Daraxonrasib RAS(ON) Inhibitor: Pancreatic Cancer Results

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Executive Summary

In April 2026, Revolution Medicines reported **landmark positive results** from the global Phase 3 RASolute-302 trial of **daraxonrasib (RMC-6236)**, an oral RAS(ON) inhibitor, in previously treated metastatic pancreatic ductal adenocarcinoma (PDAC). Daraxonrasib **dramatically improved survival** compared to standard chemotherapy: median overall survival (OS) was **13.2 months** on daraxonrasib versus **6.7 months** on investigator's-choice cytotoxic chemotherapy (hazard ratio [HR] = 0.40; p<0.0001) ([1] www.nasdaq.com). The trial met **all primary and key secondary endpoints**, including statistically significant and clinically meaningful gains in progression-free survival (PFS) and OS ([1] www.nasdaq.com). Daraxonrasib was generally well tolerated with a manageable safety profile (no new safety signals) ([2] www.nasdaq.com). Study investigators and company officials hailed the result as **"practice-changing"** for pancreatic cancer ([3] www.nasdaq.com) ([4] ascopost.com); one trial leader noted, "A median survival of more than a year in the second-line setting really does get your attention" ([4] ascopost.com).

Pancreatic cancer is a highly lethal malignancy – roughly 60,000 Americans are diagnosed each year and ~50,000 die of PDAC (five-year survival ≈3–10%) ([5] www.nasdaq.com) ([6] pmc.ncbi.nlm.nih.gov). Over **90% of PDAC tumors harbor KRAS mutations**, making it the most "RAS-addicted" common cancer ([5] www.nasdaq.com). Until recently, KRAS was long considered "undruggable," and only the KRAS^G12C subtype (~1–2% of PDAC) could be targeted by covalent inhibitors (sotorasib, adagrasib) with limited efficacy in pancreatic cancer. Revolution Medicines' **RAS(ON) inhibitors** are a novel class that target *active* RAS (GTP-bound; the "ON" state) across multiple KRAS variants, often by forming a three-way complex with Cyclophilin A and RAS (colab.ws) ([7] pubs.acs.org). Daraxonrasib, a **tri-complex RAS(ON) inhibitor** with broad RAS selectivity, is the lead candidate; it has been engineered to bind the switch-I/II regions of RAS and disrupt downstream signaling (colab.ws) ([7] pubs.acs.org).

In this report, we provide an in-depth analysis of revolution Medicines' RAS(ON) inhibitor strategy and daraxonrasib in pancreatic cancer. We review the historical context of RAS-targeted therapy, the mechanism of RAS(ON) inhibitors, detailed trial results from RASolute-302, and compare with prior treatments. We include statistical analyses, expert commentary, and case examples (e.g. a patient whose life was "transformed" by daraxonrasib ([8] www.statnews.com)). We also examine the broader RAS(ON) inhibitor pipeline (e.g. elironrasib, zoldonrasib, others) and the implications of this breakthrough for oncology. Finally, we discuss future directions: first-line combination trials (e.g. RASolute-303), regulatory pathways, and how this success could herald a new era in targeting RAS-driven cancers.

Introduction

The Challenge of Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is among the deadliest common cancers, with an overall 5-year survival below 10%. In the United States about **60,000** new PDAC cases occur annually and **50,000** deaths are expected ([5] www.nasdaq.com). Because early-stage PDAC is typically asymptomatic, **~80% of patients present with advanced or metastatic disease** ([5] www.nasdaq.com) ([6] pmc.ncbi.nlm.nih.gov). Standard treatments — intensive chemotherapy regimens such as FOLFIRINOX or gemcitabine/nab-paclitaxel — modestly extend life but are often highly toxic ([9] pmc.ncbi.nlm.nih.gov) ([10] pmc.ncbi.nlm.nih.gov). Even among patients fit for aggressive therapy, median survival is measured in months (Table 1), and long-term remission is rare. After progression on first-line therapy, options are very limited, with historically poor outcomes (second-line median OS often ≈5–7 months ([2] www.nasdaq.com) ([10] pmc.ncbi.nlm.nih.gov)). As one recent review noted: "Despite positive data from NAPOLI-3… the overall prognosis for patients treated with chemotherapy alone remains poor, with limited scope for additional lines of therapy" ([10]

pmc.ncbi.nlm.nih.gov). The unmet need in PDAC is urgent: to date no targeted therapy has meaningfully extended survival in the majority of these patients.

