Daraxonrasib in Advanced Pancreatic Cancer

A pan-RAS(ON) Inhibitor for the 90% Left Behind by G12C Drugs

Clinician-Facing Technical Brief for Tumor-Board Review

K-Dense Web
contact@k-dense.ai

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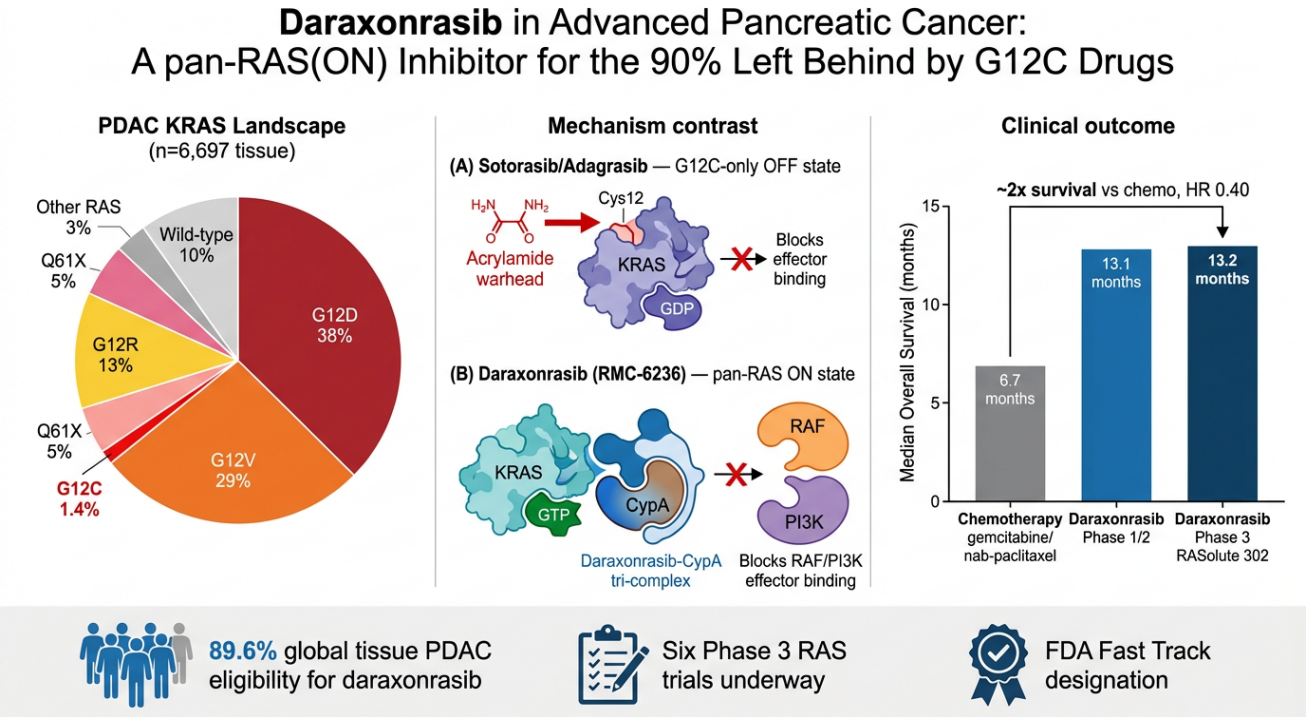


Figure 1: Graphical abstract. Daraxonrasib (RMC-6236), the first oral pan-RAS(ON) tri-complex inhibitor to read out positive in a Phase 3 pancreatic-cancer trial, addresses ∼**89.6%** of tissue-PDAC patients globally—roughly 60–90× the addressable population of the legacy KRAS-G12C(OFF) covalent inhibitors sotorasib and adagrasib (1.4%). In the pivotal RASolute-302 Phase 3 in 2L PDAC, daraxonrasib monotherapy approximately doubled median overall survival vs. physician's choice chemotherapy (13.2 vs. 6.7 months; HR 0.40) [Revolution Medicines, 2026].

Tumor-Board Bottom Line

- **Drug.** Daraxonrasib (RMC-6236; Revolution Medicines) is an oral, non-covalent, pan-RAS(ON) multi-selective inhibitor that engages active (GTP-bound) RAS via a cyclophilin A (CypA)-mediated ternary complex [Wasko et al., 2024, Kim et al., 2024].
- **Pivotal data.** Phase 1/2 *NEJM* 2026 (Wolpin et al., $n = 168$, 2L+ RAS-mutant metastatic PDAC): ORR 29%, median PFS 8.1–8.5 mo, median OS 13.1–15.6 mo [Wolpin et al., 2026]. Phase 3 RASolute-302 (NCT06625320, $n = 500$): median OS 13.2 vs. 6.7 mo, HR 0.40 [Revolution Medicines, 2026, Revolution Medicines, Inc., 2024]. FDA Fast Track / expanded access "safe-to-proceed" (May 2026).
- **Eligibility (this brief).** *Global tissue-PDAC ($n = 6{,}697$): 89.6% daraxonrasib-addressable vs. 1.4% G12C-addressable; +88.2 percentage-point incremental gain.* Eligibility is uniform across continents (86.1%–91.7%).
- **Order at diagnosis.** Comprehensive genomic profiling (tissue or ctDNA) covering KRAS/NRAS/HRAS codons 12, 13, 61, and A146; report the specific allele to the board.
- **Who is still left out.** (i) RAS wild-type PDAC (∼10%; alternative drivers); (ii) atypical RAS variants such as A146X and in-frame indels; (iii) ctDNA-negative liquid biopsies (sensitivity ceiling, not biology); (iv) frail patients (ECOG ≥2) excluded from the registrational trials; (v) CNS metastases (limited BBB penetration).

