protein
- This site is largely inaccessible to small molecule inhibitors
- K-Ras has significantly high affinity for GTP/GDP picomolar (10^{-12})
- Contrast to micromolar binding affinity for ATP with BCR/ABL or EGFR TK

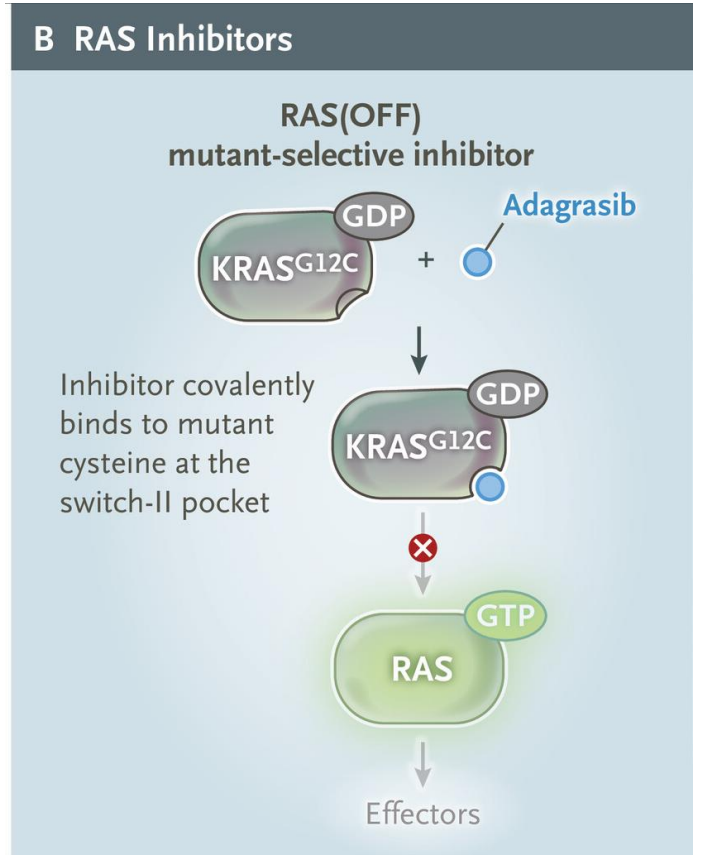
Karasu N et al. Med Oncol **38**, 120 (2021), Brugger W et al. Lung Cancer. 2012 Jul;77(1):2-

Targeting K-Ras in pancreatic cancer: engineering pockets





- K-Ras G12C mutation uncovers a switch pocket
- Small molecule sits in the pocket and distorts Kras-GDP (RAS-Off)
- This allows allosteric inhibition of Ras-GDP/GTP transition.
- Kras is is now druggable!

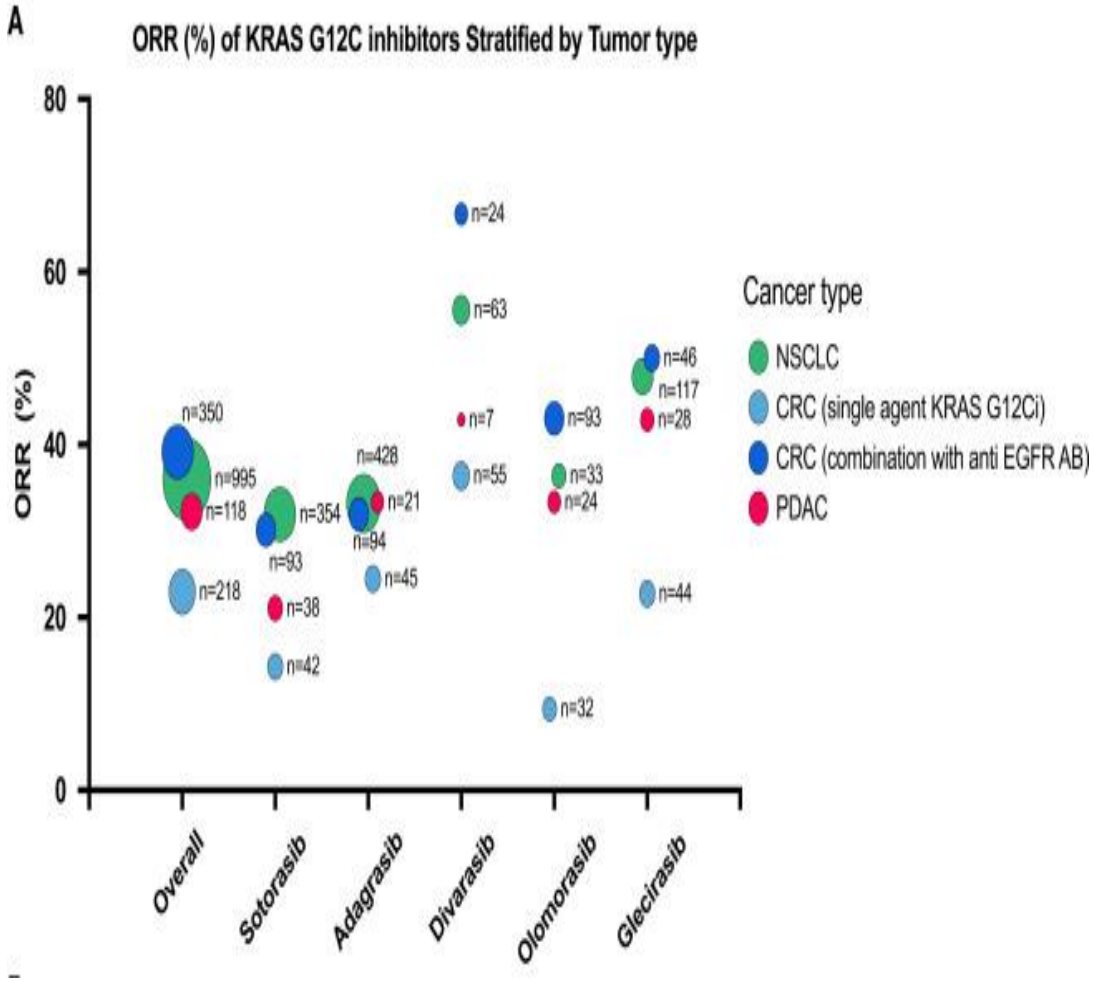


Ostrem J et al Nature 2013;503:548-551.