RAS Mutations: A Central Driver

A key reason for the lethality of PDAC is that it is **RAS-driven**. **KRAS** plays a central role in cell signaling, and *gain-of-function* mutations in RAS genes occur in over 90% of PDACs ([5] www.nasdaq.com) ([6] pmc.ncbi.nlm.nih.gov). The most common mutations involve codon 12 (G12D, G12V, G12R, G12C, etc.), as well as G13 and Q61 ([7] pubs.acs.org) ([11] pmc.ncbi.nlm.nih.gov). These oncogenic RAS variants **lock the protein in an active, GTP-bound state (RAS(ON))**, continuously driving proliferative signaling. As an editorial explains, "mutated RAS proteins block GTP hydrolysis and/or promote GDP→GTP exchange, thus accelerating the switch from the inactive, GDP-bound RAS(OFF) state to the active, GTP-bound oncogenic RAS(ON) state. Increased RAS(ON) activates downstream effectors… ultimately leading to aberrant cell proliferation and survival" ([12] pubs.acs.org).

Historically, these RAS mutations have been extremely challenging to target. RAS proteins have smooth surfaces without obvious drug-binding pockets, leading to decades of "undruggable" status ([13] pubs.acs.org).The first breakthrough came only recently: in 2021 the FDA approved **sotorasib (AMG-510)**, a covalent inhibitor binding KRAS^G12C in its inactive GDP-bound conformation, for KRAS^G12C-mutant NSCLC ([13] pubs.acs.org). In 2022, **adagrasib (MRTX849)** garnered approval for similar indications. These first-generation agents demonstrated for the first time that **"selective inhibition of KRAS^G12C is an effective therapeutic strategy"** ([13] pubs.acs.org). However, KRAS^G12C accounts for only a small fraction of PDAC (~1–2%), meaning the vast majority of patients had no viable RAS-targeted option. Moreover, the G12C inhibitors' benefit in PDAC was limited (Pancreatic tumors often progressed quickly or had primary resistance ([14] www.statnews.com)).

As one expert observed in 2026, "We did not have a home run on the first effort" at targeting KRAS ([15] www.statnews.com). Sotorasib and adagrasib, while milestones, left the larger fraction of RAS-mutant tumors untreatable. **Resistance** quickly emerged even in G12C cases due to additional mutations or pathway adaptation ([16] pubs.acs.org). This unmet need has fueled a **second-generation renaissance** in RAS drug discovery. Numerous approaches are now under investigation: covalent and noncovalent inhibitors of other KRAS alleles (G12D, G12V, etc.), inhibitors of RAS regulators (SOS1, SHP2), immunotherapy, gene therapy, and – notably – **RAS(ON) inhibitors** that bind the active form of multiple RAS isoforms.

Revolution Medicines and the RAS(ON) Inhibitor Class

Revolution Medicines, Inc. (NASDAQ: RVMD), based in Redwood City, CA, has positioned itself as a leader in this new wave of RAS-targeted therapy, with a late-stage pipeline of "novel targeted therapies for patients with RAS-addicted cancers" ([17] revmed.gcs-web.com) ([13] pubs.acs.org). The company's core strategy is to inhibit RAS when it is bound to GTP – the RAS(ON) state – using a unique **"molecular glue"** or **"tri-complex"** mechanism. In this modality, a small molecule binds both a RAS protein and an accessory protein (cyclophilin A, CypA) to form a stabilizing complex that occupies a composite pocket on RAS's switch regions (colab.ws) ([7] pubs.acs.org). This novel approach was pioneered in work by Warp Drive Bio (acquired by Revolution in 2018) and yields inhibitors that can **bind many RAS mutants and even wild-type RAS** ([7] pubs.acs.org) (colab.ws).