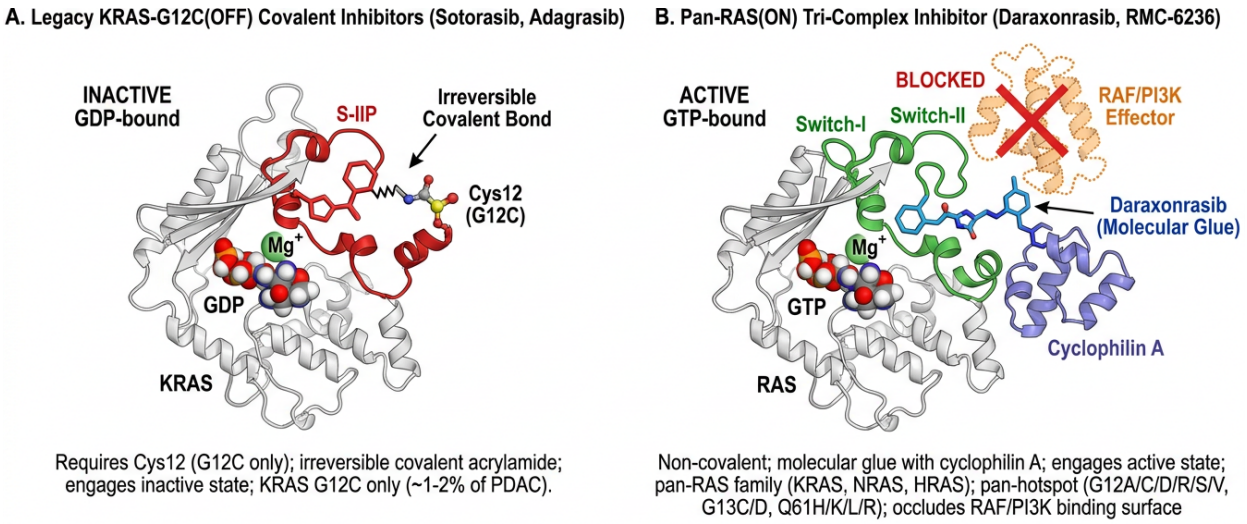
1 Why this matters Monday morning

Pancreatic ductal adenocarcinoma (PDAC) is on track to become the second leading cause of cancer death in the United States and a similar trajectory is observed globally [Rahib et al., 2014, Siegel et al., 2024, International Agency for Research on Cancer, 2024]. For the better part of two decades, the standard of care for advanced PDAC has been combination chemotherapy—FOLFIRINOX [Conroy et al., 2011], gemcitabine plus nab-paclitaxel [Von Hoff et al., 2013], or, more recently, NALIRIFOX [Wainberg et al., 2023]—with median overall survival plateauing at 9–11 months in the first line and only 5–7 months in the second line. The disease has been described as the graveyard of targeted therapy: HER2, EGFR, VEGF and immune checkpoint programs have all failed to move the needle in unselected PDAC.

The 2026 readout of daraxonrasib (RMC-6236) in the *New England Journal of Medicine* [Wolpin et al., 2026] and the subsequent Phase 3 RASolute-302 topline announcement [Revolution Medicines, 2026] are the first credible signal in many years that a precision therapy can roughly *double* survival in this disease. Crucially, daraxonrasib does not target a 1–2% niche allele like KRAS-G12C; it engages the dominant 86–92% of PDAC tumors that harbor any of the activating RAS hotspots. That magnitude of biological coverage—together with FDA Fast Track and "safe-to-proceed" expanded access in May 2026—means that within the next 12–18 months the tumor board's default question for every newly diagnosed advanced PDAC patient may shift from "*which chemo backbone?*" to "*which RAS variant?*".

This brief synthesizes the molecular pharmacology, the global mutation landscape, the apples-to-apples eligibility math against legacy G12C inhibitors, and the parallel/follow-on trial portfolio so a multidisciplinary team can act on daraxonrasib evidence at the next tumor board.

2 Mechanism: why a tri-complex pan-RAS(ON) drug is different



Feature	KRAS-G12C(OFF) Inhibitors (Sotorasib/Adagrasib)	Pan-RAS(ON) Tri-Complex Inhibitor (Daraxonrasib/RMC-6236)
Target state	Inactive (GDP-bound)	Active (GTP-bound)
Binding mode	Covalent, irreversible (via acrylamide)	Non-covalent, molecular glue (via tri-complex with CypA)
RAS family coverage	KRAS only	Pan-RAS (KRAS, NRAS, HRAS)
Hotspot alleles engaged	G12C only	Pan-hotspot (multiple G12, G13, Q61)
Drug-resistant alleles	G12C plus secondary mutations (e.g., Y96D, G13D)	Potential for diverse resistance or CypA-dependent mutations

Figure 2: Tri-complex (ON-state) vs. covalent (OFF-state) pharmacology. Left, sotorasib/adagrasib bind the switch-II pocket (S-IIP) on *GDP-bound* KRAS and form an irreversible covalent bond with the mutant Cys-12 of KRAS-G12C—hence the absolute requirement for a cysteine at position 12. Right, daraxonrasib (a "molecular glue") first binds cyclophilin A (CypA); the resulting binary drug–chaperone complex docks onto *GTP-bound* (active) RAS at the switch-I/II interface, sterically occluding RAF/PI3K effector binding. Because the contact surface does not require Cys-12, the drug engages all common KRAS, NRAS and HRAS hotspots at codons 12, 13 and 61 [Wasko et al., 2024, Kim et al., 2024, Revolution Medicines, 2024].

2.1 Legacy mechanism: covalent OFF-state G12C inhibitors

Sotorasib (AMG 510, Lumakras) and adagrasib (MRTX849, Krazati) were a landmark in cancer pharmacology because they showed it was possible to drug the previously "undruggable" KRAS oncogene [Canon et al., 2019, Hallin et al., 2020]. Their mechanism, however, imposes two strict requirements that limit applicability to PDAC.

First, both drugs are *covalent* inhibitors carrying an acrylamide warhead engineered to react with a thiol side chain. They form an irreversible thioether bond with the mutant Cys-12 residue created by the KRAS-G12C amino-acid substitution. By definition, the chemistry only works on G12C—no other KRAS hotspot (G12D, G12V, G12R, G13D, Q61H/L/R/K) supplies a cysteine at that position.

Second, both drugs bind the so-called switch-II pocket (S-IIP), a cryptic allosteric cleft that opens transiently only when KRAS is in its inactive, GDP-bound conformation [Canon et al., 2019, Hallin et al., 2020, Simanshu et al., 2017]. Once covalently locked into S-IIP, KRAS-G12C is trapped in the non-signaling OFF state and cannot exchange GDP for GTP, suppressing downstream MAPK/PI3K signaling.

The clinical readout in PDAC was modest. In the largest dataset to date—the CodeBreaK 100 PDAC cohort [Strickler et al., 2023]—sotorasib produced a 21% objective response rate, 4.0 month median PFS, and 6.9 month median OS in 38 heavily pretreated KRAS-G12C-mutant pancreatic-cancer

patients. KRYSTAL-1 reported adagrasib activity in a similar setting, with 41% ORR among a small G12C-mutant GI cohort [Bekaii-Saab et al., 2023]. Both readouts are encouraging proof-of-mechanism but irrelevant for >97% of PDAC patients because *they do not carry the G12C allele.*

2.2 The ON-state tri-complex mechanism of daraxonrasib

Daraxonrasib (RMC-6236) is built on Revolution Medicines' tri-complex inhibitor platform—a class of small-molecule "molecular glues" that co-opt the abundant cellular chaperone cyclophilin A (CypA) [Wasko et al., 2024, Kim et al., 2024, Revolution Medicines, 2024]. The mechanism unfolds in three steps:

1. **Drug binds CypA.** Daraxonrasib has a sanglifehrin-like scaffold that occupies the proline isomerase active site of CypA, forming a binary daraxonrasib–CypA complex. CypA is one of the most abundant proteins in the cytoplasm, so this binary complex forms readily at therapeutic exposures.
2. **Binary complex engages active RAS.** Daraxonrasib presents a *neo-substrate surface* on the binary complex that is complementary to a shallow groove at the switch-I/II interface of *GTP-bound* RAS—a surface that does not exist on free daraxonrasib or free CypA.
3. **Effector binding is blocked.** The ternary drug–CypA–RAS complex sterically occludes the surface RAS uses to recruit RAF and PI3K effectors, shutting down active-state signaling without any covalent bond.