Der CJ et al. N Engl J Med 2026;394:1857-1861

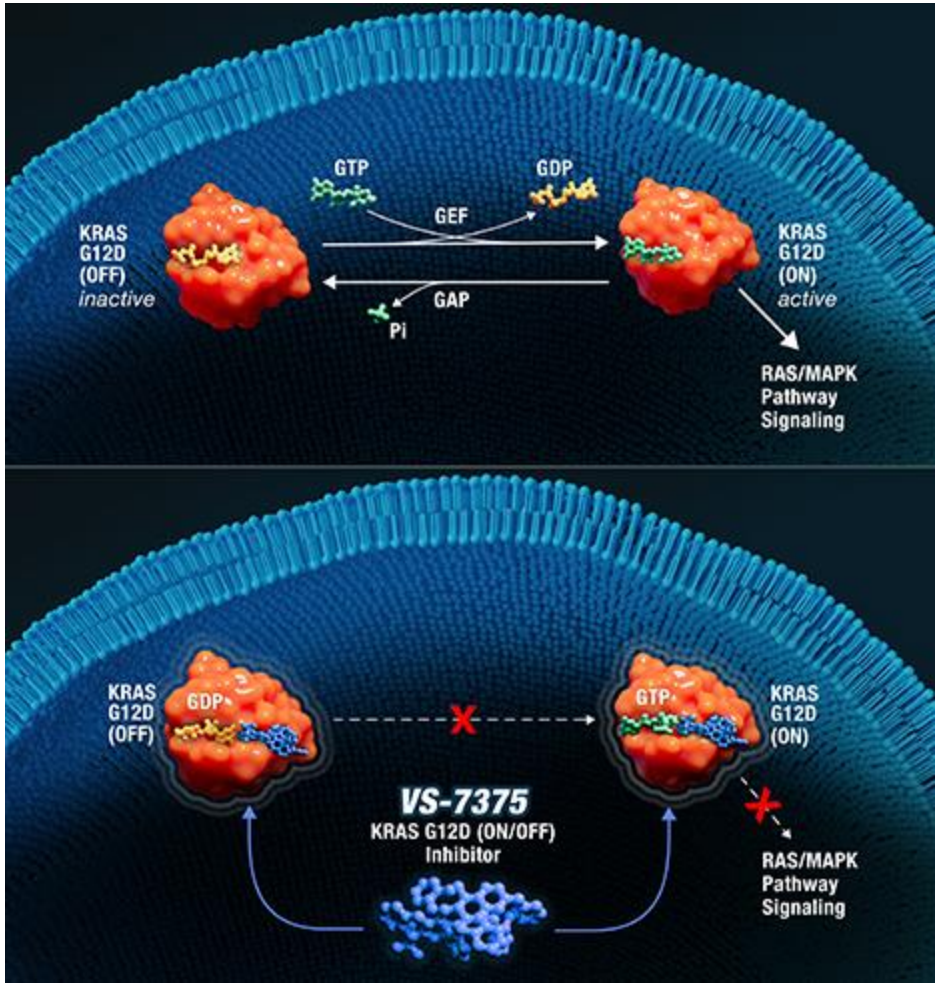
Ras-GDP inhibition: Limitations and Lesson Learned.

- K-Ras G12C is present in only 1-2% of PDAC
- Response in pancreatic cancer is not as durable or robust as it is in other cancers
- May need to be combined with EGFR blockade



KRAS G12D ON/OFF Dual state inhibitors

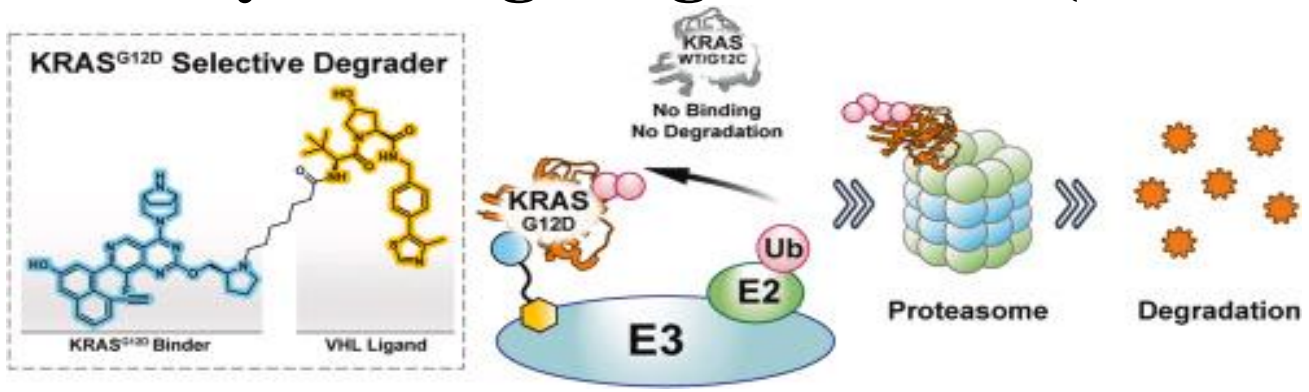
Efficacy and Safety of GFH375 Monotherapy in Previously Treated Advanced KRAS G12D Mutant PDAC



- Phase I/II Study of GFH375/VS7375 in KRAS G12D PDAC
- 66 patients received 600mg QD dose.
- 68% had received at least 2 prior lines
- ORR: 41% (90% CI 30, 52%)
- Median PFS: 5.5 months (90% CI, 4.27-7.20)
- Median OS: NR months (median fu 5.65months)
- Grade 3 toxicities:31%
- Most common diarrhea, n&v, cytopenias.

Zhou A et al, Annals of Oncology, 36S1626

Proteolysis Targeting Chimera (PROTAC) protein degrader: ASP3082



- Phase 1 Study of Setidegrasib (ASP3082) in KRAS G12D PDAC
- N=21. IV 600mg weekly
- Median two (range 1-5) previous treatments
- ORR was 24% (95% CI 8-47)
- Median PFS, 3 months (95% CI 1.4- 6.9)
- Median OS, 10.3 months (95% CI 4.2-13.0)

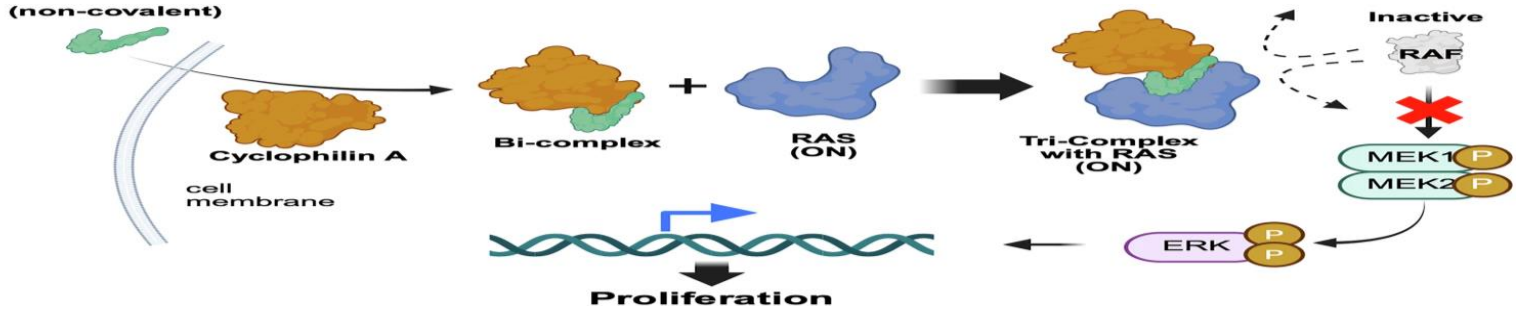
Table 2. Adverse Events in Patients Who Received 600 mg of Setidegrasib Monotherapy.

Event	Patients (N = 76)
Adverse events that emerged during treatment — no. (%)	
Any	76 (100)
Grade ≥3	32 (42)
Serious	25 (33)
Leading to treatment interruption	59 (78)
Leading to dose reduction	4 (5)
Leading to permanent discontinuation	2 (3)
Treatment-related adverse events — no. (%)	
Any	71 (93)
Grade ≥3	7 (9)
Alanine aminotransferase increased	2 (3)
Neutropenia*	2 (3)
Neutrophil count decreased	2 (3)
Iron deficiency anemia	1 (1)
Cholangitis*	1 (1)
Serious	4 (5)
Leading to treatment interruption	53 (70)
Infusion-related reactions	48 (63)
Noninfusion-related-reaction adverse events	8 (11)
Leading to dose reduction	4 (5)
Leading to permanent discontinuation	0
Occurring in ≥20% of patients	
Infusion-related reactions	61 (80)
Nausea	23 (30)
Infusion-related reactions	
Cycle — no./total no. (%)†	
Cycle 1, week 1	59/76 (78)
Cycle 1, week 2	10/62 (16)
Cycle 1, week 3	12/60 (20)
Cycle 2	20/65 (31)
Cycle 3	8/56 (14)
Cycle 4	8/54 (15)
Cycle 5	4/46 (9)
Cycle 6	2/40 (5)
Grade ≥3 — no. (%)	0
Occurring in ≥20% of patients — no. (%)	
Pruritus	23 (30)
Rash	23 (30)
Urticaria	19 (25)

* One patient had both neutropenia and cholangitis.
† Shown are the numbers of patients with at least one infusion-related reaction that emerged during the cycle and week divided by the number of patients.