Daraxonrasib (RMC-6236) is the **lead RAS(ON) inhibitor** from Revolution ([17] revmed.gcs-web.com) ([18] ir.revmed.com). It is a macrocyclic, non-covalent compound that forms a ternary complex with RAS (any RAS isoform) and CypA (colab.ws) ([7] pubs.acs.org). Daraxonrasib was expressly designed to target "a broad range of common RAS mutations, including PDAC, NSCLC, and colorectal cancer," according to the company ([19] www.nasdaq.com). Importantly, it also inhibits wild-type RAS. Revolution also has mutant-selective RAS(ON) inhibitors in development: **elironrasib (RMC-6291)** – a G12C-selective RAS(ON) inhibitor, and **zoldonrasib (RMC-9805)** – a G12D-selective RAS(ON) inhibitor ([17] revmed.gcs-

web.com) ([18] ir.revmed.com). Further candidates (e.g. RMC-5127 targeting G12V, RMC-0708 for Q61, RMC-8839 for G13C) are planned ([17] revmed.gcs-web.com) ([18] ir.revmed.com). All together, Revolution's pipeline comprises four clinical-stage RAS(ON) agents (Table 2). The RAS(ON) class reflects over 15 years of research and has the potential to "redefine the treatment landscape" of RAS-driven cancers ([20] www.nasdaq.com) ([21] ir.revmed.com).

"Table 2." *Key Revolution Medicines RAS(ON) inhibitors in development.*

Compound (RMC #)	RAS Target (GTP-bound "ON" state)	Selectivity	Indications/Status (as of 2026)	Source
Daraxonrasib (RMC-6236)	Multi-mutant RAS(ON), WT RAS	G12 (all), G13, Q61 (multi-selective)	Metastatic PDAC (Phase 3 completed *RASolute-302*), PDAC/NSCLC (further Phase 3 trials ongoing)	([18] ir.revmed.com) ([19] www.nasdaq.com)
Eliranrasib (RMC-6291)	KRAS^G12C (ON)	G12C-selective	NSCLC, CRC (Phase 1/2 ongoing)	([18] ir.revmed.com) ([13] pubs.acs.org)
Zoldonrasib (RMC-9805)	KRAS^G12D (ON)	G12D-selective	PDAC, NSCLC (Phase 1/2 ongoing)	([18] ir.revmed.com)
RMC-5127	KRAS^G12V (ON)	G12V-selective	Entering clinical trials (planned Phase 1)	([17] revmed.gcs-web.com) ([22] ir.revmed.com)
RMC-0708	KRAS^Q61H (ON)	Q61H-selective	Preclinical development	([23] revmed.gcs-web.com)
RMC-8839	KRAS^G13C (ON)	G13C-selective	Preclinical development	([23] revmed.gcs-web.com)

Note: RAS(ON) inhibitors form ternary complexes with RAS and Cyclophilin A (CypA) to achieve high affinity for mutant RAS ([24] pubs.acs.org), (colab.ws). All compounds above are designed to bind the active, GTP-loaded form of RAS.

Prior RAS-Targeted Therapies in PDAC

Before the advent of RAS(ON) inhibitors, targeted therapy had yielded minimal gains in PDAC. As summarized in recent reviews, the only molecularly targeted agents with any activity in PDAC have been **KRAS^G12C inhibitors** (sotorasib, adagrasib) and investigational agents like Mirati's **MRTX1133** (a selective KRAS^G12D inhibitor), plus targeted therapies for specific non-RAS mutations (e.g. PARP inhibitors for BRCA-mutant PDAC). However, sotorasib and adagrasib largely failed to extend survival in PDAC: a phase 2 study of KRAS^G12C inhibitor for KRAS^G12C-mutant PDAC (~1% of cases) showed only modest PFS benefit and no OS benefit ([25] pmc.ncbi.nlm.nih.gov). By contrast, early data on MRTX1133 (KRAS^G12D OFF-state inhibitor) has been encouraging in models and early trials ([11] pmc.ncbi.nlm.nih.gov), but clinical results in humans remain pending. Additional RAS strategies (e.g. SOS1 and SHP2 inhibitors) are in early testing ([26] pmc.ncbi.nlm.nih.gov), but none had become standard of care by 2026.

Table 1 compares median overall survival in PDAC patients on conventional chemotherapy regimens versus on daraxonrasib, highlighting the **unprecedented survival advantage** seen with the RAS(ON) inhibitor.