The pharmacological consequences are striking. Because the contact surface does not depend on a cysteine—or on the GDP-bound conformation—daraxonrasib engages *any* amino-acid change at RAS codons 12, 13 and 61 that preserves a functional GTPase fold. Preclinical and clinical data confirm activity against KRAS G12A, G12C, G12D, G12R, G12S, G12V, G13C, G13D, Q61H, Q61K, Q61L and Q61R, spanning all three RAS family members (KRAS, NRAS, HRAS) [Wasko et al., 2024, Wolpin et al., 2026, Revolution Medicines, 2024]. Notably, normal wild-type RAS appears to be relatively spared at clinically relevant exposures, providing a therapeutic window [Wasko et al., 2024, Kim et al., 2024].

Table 1 summarizes the head-to-head pharmacology.

Table 1: Side-by-side pharmacology: pan-RAS(ON) tri-complex vs. legacy KRAS-G12C(OFF) covalent inhibitors.

Attribute	Daraxonrasib (RMC-6236)	Sotorasib (AMG 510)	Adagrasib (MRTX849)
Class	pan-RAS(ON) tri-complex	KRAS-G12C(OFF) covalent	KRAS-G12C(OFF) covalent
RAS conformer engaged	Active (GTP-bound)	Inactive (GDP-bound)	Inactive (GDP-bound)
Binding partner	Cyclophilin A (CypA)	None (direct binder)	None (direct binder)
Binding pocket	Neo-substrate groove at switch-I/II of GTP-RAS	Switch-II pocket (S-IIP) of GDP-KRAS	Switch-II pocket (S-IIP) of GDP-KRAS
Covalent?	No	Yes (acrylamide → Cys-12 thioether)	Yes (acrylamide → Cys-12 thioether)
Mutant residue required	None	Cys-12 (G12C only)	Cys-12 (G12C only)
RAS family coverage	KRAS + NRAS + HRAS	KRAS only	KRAS only
Hotspot codons engaged	12, 13, 61	12 (G12C only)	12 (G12C only)
Specific alleles engaged	G12A/C/D/R/S/V; G13C/D; Q61H/K/L/R	G12C only	G12C only
Half-life / route	Daily oral	Daily oral	Twice-daily oral
PDAC clinical phase	Phase 3 (RASolute-302 readout)	Phase 2 (CodeBreaK 100)	Phase 1/2 (KRYSTAL-1)
PDAC mOS reported	13.2 mo (Ph 3); 13.1–15.6 mo (Ph 1/2)	6.9 mo	Not yet reported (small cohort)

2.3 Why the mechanism predicts the eligibility numbers

The biology in this section dictates the eligibility math in Section 3. Because daraxonrasib does not require Cys-12, every PDAC tumor with *any* canonical RAS hotspot at codons 12, 13 or 61 is, in principle, on-mechanism. Because PDAC is the canonical RAS-mutant tumor type—KRAS is mutated in 85–96% of tissue PDAC across continents—the drug's biology and the disease's biology are in unusual alignment. The G12C-selective drugs, by contrast, address the wrong ∼1.5% of PDAC.

3 The mutation landscape: who is and is not a candidate

3.1 Headline numbers

We assembled a continent-stratified PDAC mutation atlas combining 21 curated cBioPortal studies with six published cohorts (Yachida, Japan; Lu and Chen, China; Stenzinger, Germany; Ben-Aharon, Mediterranean; Singhi, multi-Latin-American ctDNA subset) [Cerami et al., 2012, Yachida et al., 2018, Lu et al., 2019, Chen et al., 2021, Stenzinger et al., 2023, Ben-Aharon et al., 2022, Singhi et al., 2019]. After excluding non-PDAC pancreatic tumors (PNET, ACC) and isolating the one ctDNA cohort (`pancreas_ctdna_msk_2025`) for separate analysis, the apples-to-apples *tissue-only* PDAC denominator is $n = 6{,}697$ patients distributed across five continents (Table 2).

Table 2: Per-continent KRAS mutational prevalence in tissue PDAC and daraxonrasib vs. G12C-inhibitor eligibility. Source: integrated cBioPortal + literature-cohort meta-analysis ($n = 6{,}697$ PDAC tissue samples). Liquid-biopsy (MSK ctDNA, $n = 412$) reported separately. "Incremental gain" = pct daraxonrasib eligible minus pct G12C-inhibitor eligible.

Continent	Contributing tissue cohorts	*n* tissue	% KRAS-mut	% G12C only	% daraxonrasib	Δ pp
Asia	cBio + Yachida/Lu/Chen	1,025	91.1	2.1	91.1	+89.0
Europe	cBio + Stenzinger/Ben-Aharon	1,678	88.1	1.5	88.1	+86.6
North America	9 cBio tissue cohorts	3,390	90.4	1.1	89.6	+88.5
Oceania	ICGC + QCMG-UQ	482	92.1	1.2	91.7	+90.5
South America	Singhi LatAm subset	122	86.1	1.6	86.1	+84.4
Global tissue	*Apples-to-apples baseline*	**6,697**	**90.0**	**1.4**	**89.6**	**+88.2**
Global ctDNA (MSK, $n = 412$)	ctDNA only	412	41.3	0.5	41.0	+40.5

The eligibility math is striking and uniform across continents: *∼89.6% of tissue PDAC* carries

a daraxonrasib-engageable RAS hotspot, vs. ∼*1.4%* for sotorasib/adagrasib—a ∼60–90× increase in addressable patients. The 86–92% band is biologically tight; the only outlier (41%) is the ctDNA-only MSK cohort, where the limit is assay sensitivity rather than tumor biology (Section 6).