Jeon E et al EJMC 2025 . Park et al, NEJM 2026.

Molecular Glue: KRAS G12D ON state Tri-complex Inhibitors



- Phase 1 Study of Zoldonrasib in KRAS G12D PDAC
- N= 104. PO1200mg QD dose.
- Median 2 (0-6) previous treatments
- ORR was 30% (95% CI 8-47).

Zoldonrasib Treatment Related Adverse Events (TRAEs)

Maximum severity of TRAEs	Grade 1	Grade 2	Grade 3	Any Grade
	All Patients Treated with Zoldonrasib (N = 179)			
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	48 (27%)	5 (3%)	0	53 (30%)
Diarrhea	24 (13%)	5 (3%)	0	29 (16%)
Vomiting	20 (11%)	6 (3%)	0	26 (15%)
Other select TRAEs, n (%)				
ALT increased	12 (7%)	0	1 (1%)	13 (7%)
AST increased	10 (6%)	1 (1%)	0	11 (6%)
Rash[a]	11 (6%)	0	0	11 (6%)
Stomatitis	0	0	0	0
TRAEs leading to dose reduction, n (%)	5 (3%)	0	0	5 (3%)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	0
	Patients Treated with Zoldonrasib 1200 mg Daily (1200 mg QD, N = 60 or 600 mg BID, N = 39)			
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	23 (23%)	4 (4%)	0	27 (27%)
Diarrhea	16 (16%)	4 (4%)	0	20 (20%)
Vomiting	13 (13%)	2 (2%)	0	15 (15%)
Rash[a]	10 (10%)	0	0	10 (10%)
Other select TRAEs, n (%)				
ALT increased	5 (5%)	0	1 (1%)	6 (6%)
AST increased	3 (3%)	1 (1%)	0	4 (4%)
Stomatitis	0	0	0	0
TRAEs leading to dose reduction, n (%)	4 (4%)	0	0	4 (4%)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	0

No treatment-related Grade 4 or 5 AEs or SAEs were reported

Choucair et al, Sig Transduct Target Ther 2025
Spira AI, et al. *J Clin Oncol*. 2025;43(4_suppl):724

Daraxonrasib (RMC-6236) Multi-Selective Ras (ON) Inhibitor

RASolute 302

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.

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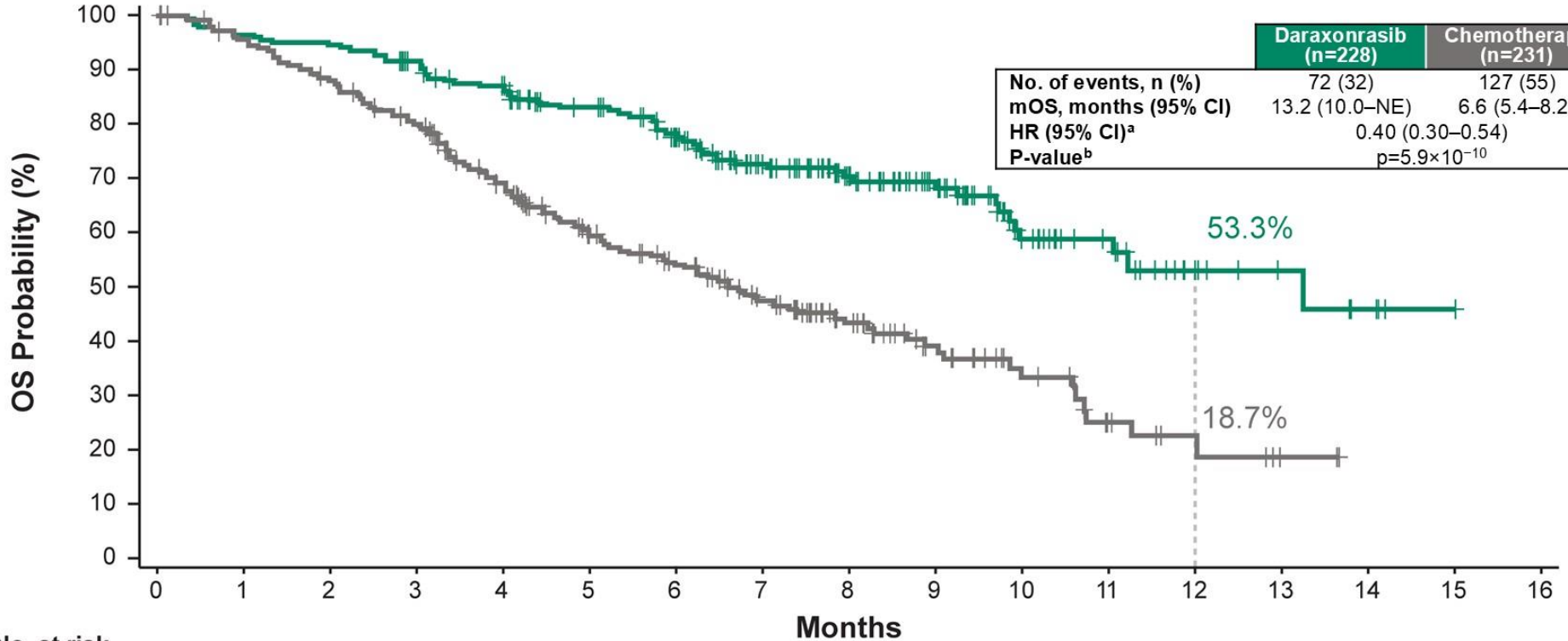
Primary Endpoint: Overall Survival in the RAS G12 Population



	Daraxonrasib (n=228)	Chemotherapy (n=231)
No. of events, n (%)	72 (32)	127 (55)
mOS, months (95% CI)	13.2 (10.0–NE)	6.6 (5.4–8.2)
HR (95% CI)[a]	0.40 (0.30–0.54)	
P-value[b]	$p=5.9\times10^{-10}$	

No. at risk																	
Daraxonrasib	228	220	217	206	191	171	150	112	81	57	33	23	11	7	4	1	0
Chemotherapy	231	214	197	175	144	113	96	69	49	32	19	10	5	2	0		

Data cutoff: 10 Feb 2026. Median (range) follow-up time was 8.5 (3.2−15.9) months.

m, median; NE, not estimable; OS, overall survival.

[a]HRs and 95% CIs were based on the stratified Cox model with Efron's method of tie handling. [b]P-values were calculated using the stratified log-rank test.