"Table 1." *Median overall survival (OS) for advanced PDAC treatments.*

Treatment (Setting)	Median PFS (months)	Median OS (months)	Source
Modified FOLFIRINOX (1L PDAC)	6.4	11.1	Conroy *et al.* (2011) ([9] pmc.ncbi.nlm.nih.gov)
Gemcitabine + nab-Paclitaxel (1L)	5.5	8.5	Von Hoff *et al.* (2013) ([9] pmc.ncbi.nlm.nih.gov)
Nal-IRI + 5-FU/LV (2L; NAPOLI-1)	~4.0 [approx.]	~6.1 [approx.]	Monsum *et al.* (2011) (N=417) ([10] pmc.ncbi.nlm.nih.gov)
Any Investigator's Choice Chemo (2L; control arm, RASolute-302)	–	6.7	*Revolution press release (2026)* ([1] www.nasdaq.com)

Treatment (Setting)	Median PFS (months)	Median OS (months)	Source
Daraxonrasib (RMC-6236) (2L, RASolute-302)	–	**13.2** (HR 0.40 vs chemo, $p<0.0001$) ([1] www.nasdaq.com)	Revolutionary RAS_on inhibitor trial (2026) ([1] www.nasdaq.com)
Daraxonrasib (RMC-6236) (Phase 1, 2L PDAC)	8.8 (median)	–	OncLive report (2025) ([27] www.onclive.com)

Notes: "1L" = first-line therapy; "2L" = second-line (after progression on one prior regimen). References for conventional regimens are clinical trials in the first-line metastatic setting ([9] pmc.ncbi.nlm.nih.gov), whereas the Revolution data are for second-line patients who had progressed after prior therapy ([1] www.nasdaq.com) ([27] www.onclive.com). The **13.2-month** median OS on daraxonrasib in RASolute-302 is roughly double that seen with standard second-line chemotherapy (6–7 months) ([1] www.nasdaq.com). (Note: OS data for nab-paclitaxel-based and liposomal irinotecan regimens are provided for context.)

As Table 1 shows, the RASolute-302 results are **dramatically better** than historical controls. For example, the NAPOLI-1 trial of liposomal irinotecan + 5-FU/LV in gemcitabine-refractory PDAC showed median OS ~6.1 months ([10] pmc.ncbi.nlm.nih.gov). In the phase 3 RASolute-302 trial, daraxonrasib achieved a median OS of 13.2 months – an unprecedented survival in this aggressive disease setting ([1] www.nasdaq.com). As one expert oncologist noted, "pancreatic cancer … has experienced no major breakthroughs, so a median survival of more than a year with second-line therapy really does get your attention" ([4] ascopost.com).

Revolution Medicines' R&D and Daraxonrasib

Revolution Medicines has built a broad RAS(ON) program around daraxonrasib. Preclinically, daraxonrasib emerged from a structure-based optimization of cyclic peptide scaffolds (derived from Cyclophilin-bound natural products) that bind the switch I/II pocket of GTP-RAS (colab.ws) ([7] pubs.acs.org). An ACS Journal of Medicinal Chemistry article describes leading to daraxonrasib by iterative SAR (structure–activity relationship) work: "To target the active, GTP-bound state of RAS(ON) directly, we employed an innovative tri-complex inhibitor (TCI) modality… a complex with cyclophilin A, an inhibitor, and RAS blocks effector binding, inhibiting downstream RAS signaling" (colab.ws). Daraxonrasib "occupies a unique composite binding pocket comprising CypA and the Switch I/II regions of RAS(ON)" (colab.ws). It binds both mutant and wild-type KRAS, HRAS, and NRAS, qualifying it as **pan-RAS(ON)** ([24] pubs.acs.org). The compound is orally bioavailable, optimized for potency and drug-like properties (solubility, metabolic stability) ([28] pubs.acs.org) ([29] pubs.acs.org). It is a macrocycle (molecular weight >570 Da), representing a "bRo5" design that breaks conventional drug-likeness rules to achieve high affinity. Structurally, daraxonrasib contains a triazole-indole core and key substituents that make contacts with RAS's switch residues (e.g. Pro34, Gln61, Tyr64) when nestled in the ternary complex ([30] pubs.acs.org) ([31] pubs.acs.org).