3.2 Allele-level heatmap

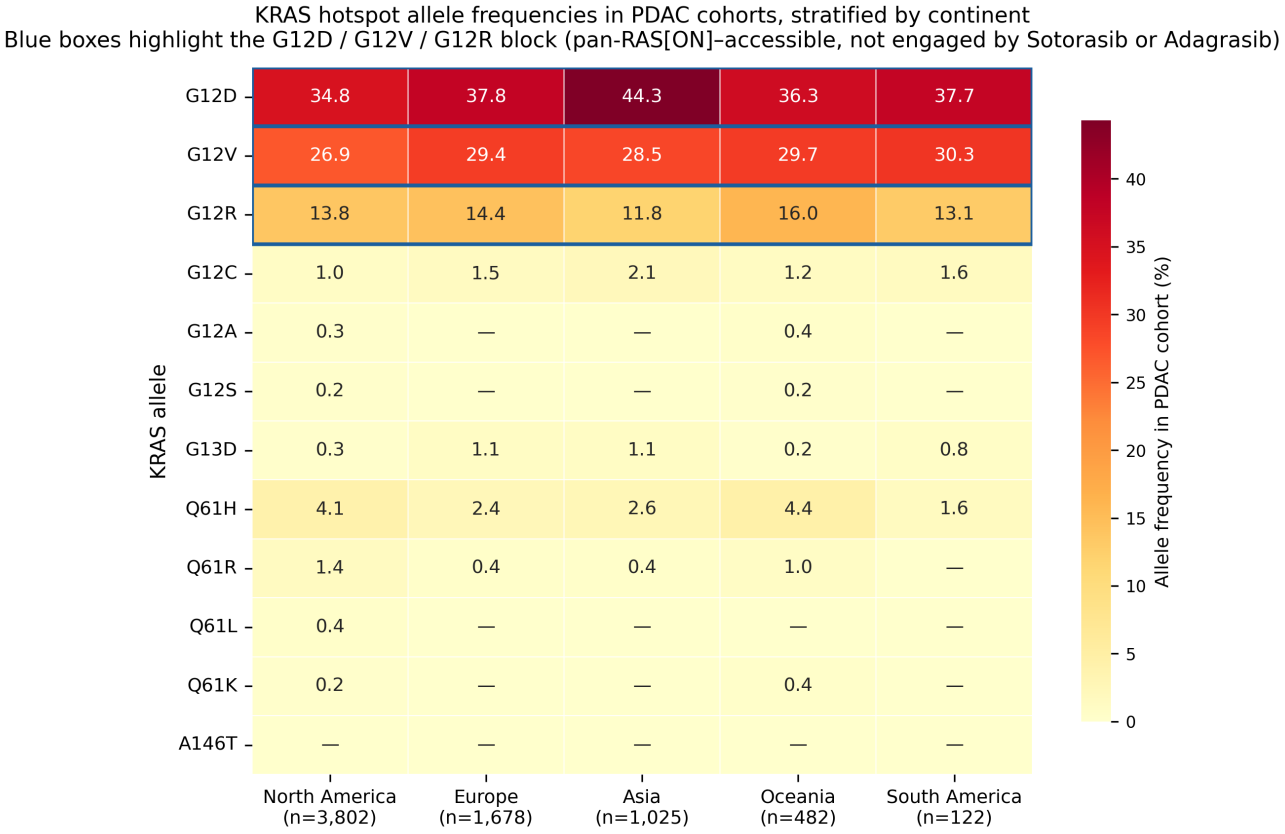


Figure 3: KRAS hotspot-allele heatmap across PDAC cohorts by continent (n = 3,802 North America; n = 1,678 Europe; n = 1,025 Asia; n = 482 Oceania; n = 122 South America). Each cell shows the percentage of sequenced PDAC tumors carrying the indicated KRAS allele. The blue-outlined block (G12D + G12V + G12R) is dominant on every continent (combined 73–85% of PDAC) and is invisible to sotorasib/adagrasib. G12C remains a rare allele (1.0–2.1%). Dashes indicate "<0.5% or absent."

The dominant alleles are uniform across continents and consistent with all major PDAC genomic atlases [Bailey et al., 2016, Waddell et al., 2015, Biankin et al., 2012, Witkiewicz et al., 2015, Hall et al., 2025, Singhi et al., 2024]:

- **KRAS G12D** 34.8–44.3% (enriched in Asia, $\Delta = +7.6$ pp vs. North America; FDR-significant);
- **KRAS G12V** 26.9–30.3% (uniformly distributed, $p_{\text{omni}} = 0.95$);
- **KRAS G12R** 11.8–16.0% (relatively higher in Oceania);
- **KRAS Q61X** 1.6–6.6% (enriched in North America, FDR-significant; possibly panel-sensitivity-driven);
- **KRAS G12C** 1.0–2.1% (rare and uniform);

- **KRAS G13D** 0.2–1.1% (rare; enriched in Europe).

Cross-continent omnibus testing (Pearson χ^2 or Fisher–Freeman–Halton Monte Carlo with $B = 10^5$, BH-FDR) identified three FDR-significant allele-level differences across continents (Q61X, G12D, G13D); effect sizes are small (Cramer's V <0.1), so although the differences are real they amount to a few percentage points and do not change practice. The clinically actionable conclusion is that *the G12D/G12V/G12R triad dominates PDAC on every continent.*

3.3 Stacked-bar visualization

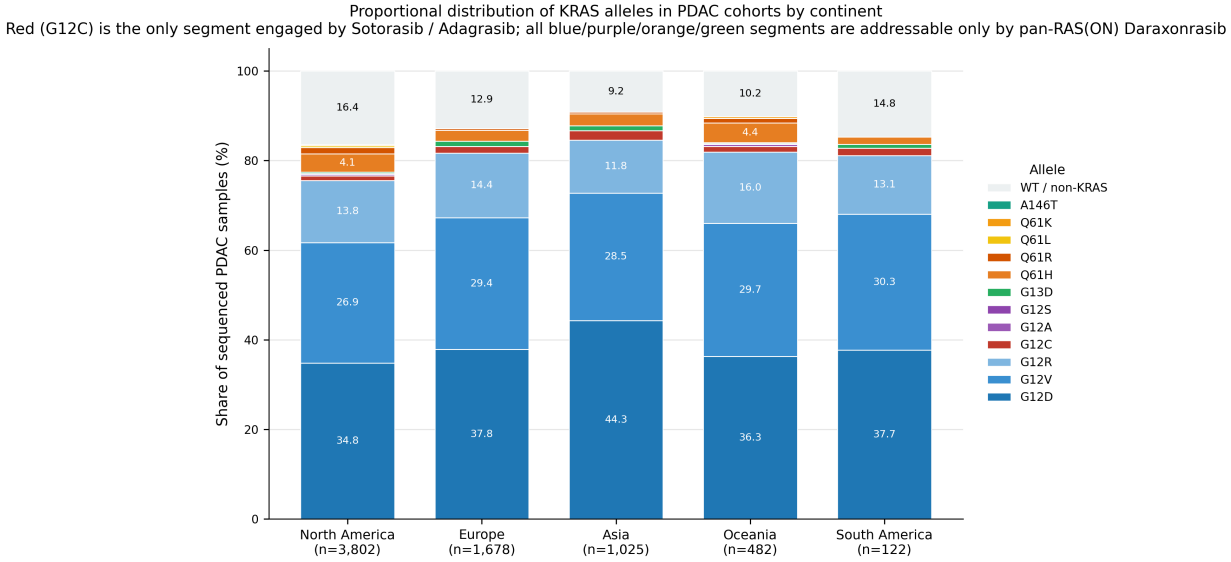


Figure 4: Proportional distribution of KRAS alleles in PDAC cohorts by continent. Red (G12C) is the only allele engaged by sotorasib/adagrasib; every blue/purple/orange/green segment is addressable only by pan-RAS(ON) daraxonrasib. Gray represents WT/non-KRAS tumors. The visual translates the heatmap's allele-by-allele numbers into the clinician's mental model of "what fraction of my next 100 PDAC patients can I match to which drug?".