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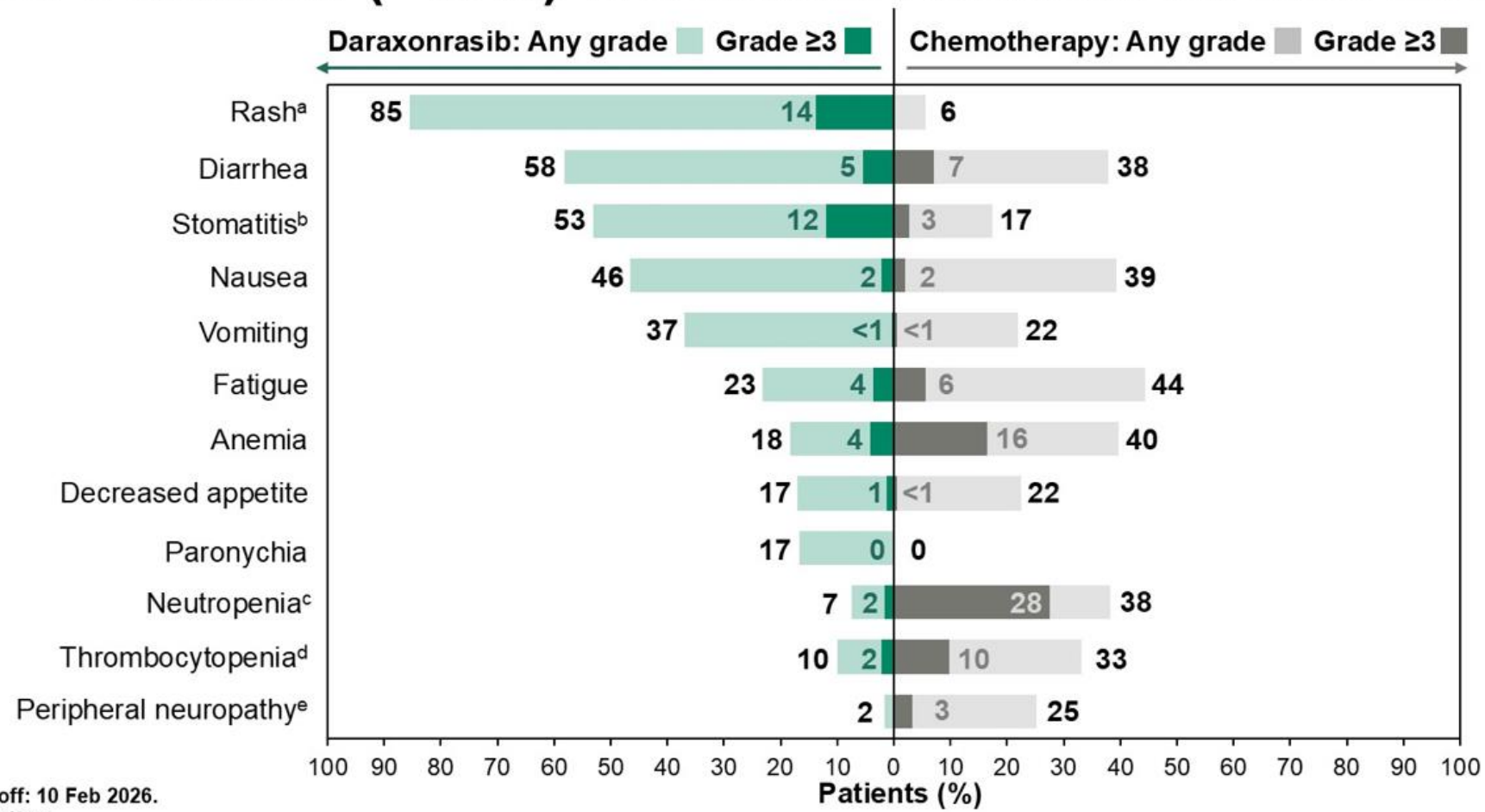
Most Common (>15%) Treatment-Related Adverse Events



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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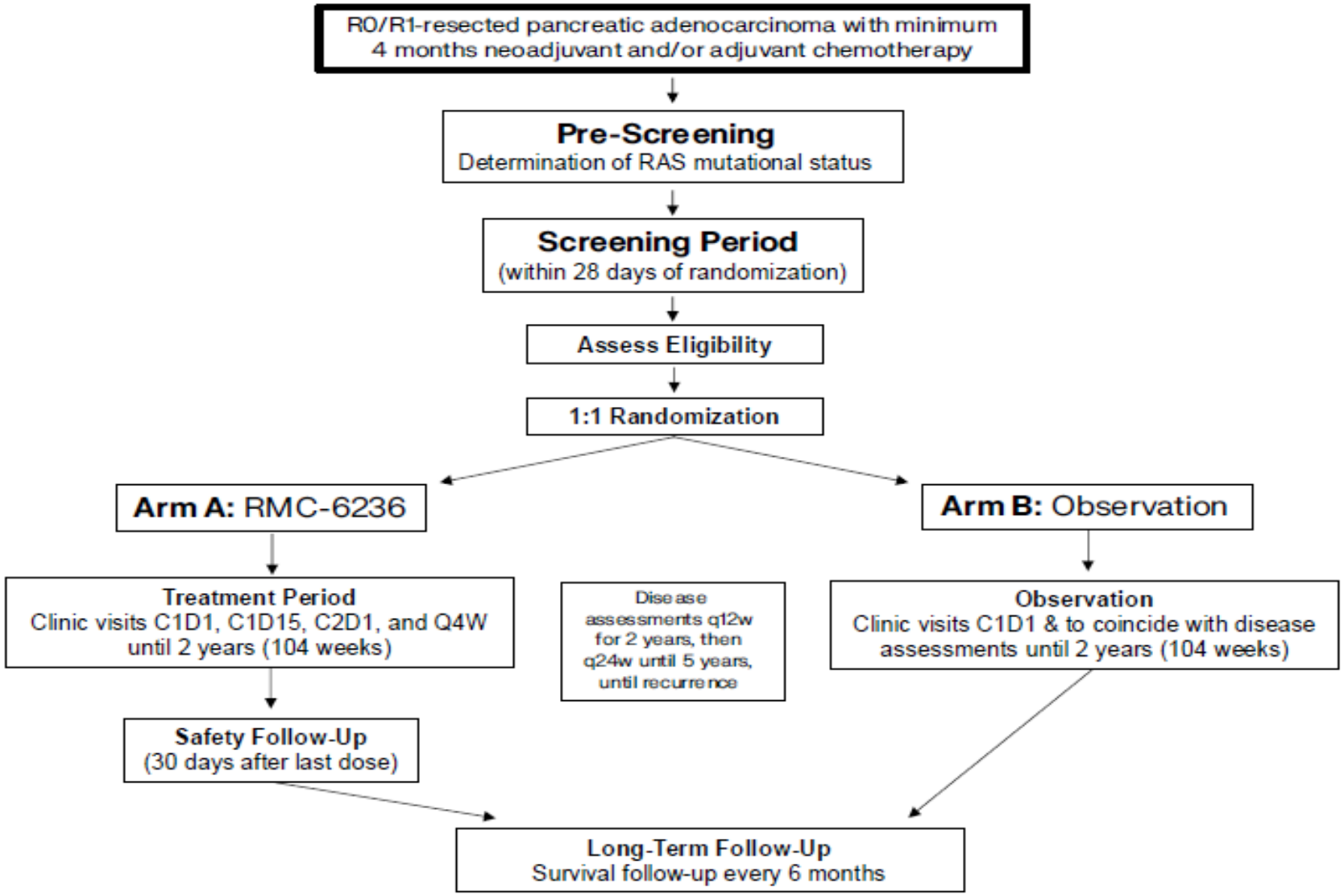
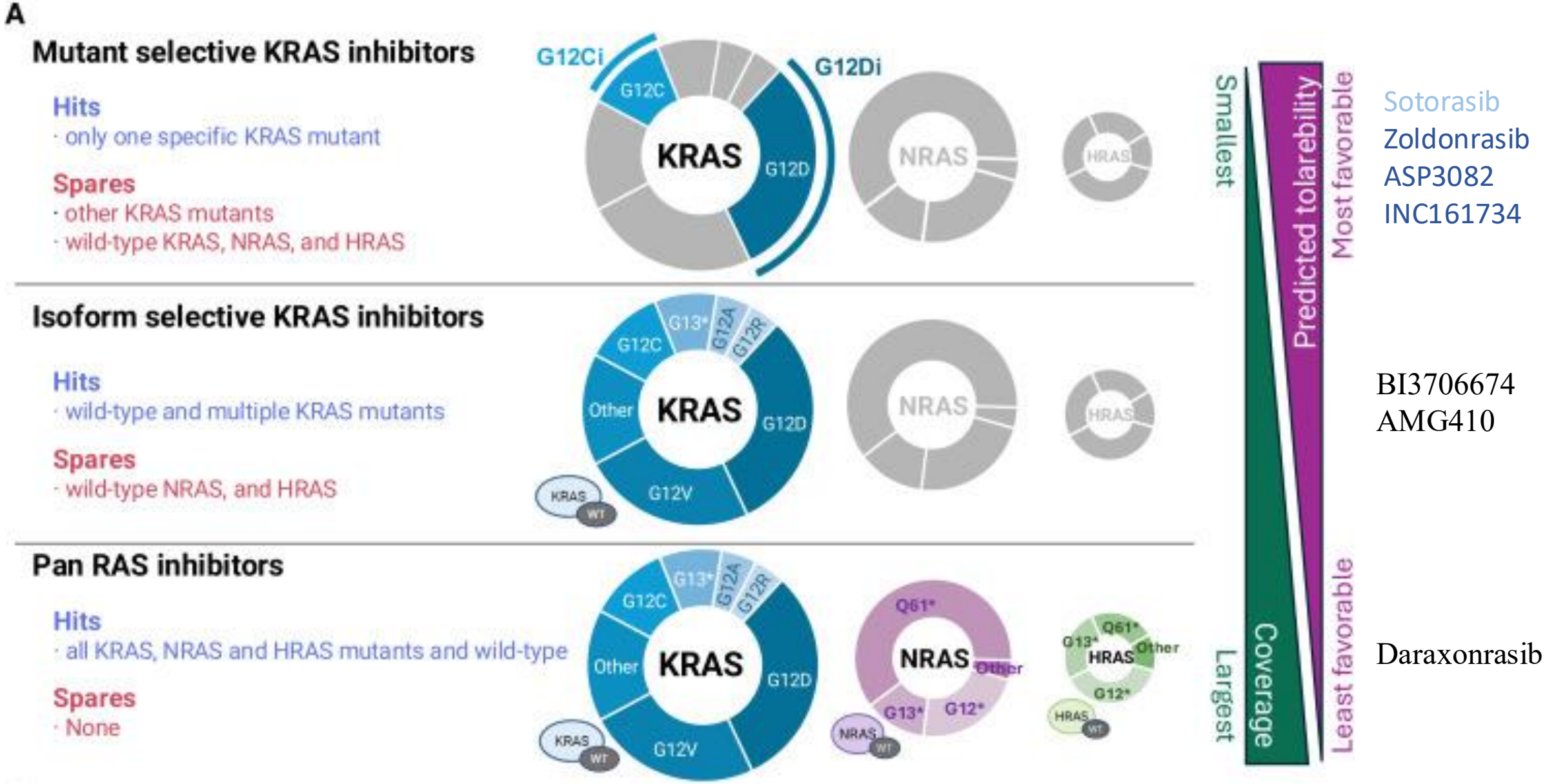
RASolute 304: Adjuvant Daraxonrasib vs observation in resected PDAC.

Figure 1: RMC-6236-304 Study Schema



Open and enrolling at Winship.

RAS targeting agents: selectivity and tolerability.



Sotorasib
Zoldonrasib
ASP3082
INC161734

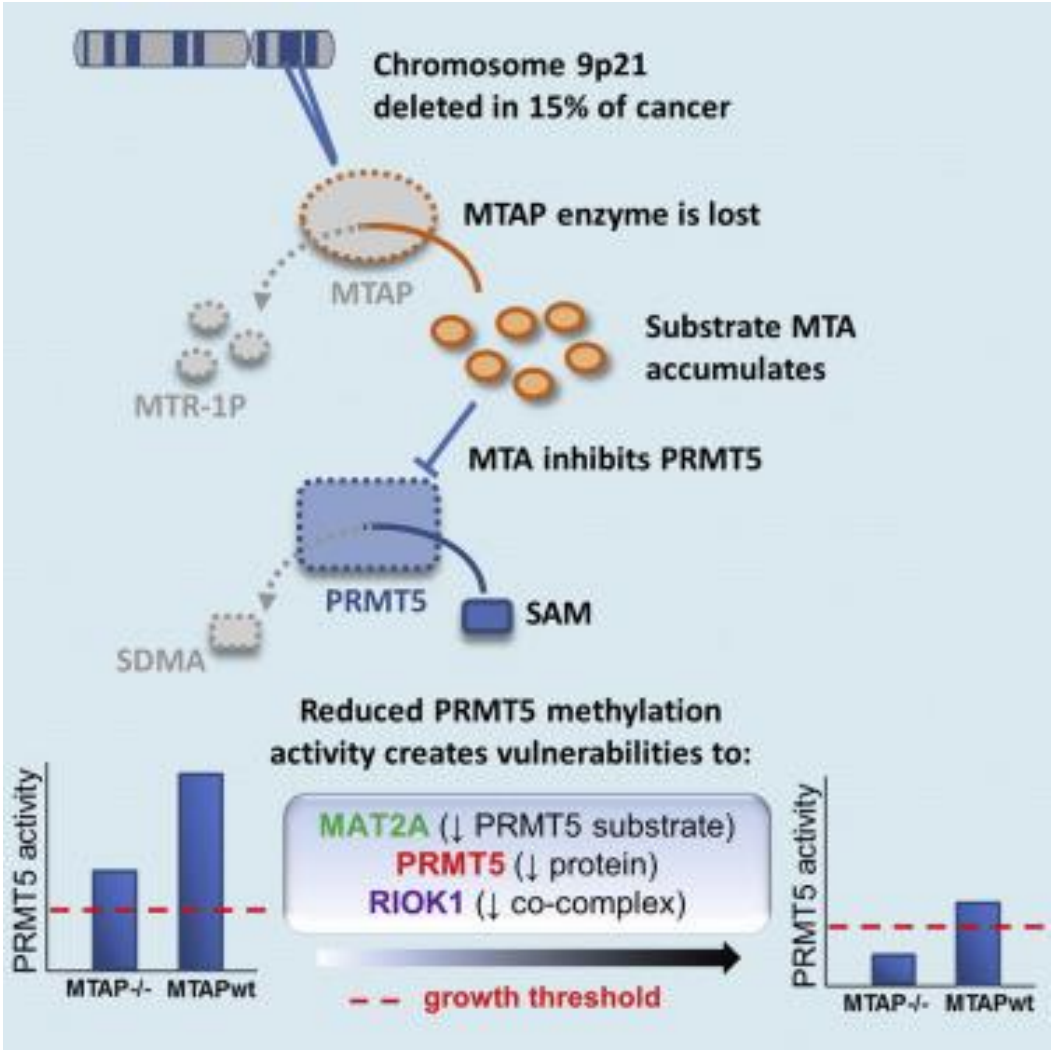
BI3706674
AMG410

Daraxonrasib

Riedl J et al. Cancer Cell, 2026; 44, 471-497

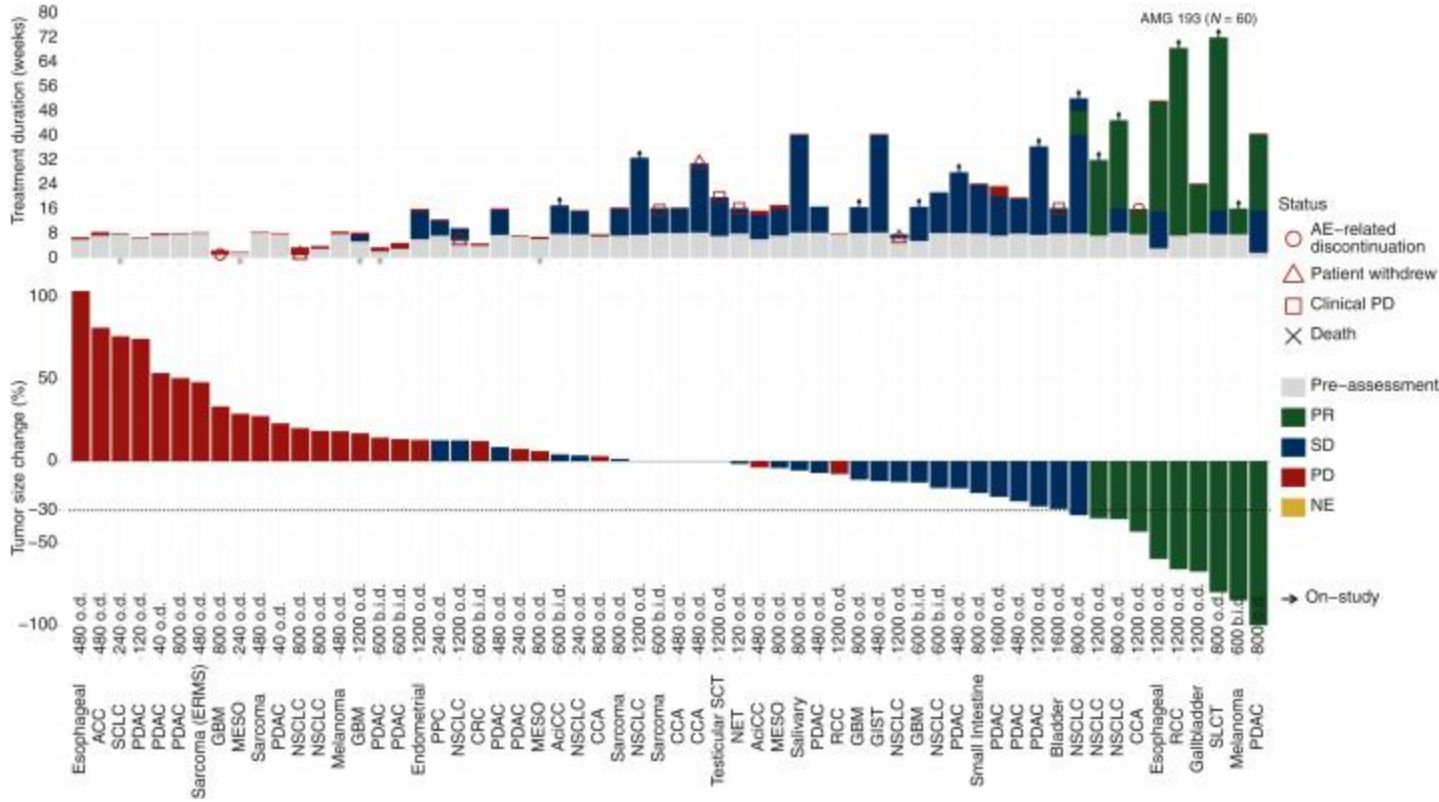
Other targets: Methylthioadenosine phosphorylase (MTAP) loss

- MTAP gene is adjacent to CDKN2A on # 9p21
- Co-deleted in ~35% of PDAC.
- Without MTAP, MTA accumulates and partially inhibits PRMT5 (an arginine methyltransferase).
- MTAP-deleted cells are dependent on residual PRMT5 activity — a synthetic-lethal vulnerability.