3.4 Eligibility comparison: drug-class addressable populations

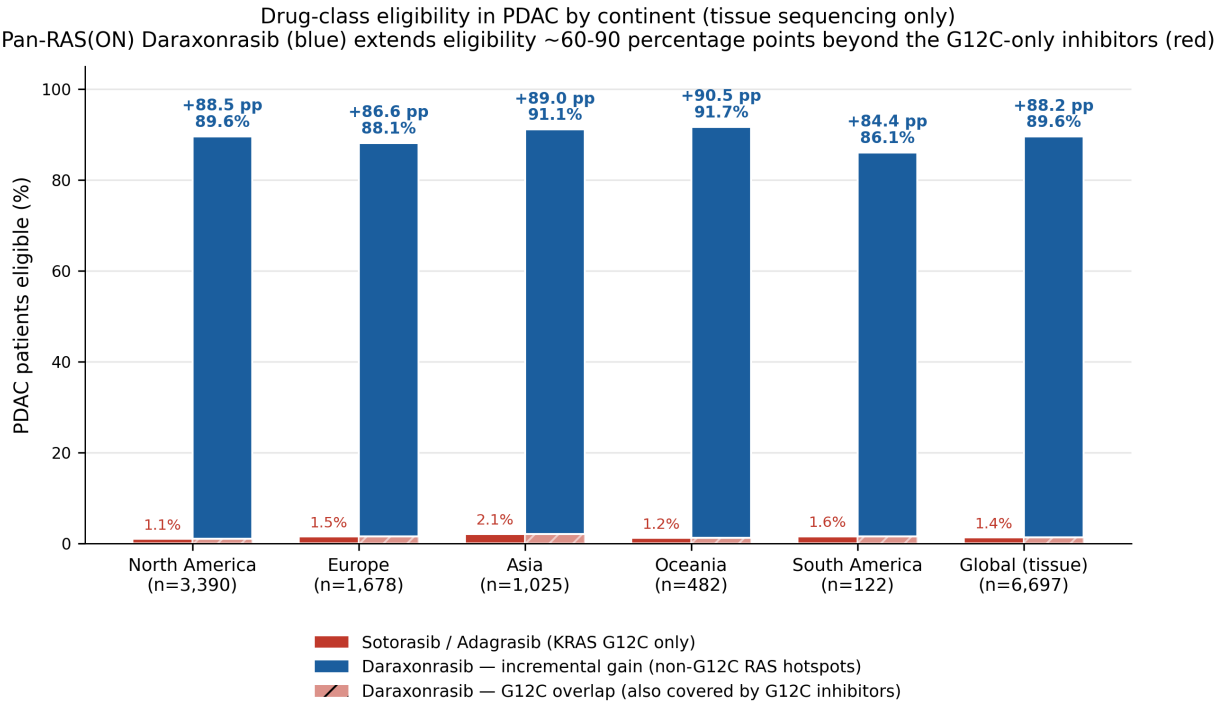


Figure 5: Per-continent and global drug-class eligibility in tissue PDAC. Red bars: sotorasib/adagrasib (KRAS-G12C only). Blue bars: daraxonrasib (any RAS hotspot). The faint pink "⊂ G12C overlap" bar marks the small fraction of the daraxonrasib population that is also addressable by G12C drugs. The incremental gain (top annotation, percentage points) is the absolute number of extra PDAC patients per continent who become candidates because the drug is pan-RAS rather than G12C-only.

3.5 Patient triage at the tumor board

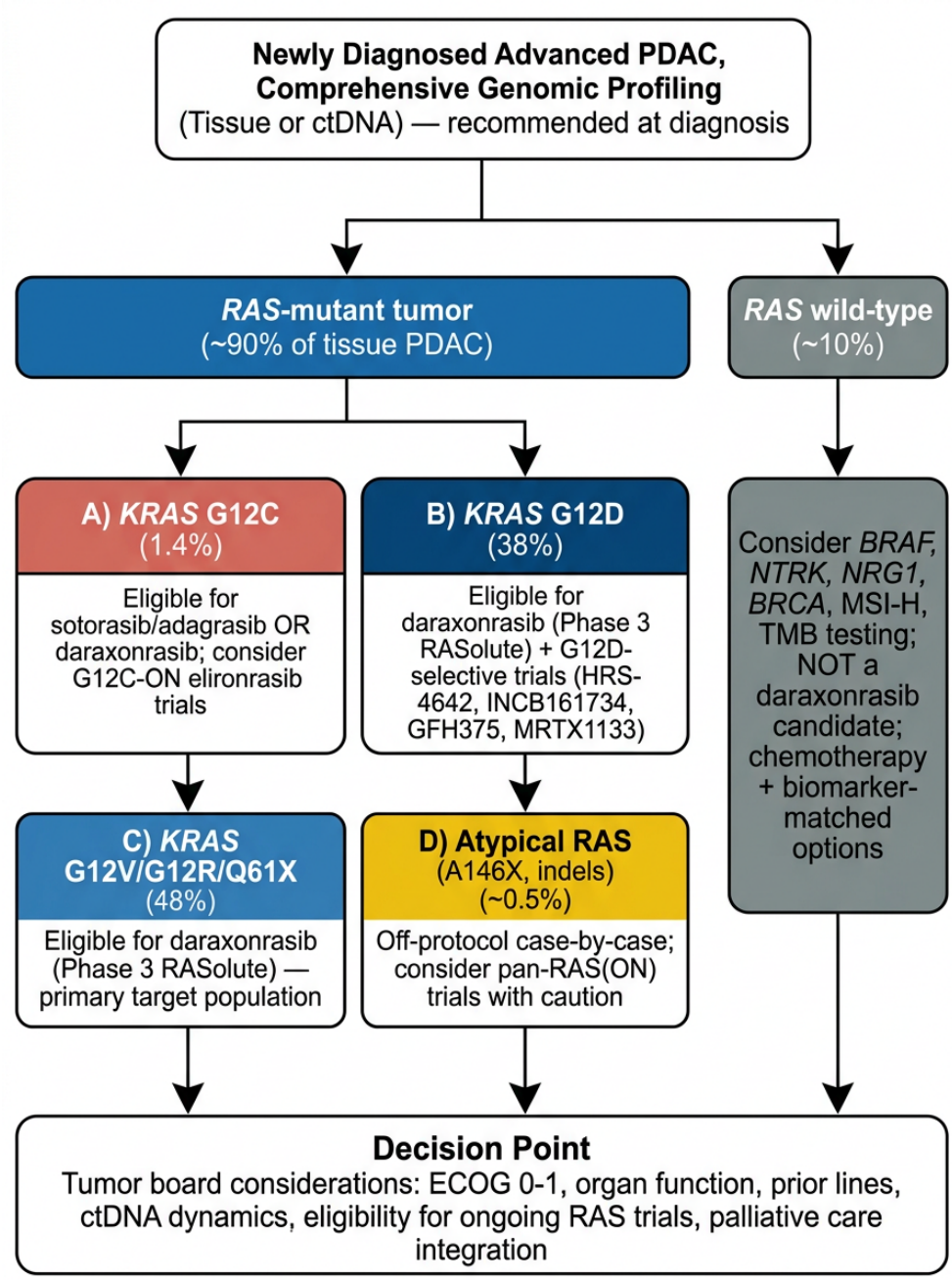


Figure 6: Tumor-board triage algorithm for advanced PDAC. Comprehensive RAS genomic profiling (tissue or ctDNA) at diagnosis feeds into one of four mutation classes: G12C (rare, G12C-selective *or* daraxonrasib eligible), G12D (38% of PDAC, pan-RAS(ON) and G12D-selective trials), G12V/G12R/Q61X (collectively 48%, primary daraxonrasib target population), and atypical RAS variants (A146X, in-frame indels; off-protocol consideration). Wild-type tumors should be tested for BRAF/NTRK/NRG1/BRCA/MSI-H/TMB and are *not* daraxonrasib candidates.

4 Daraxonrasib clinical data in PDAC

4.1 Phase 1/2 RMC-6236-001 (NCT05379985)

The pivotal Phase 1/2 monotherapy trial (RMC-6236-001; NCT05379985 [Revolution Medicines, Inc., 2022]) enrolled 168 previously treated patients with metastatic PDAC harboring activating RAS mutations at codons 12, 13 or 61 (any RAS family member). The recommended Phase 2 dose was 300 mg orally once daily, selected on the basis of PK/PD modelling and target-engagement biomarkers including circulating tumor DNA (ctDNA) dynamics.

Pivotal efficacy was reported by Wolpin et al. in the *NEJM* (May 2026) [Wolpin et al., 2026]:

- Among 38 patients with RAS G12/G13/Q61 mutations at ≥300 mg, **objective response rate (ORR) was 29% (95% CI 15–46%)**.
- In the 26-patient 2L RAS-G12 subgroup, **ORR 35% (95% CI 17–56%)**.
- Median duration of response: **8.2 months** (95% CI 3.8–8.8).
- Median PFS: **8.1–8.5 months**.
- Median OS: **15.6 months** (all-RAS) and **13.1 months** (G12 subgroup)—roughly double the ∼6–7 month historical benchmark for second-line PDAC chemotherapy.
- Biomarker signal: >50% ctDNA reduction in 93% of 68 evaluable patients; complete molecular response in 47%.

The safety profile included grade ≥3 treatment-related adverse events (TRAEs) in 30%, dominated by rash, diarrhea, nausea, fatigue and stomatitis—a class of toxicity consistent with the expected on-target pharmacology of RAS/MAPK pathway inhibition [Wolpin et al., 2026, 2025].

4.2 Phase 3 RASolute-302 (NCT06625320)

The pivotal Phase 3 RASolute-302 trial (NCT06625320) randomized 500 previously treated metastatic PDAC patients (any RAS hotspot at codons 12, 13 or 61) to daraxonrasib 300 mg monotherapy vs. investigator's choice chemotherapy (gemcitabine + nab-paclitaxel, liposomal irinotecan + 5-FU/leucovorin, FOLFIRINOX components, or oxaliplatin-based regimens) [Revolution Medicines, Inc., 2024]. The topline announcement (Revolution Medicines, April–May 2026) reported [Revolution Medicines, 2026]:

- **Median OS 13.2 vs. 6.7 months; HR 0.40 ($p < 0.0001$)**—a near-doubling vs. standard-of-care chemotherapy.
- Statistically significant PFS benefit.
- Safety profile consistent with Phase 1/2.
- FDA "safe-to-proceed" for expanded access (May 2026); registrational filing anticipated 2026–2027.

The HR of 0.40 is among the largest magnitudes ever reported in metastatic PDAC. For context, the survival hazard ratios in the landmark first-line trials were ∼0.57 (FOLFIRINOX vs. gemcitabine [Conroy et al., 2011]), ∼0.72 (Gem/nab-P [Von Hoff et al., 2013]) and ∼0.84 (NALIRIFOX [Wainberg et al., 2023]); all of those compared chemo regimens to chemo regimens, not a targeted oral monotherapy to chemo.

4.3 Limitations and unknowns

The Phase 3 readout to date is by press release and ASCO-level abstracts; full peer-reviewed Phase 3 publication is anticipated in the second half of 2026. Median follow-up at the interim analysis was relatively short, and overall-survival data may continue to mature. Direct comparisons with first-line chemotherapy combinations (FOLFIRINOX/NALIRIFOX) and head-to-head data against G12D-selective inhibitors are not yet available. The 30% grade $\geq$3 TRAE rate indicates the drug is not trivially well tolerated, and the on-target toxicity of MAPK inhibition (rash, diarrhea, mucositis) will need attentive supportive care.

5 The parallel and follow-on trial landscape

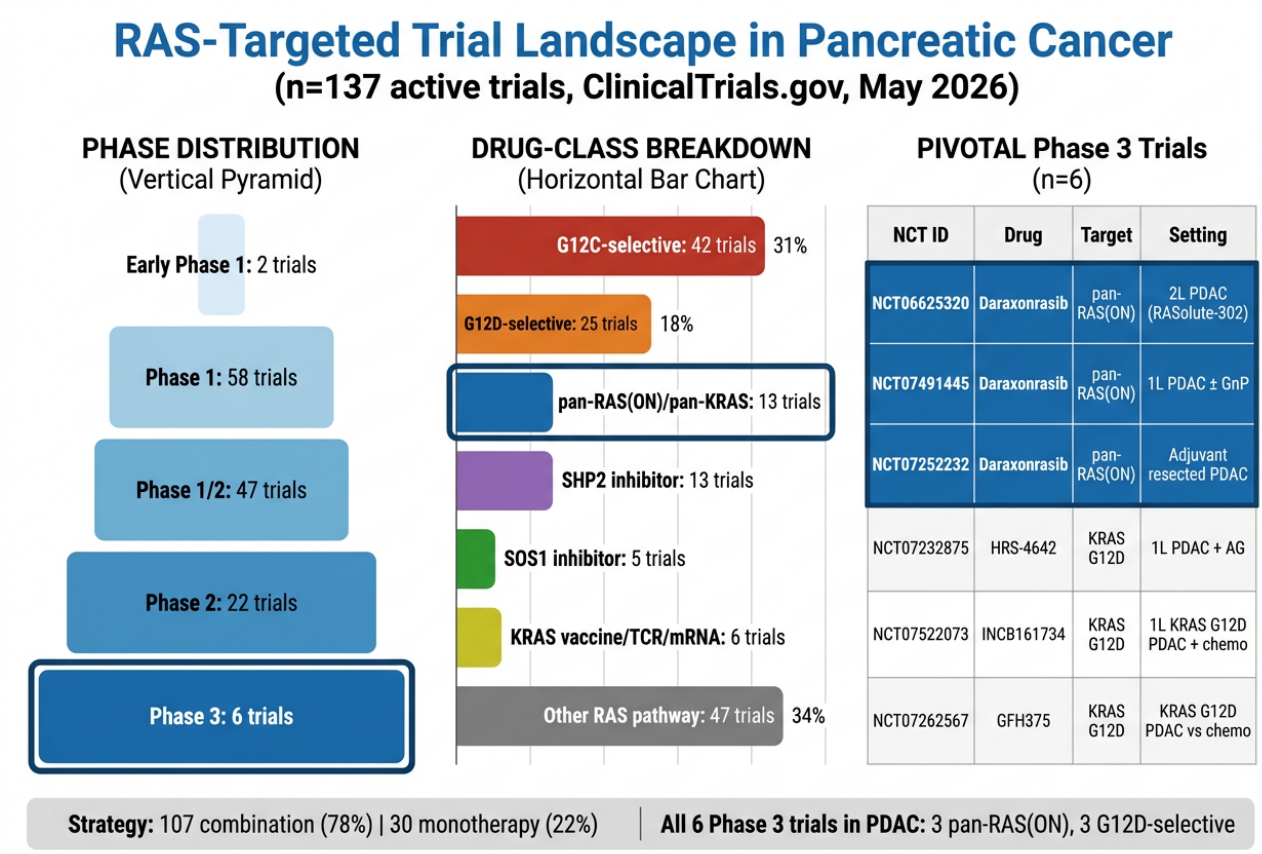


Figure 7: Pancreatic-relevant RAS-targeted trial landscape (May 2026; $n = 137$ active trials, ClinicalTrials.gov). Left, phase pyramid (58 Phase 1, 47 Phase 1/2, 22 Phase 2, 6 Phase 3). Center, drug-class breakdown (G12C 42, G12D 25, SHP2 13, pan-RAS(ON) 13, KRAS vaccine/TCR 6, SOS1 5, other 47). Right, the six pivotal Phase 3 trials—all in PDAC: three daraxonrasib programs (highlighted) and three G12D-selective programs.