- MTA-cooperative PRMT5 inhibition a biomarker-selected, druggable target.



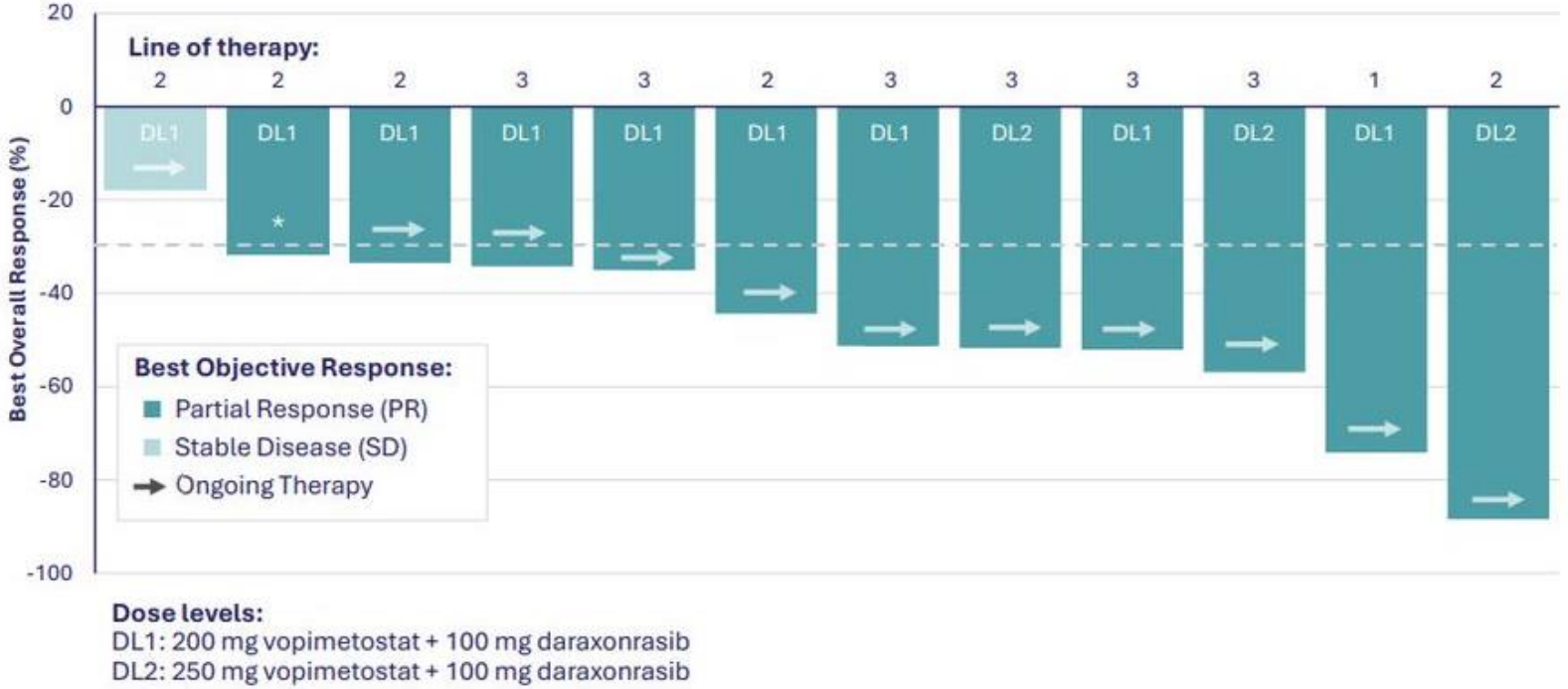
First-in-human study of AMG 193, an MTA-cooperative PRMT5 inhibitor, in patients with MTAP-deleted solid tumors: results from phase I dose exploration

- 80 patients with MTAP deleted tumors
- 19 patients (24%) PDAC
- ORR was 21.4%
- Median duration of response was 8.3 months
- Grade 3 or higher AE in 13.8%
- Grade 3 or higher cytopenias >10%



Targeting MTAP-deleted/KRAS mutant cancers using the combination of PRMT5 inhibitor and RAS (ON) inhibitor