5.1 Phase 3: pan-RAS(ON) anchors the late-stage portfolio

ClinicalTrials.gov queried in May 2026 returns six Phase 3 RAS-targeted trials, *all* in pancreatic cancer (Table 3). Three test daraxonrasib across distinct PDAC settings (2L+, 1L combination, and adjuvant), and three test G12D-selective small molecules in the first-line setting.

Table 3: Six pivotal Phase 3 RAS-targeted PDAC trials (May 2026).

NCT	Drug & sponsor	Target	Setting	Status
NCT06625320	**Daraxonrasib** (Revolution Medicines)	pan-RAS(ON)	2L+ metastatic PDAC vs. investigator's choice (RASolute-302)	Active, not recruiting [Revolution Medicines, Inc., 2024]
NCT07491445	**Daraxonrasib** (Revolution Medicines)	pan-RAS(ON)	1L metastatic PDAC: daraxonrasib ± gem/nab-P	Recruiting [Revolution Medicines, Inc., 2026]
NCT07252232	**Daraxonrasib** (Revolution Medicines)	pan-RAS(ON)	Adjuvant resected PDAC (monotherapy)	Recruiting [Revolution Medicines, Inc., 2025]
NCT07232875	HRS-4642 (Jiangsu HengRui)	KRAS G12D	1L metastatic PDAC: HRS-4642 + AG vs. placebo + AG	Not yet recruiting [Jiangsu HengRui Medicine Co., Ltd., 2025]
NCT07522073	INCB161734 (Incyte)	KRAS G12D	1L KRAS-G12D PDAC + chemo	Recruiting [Incyte Corporation, 2026]
NCT07262567	GFH375/VS-7375 (GenFleet)	KRAS G12D	KRAS-G12D PDAC vs. chemo	Not yet recruiting [Genfleet Therapeutics, 2025]

Daraxonrasib accounts for 3/6 pivotal trials and is the only agent to span 2L, 1L combination and adjuvant settings—a direct mechanistic echo of the eligibility analysis, since pan-RAS(ON) coverage of ∼89.6% of PDAC is plausibly the relevant addressable population across every line of therapy. The remaining three Phase 3 trials are all KRAS-G12D-selective programs in 1L PDAC, mirroring the G12D dominance (34–45% of PDAC) demonstrated in Section 3.

5.2 Phase 2: emerging classes

There are 22 Phase 2 trials, with the largest blocks being: G12C-selective combinations (8 trials), G12D-selective combinations (7 trials), and a mix of pan-RAS(ON) combination, G12D degrader monotherapy, personalized neoantigen vaccine, and various RAS-pathway combinations. These trials are largely confirmatory or combinatorial relative to the Phase 3 anchors.

5.3 Phase 1 / Phase 1/2: the pipeline

The bulk of the landscape sits in early-phase exploration: 58 Phase 1 and 47 Phase 1/2 trials. Notable themes:

- **Allele-selective small molecules.** G12C "ON-state" binders (e.g., elironrasib/RMC-6291), G12D-selective binders (MRTX1133, HRS-4642, INCB161734, ASP3082, GFH375), and the first G12D-selective degrader [Wang et al., 2022, Liu et al., 2024, Incyte Corporation, 2025, GenFleet Therapeutics, 2025].
- **Vertical pathway inhibition.** SHP2 inhibitors (13 trials; e.g., RMC-4630, TNO155) and SOS1 inhibitors (5 trials; e.g., BI-3406, MRTX0902) targeting RTK feedback reactivation [Chen et al., 2016, Hofmann et al., 2021, Fedele et al., 2021].
- **Combinatorial RAS(ON) regimens.** "Vertical" RAS-RAS combinations are already in the clinic, including the G12C-ON elironrasib + pan-RAS(ON) daraxonrasib doublet (NCT06128551 [Revolution Medicines, Inc., 2023a]) and the G12D-ON zoldonrasib (RMC-9805) + daraxonrasib doublet (NCT06162221 [Revolution Medicines, Inc., 2023b]). These bet that maximal upstream blockade reduces adaptive resistance.
- **Mutant-KRAS vaccines and adoptive cell therapy.** Personalized mRNA neoantigen vaccines (autogene cevumeran; Rojas *et al. Nature* 2023 [Rojas et al., 2023]) and off-the-shelf amphiphile peptide vaccines (ELI-002; Pant *et al. Nat. Med.* 2024 [Pant et al., 2024]) are being advanced primarily

in the adjuvant / minimal-residual-disease setting, where the immune system has the best chance of clearing residual disease.

5.4 Combination chemistry: 78% of all RAS trials are combos

107 of 137 trials (78%) are combination studies. Recurring partner classes include MEK/ERK inhibitors (trametinib, RMC-5552), SHP2/SOS1 inhibitors, EGFR antibodies (cetuximab, panitumumab), immune checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab) and chemotherapy backbones (gemcitabine + nab-paclitaxel; FOLFIRINOX components). The strategic intent is twofold: (a) deepen and prolong response by blocking RTK-mediated feedback reactivation of the MAPK pathway, and (b) keep the chemotherapy backbone available for patients whose disease is too aggressive for monotherapy.

6 Who is still left out?

The 89.6% headline is a ceiling, not a guarantee. The board should recognize five populations that remain unserved or under-served by the current RAS therapeutic toolkit.

6.1 RAS wild-type PDAC (∼10%)

Roughly 10% of tissue PDAC has no detectable activating RAS hotspot on routine NGS. This is a real biological category—these tumors are enriched for alternative drivers including BRAF V600E, NTRK1/2/3 fusions, NRG1 fusions, FGFR2 fusions, BRCA1/2 germline mutations, and rarely MSI-H/dMMR or high TMB [Singhi et al., 2019, Hall et al., 2025, Singhi et al., 2024]. These patients should be re-prioritized into the appropriate biomarker-matched trial or off-label targeted regimen and are *not* daraxonrasib candidates.

6.2 Atypical RAS variants (<1%)

A small but real fraction of PDAC tumors carry atypical RAS lesions that may not be engaged by daraxonrasib: A146T/V (GAP-independent), in-frame insertions/duplications distant from switch-II (e.g., D54_E62dup, E62_E63insDDTAGQE), and the rare A11_G12delinsGC. The pan-RAS(ON) tri-complex mechanism requires a topologically intact switch-I/II interface; mutations that disrupt that interface or shift GAP-dependence may escape inhibition. Affinity for many of these variants is uncharacterized. In our dataset, these collectively contributed 0.0–0.8% of PDAC per continent. Off-protocol case-by-case consideration is reasonable but should be flagged at the tumor board.

6.3 ctDNA-negative liquid biopsies (assay-driven, not biological)

The MSK ctDNA-only PDAC cohort ($n = 412$, 2025) returned 41% RAS positivity *not* because PDAC biology has changed in that population, but because cell-free DNA sensitivity is fundamentally lower than tissue sequencing—especially in early-stage or low-tumor-burden disease. A negative ctDNA RAS result in PDAC must be confirmed on tissue before excluding a patient from a daraxonrasib trial. This is a routine genomic-medicine pitfall that will become more common as ctDNA testing scales.

6.4 Frail patients (ECOG ≥2) and older adults

The pivotal RMC-6236-001 [Wolpin et al., 2026] and RASolute-302 [Revolution Medicines, 2026, Revolution Medicines, Inc., 2024] trials enrolled ECOG 0–1 patients. Roughly 30% experienced grade ≥3 TRAEs (rash, diarrhea, mucositis, fatigue) and the real-world tolerability in older or frail patients is

unknown. Clinicians should expect that some ECOG 2 patients will benefit (oral monotherapy compares favorably to FOLFIRINOX in this respect), but the data are not yet there to guide dosing in that population. A small expanded-access cohort and post-marketing safety reporting will fill this gap once the drug is approved.

6.5 Brain and leptomeningeal metastases

Daraxonrasib has limited blood–brain-barrier penetration in preclinical models without concurrent inhibition of efflux transporters (P-gp/BCRP), and the pivotal trials did not allow active CNS disease. Patients with brain or leptomeningeal metastases should be counseled accordingly and considered for whole-brain radiotherapy, neurosurgical management, or trials of CNS-penetrant RAS-pathway agents [Hallin et al., 2020, Bekaii-Saab et al., 2023].

6.6 Frontline (1L) and adjuvant disease—data are still maturing

The pivotal Phase 3 readout (RASolute-302) is in the second-line+ setting. The 1L combination Phase 3 (NCT07491445 [Revolution Medicines, Inc., 2026]) testing daraxonrasib ± gemcitabine + nab-paclitaxel is just opening enrollment; the adjuvant Phase 3 (NCT07252232 [Revolution Medicines, Inc., 2025]) in resected PDAC monotherapy is similarly early. Until those read out (anticipated 2028–2029), 1L metastatic and adjuvant patients will need to be matched to existing chemotherapy standards (FOLFIRINOX/NALIRIFOX/Gem-nabP [Conroy et al., 2011, Von Hoff et al., 2013, Wainberg et al., 2023]) or to a clinical trial.

6.7 Resistance: not "if" but "when"

Although the duration-of-response (8.2 mo) is the longest reported in advanced PDAC outside surgical resection, acquired resistance is inevitable and the mechanisms are emerging:

- RTK-driven reactivation of MAPK signaling (EGFR, HER2, MET, FGFR3) bypassing RAS—hence the SHP2/SOS1 combination trials [Fedele et al., 2021, Hofmann et al., 2021, Chen et al., 2016];
- Secondary RAS mutations and amplifications [Kim et al., 2024];
- MYC amplification observed in preclinical resistant lines [Wasko et al., 2024];
- Pathway reprogramming via TEAD/YAP, mTOR, and metabolic adaptation.

A practical implication is that ctDNA-guided rebiopsy at progression will become standard for these patients to triage them to the next mechanistically rational combination or sequential single-agent.

7 Practical recommendations for the tumor board

One-page checklist for the next PDAC tumor board

Diagnostic workup

1. Comprehensive genomic profiling (CGP) at diagnosis for every advanced PDAC, on tissue when available; ctDNA acceptable as adjunct or when tissue is insufficient.
2. CGP panel must cover KRAS, NRAS and HRAS at codons 12, 13, 61 *and* A146; report the *specific allele* to the board.
3. Confirm a negative ctDNA RAS result on tissue before excluding a patient from a RAS-targeted option.

Triage

1. **Any RAS hotspot at codons 12, 13, or 61 (any RAS family member):** eligible in principle for daraxonrasib or relevant RAS trial. In the 2L setting this is now an evidence-based standard option following the RASolute-302 readout; await FDA labeling for first line.
2. **KRAS G12C (1.4%):** eligible for daraxonrasib *or* sotorasib/adagrasib; consider G12C-ON elironrasib (RMC-6291) trials or G12C+pan-RAS combination trials.
3. **KRAS G12D (38%):** eligible for daraxonrasib trials *and* G12D-selective trials (HRS-4642, INCB161734, GFH375, MRTX1133 programs).
4. **KRAS G12V/G12R/Q61X (48%):** primary daraxonrasib target population; few alternative selective agents at this time.
5. **Atypical RAS (A146X, indels):** off-protocol case-by-case; pan-RAS(ON) trials may consider with caution.
6. **RAS wild-type (∼10%):** screen for BRAF, NTRK, NRG1, BRCA, FGFR2, MSI-H, TMB; *not* a daraxonrasib candidate.

Practical caveats

1. Expect grade ≥3 TRAEs in ∼30%; counsel for rash, diarrhea, mucositis, fatigue; have supportive-care plan in place before initiation.
2. Pivotal data are in ECOG 0–1; consider performance status and organ function carefully for ECOG 2.
3. Active CNS disease is not addressed by daraxonrasib; manage with local therapy first.
4. Plan for ctDNA monitoring at 8–12 week intervals during therapy.

8 Conclusion

Daraxonrasib is the first targeted oral agent to roughly double overall survival in a Phase 3 metastatic-PDAC trial. Its biology is unusually well matched to its target population: a pan-RAS(ON) tri-complex mechanism that engages ∼89.6% of tissue PDAC by leveraging the abundant chaperone cyclophilin A to recognize the GTP-bound active state of any RAS hotspot at codons 12, 13 or 61. The eligible population is roughly 60–90× larger than that of the legacy KRAS-G12C(OFF) covalent inhibitors sotorasib and adagrasib (1.4% of PDAC). Three of the six pivotal Phase 3 RAS trials in PDAC are daraxonrasib programs spanning 2L, 1L and adjuvant settings; the remaining three are KRAS-G12D-selective programs mirroring G12D's 38% dominance in PDAC.

Practical implementation requires comprehensive RAS genomic profiling at diagnosis, attention to supportive care for on-target MAPK toxicity, and ctDNA-guided rebiopsy at progression to triage resistance. A small but important fraction of patients—RAS wild-type, atypical RAS variants, frail patients, CNS metastases—will remain under-served and will need biomarker-matched or supportive-care

alternatives. The clinician's question over the next 12–18 months is shifting from "which chemotherapy backbone?" to "which RAS variant, and which RAS-targeted strategy?".

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