Daraxonrasib 100mg QD + Vopimetostat 200mg/250mg QD



N=12	
ORR	92%
DCR	100%

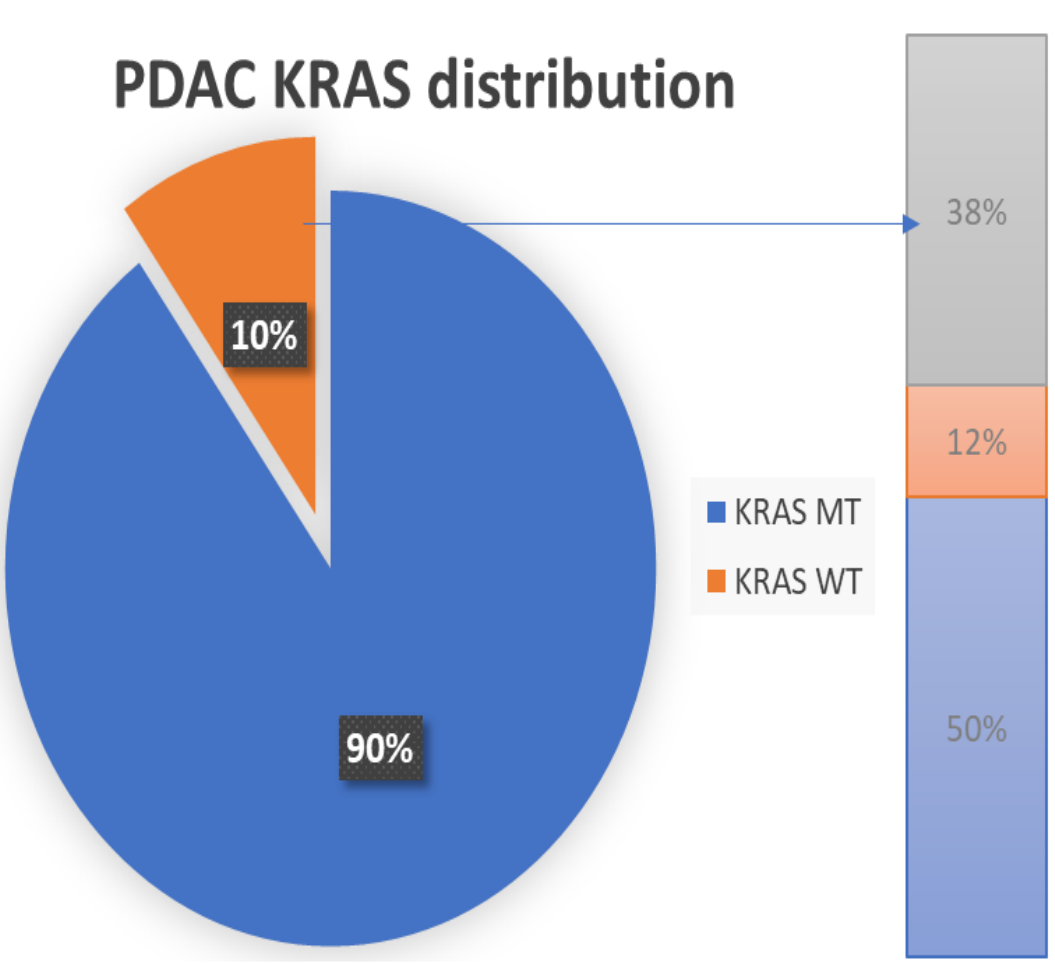
- 9 cPR
- 2 uPR pending confirmation

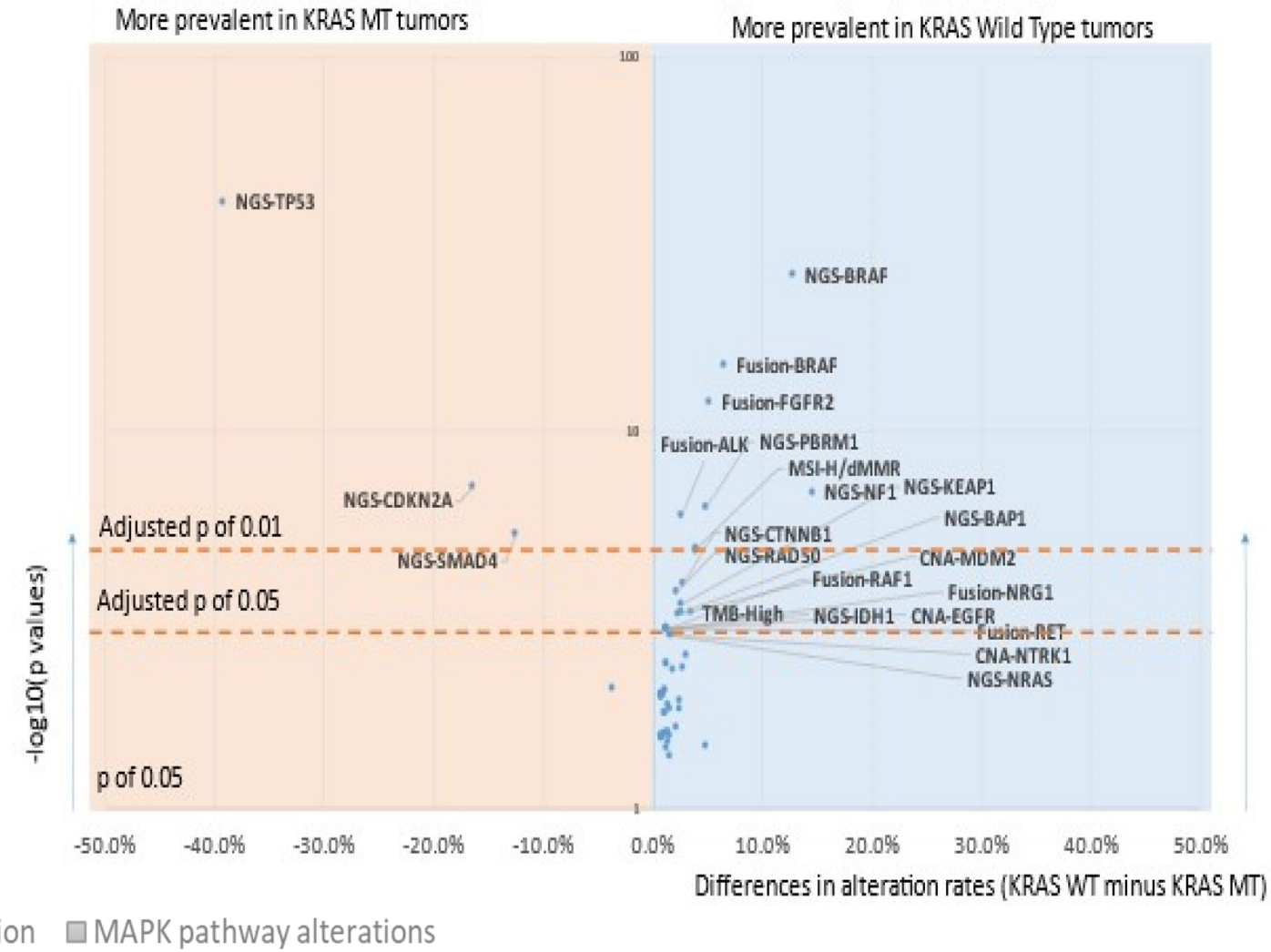
Data extract 28 May 2026. Dashed line indicates threshold for PR (-30%). Objective response rate per RECIST v1.1 includes patients who received first dose of the study drug at least 14 weeks prior to the data extract to allow for 2 post-baseline scans. Median duration of follow-up 6.8 months (3.3 - 9.7). *Patient discontinued due to non-compliance. Disease control rate (DCR) defined as fraction of patients with overall response of SD, PR, or CR at the time of the first scheduled scan. PDAC, pancreatic ductal adenocarcinoma; ORR, objective response rate; DCR, disease control rate; 2/3L, second/third line.

MountainTAP-30: A Study Comparing Navlimetostat (BMS-986504) in Combination With Nab-paclitaxel and Gemcitabine Versus Placebo in Combination With Nab-paclitaxel and Gemcitabine in Participants With Untreated Metastatic Pancreatic Ductal Adenocarcinoma With Homozygous MTAP Deletion

Open and enrolling at Winship.

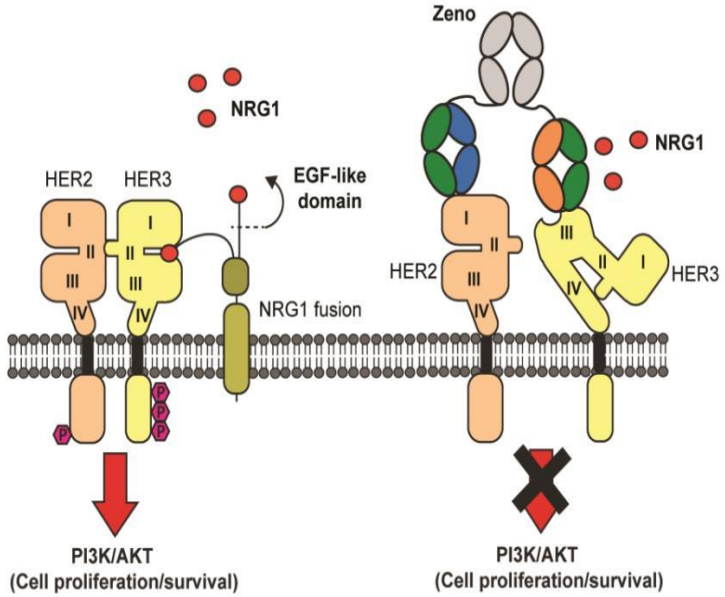
Therapeutic opportunities in KRAS WT PDAC





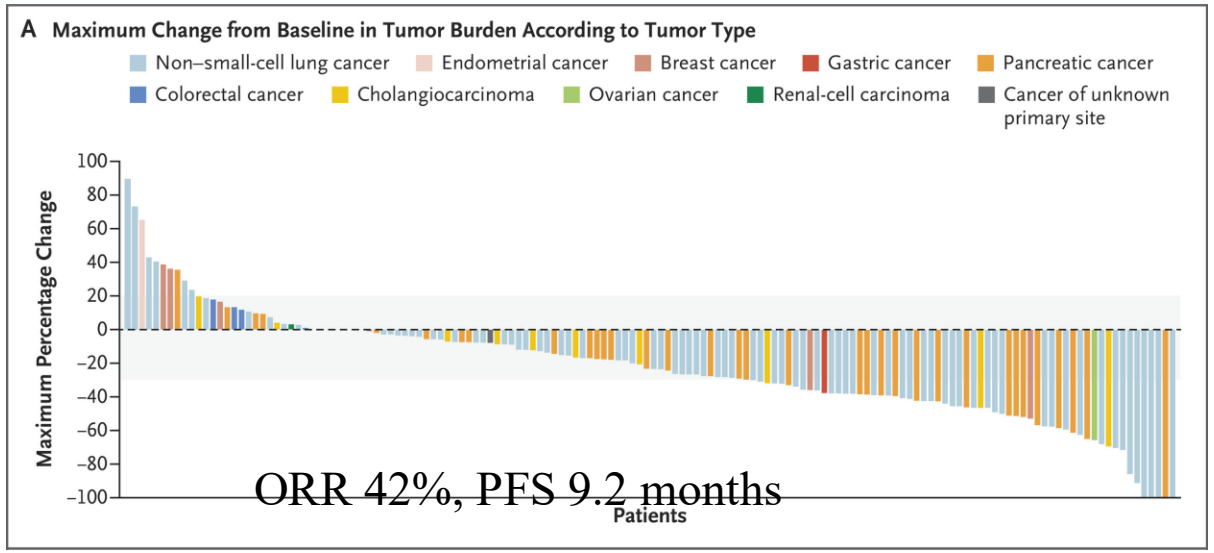
Singhi et al, Gastroenterology 2019;156:2242–2253

Efficacy of Zenocutuzumab in NRG1 Fusion-Positive Cancer



- Neuregulin 1 (NRG1) fusion is present in 0.5% to 1% of PDAC
- NRG1 binds HER3 and activates proliferation via HER2 heterodimerization
- Zenocutuzumab is a bispecific antibody against HER2 and HER3

Phase 2 eNRGy study



ORR 42%, PFS 9.2 months

Table 2. Efficacy of Zenocutuzumab in *NRG1* Fusion–Positive Cancer across Multiple Tumor Types.*

Tumor Type	Investigator Assessment			Blinded Independent Central Review		
	Overall Response†		Median Duration of Response (Range)‡	Overall Response†		Median Duration of Response (Range)‡
	no./total no.	*% (95% CI)*	*mo*	*no./total no.*	*% (95% CI)*	*mo*
All *NRG1* fusion–positive tumor types§	47/158	30 (23 to 37)	11.1 (1.7+ to 29.5+)	50/160	31 (24 to 39)	11.5 (1.9+ to 29.5+)
Non–small-cell lung cancer	27/93	29 (20 to 39)	12.7 (1.8+ to 29.5+)	29/94	31 (22 to 41)	13.4 (1.9+ to 29.5+)
Pancreatic cancer	15/36	42 (25 to 59)	7.4 (2.1+ to 20.7)	16/36	44 (28 to 62)	9.1 (1.9+ to 16.6)
Cholangiocarcinoma	2/10	20 (2 to 56)	9.2 (7.4 to 11.1)	2/10	20 (2 to 56)	8.3 (3.7 to 12.9)
Breast cancer	1/7¶	14‖	1.7+	0/8	0	NA
Colorectal cancer	0/6	0	NA	1/6¶	17‖	11.7
Cancer of unknown primary site	0/2	0	NA	0/2	0	NA
Endometrial cancer	0/1	0	NA	0/1	0	NA
Gastric cancer	1/1¶	100‖	1.9+	1/1¶	100‖	1.9+
Ovarian cancer	1/1¶	100‖	12.8	1/1¶	100‖	12.8+
Renal-cell carcinoma	0/1	0	NA	0/1	0	NA

Schram AM, et al. **N Engl J Med 2025;392:566-576**

SWOG S2433: Randomized Phase III Study of Second-Line Chemotherapy with or without Panitumumab for Locally Advanced or Metastatic KRAS Wild Type PDAC

Step 0

Inclusion Criteria

- Pancreatic ductal adenocarcinoma
- Locally advanced or metastatic
- *KRAS* WT, *BRAF* V600E WT
- 1 prior line of cytotoxic chemotherapy
- ECOG PS 0-2
- Adequate bone marrow, hepatic, and renal function

Exclusion Criteria

- No mutations in *PTEN, NRAS, EGFR* extracellular domain exons 1-16
- No amplifications of *HER2, MET*
- No gene fusions: *RET, NTRK1, ALK*

Note: Tissue NGS required

PRE-REGISTRATION

Step 1

R
1:1
N = 94

Stratification Factors
1. Stage of disease
2. Planned chemotherapy treatment

Arm A

Panitumumab + Chemotherapy*

Arm B

Chemotherapy*

*Treating investigator and participant will select the appropriate standard-of-care therapy – Nal-IRI with 5FU, FOLFIRI, or GA

Open and enrolling at Winship.

Key Takeaway Points

- **All patients** with pancreatic cancer should undergo comprehensive tumor genomic testing. *NCCN, 03/2026.*
- Multiple RAS-targeting strategies, including mutant specific (G12C, G12D), pan-KRAS and multi-RAS ON inhibitors, have now shown clinical activity in pancreatic cancer.
- The next frontier is overcoming resistance through rational combination strategies, such as with EGFR directed therapy, PRMT5, and ICI.