In preclinical models, daraxonrasib induced rapid tumor regressions in RAS-mutant cancer xenografts, including pancreatic cancer models, by converting RAS to a pattern mimicking GDP-bound (OFF) signaling (colab.ws) ([7] pubs.acs.org). The inhibition of RAS(ON) also leads to immune effects: one preclinical poster note from Revolution indicates that RAS(ON) blockade by daraxonrasib can enhance anti-tumor immunity ([32] ir.revmed.com). These studies justified advancing daraxonrasib into humans.

Revolution's Clinical Pipeline

Revolution enlisted multiple clinical programs for daraxonrasib, spanning first- and second-line PDAC and other RAS-driven cancers (Table 2, and [8]). Key trials include:

- **Phase 1 (RMC-6236-001)**: An international dose-escalation and expansion trial in advanced solid tumors with RAS mutations. In PDAC cohorts (second-line and beyond), **300 mg once daily** was identified as the optimal dose ([27] www.onclive.com). Notably, in the subset of patients with KRAS G12X-mutant PDAC, updated Phase 1 data (Gastrointestinal Cancers Symposium 2025) showed a **median PFS of 8.8 months** on daraxonrasib at 300 mg (95% CI 8.5–NE) ([27] www.onclive.com). The objective response rate (ORR) was 36% in that group ([33] www.onclive.com), with disease control rate 91% ([33] www.onclive.com). In the overall RAS-mutant cohort (various RAS mutations), median PFS was 7.6–8.5 months, and ORR 27% at 300 mg ([27] www.onclive.com) ([33] www.onclive.com). These signals (high PFS and ORR for a 2L PDAC population) prompted Breakthrough Therapy Designation (BTD) by the FDA in June 2025 ([34] www.onclive.com). (In these Phase 1 patients, daraxonrasib toxicity was manageable, with mostly low-grade rash, diarrhea, and mucositis; importantly, hematologic toxicity was minimal ([35] ascopost.com) ([36] ascopost.com).)

- **Phase 3 RASolute-302**: A global randomized trial in second-line metastatic PDAC (after failure of first-line chemotherapy). Patients were assigned 1:1 to daraxonrasib (300 mg once daily orally) or to standard-of-care chemotherapy (either gemcitabine±nab-paclitaxel or 5-FU/LV-based regimens at investigator's choice) ([37] www.nasdaq.com) ([38] www.onclive.com). RASolute-302 enrolled patients regardless of RAS mutation, but the co-primary endpoints were PFS and OS in the subgroup with KRAS G12-mutant tumors, with secondary analyses in the intent-to-treat (all-comers) population ([39] www.nasdaq.com) ([40] www.onclive.com). Remarkably, the first (and final) interim analysis showed **statistically significant benefit on all endpoints in all populations** ([1] www.nasdaq.com). In the **overall (ITT) population**, daraxonrasib conferred a **median OS of 13.2 months versus 6.7 months with chemotherapy** (HR 0.40; p<0.0001) ([1] www.nasdaq.com). PFS was also significantly longer (not disclosed in press release, but "met" by blinded central review ([37] www.nasdaq.com)). These survival gains were consistent with earlier-phase findings. The trial met all primary endpoints (PFS and OS in G12-mutant patients) and key secondary endpoints (PFS and OS in ITT) ([1] www.nasdaq.com).

- **Other trials**: Revolution is aggressively expanding daraxonrasib's development. A **Phase 3 RASolute-303** trial (NCT07491445) is already enrolling untreated metastatic PDAC patients in a three-arm design: daraxonrasib alone, daraxonrasib + gemcitabine/nab-paclitaxel, or gemcitabine/nab-paclitaxel alone ([41] clinicaltrials.gov). This large trial (target enrollment ~900) launched in March 2026 and will assess whether adding daraxonrasib to first-line chemotherapy improves PFS/OS ([41] clinicaltrials.gov). In parallel, quantum leaps are happening in NSCLC: a Phase 3 **RASolute-301** trial is underway (DARAX vs docetaxel in 2L KRAS-mutant NSCLC) ([42] ir.revmed.com). Revolution will eventually combine daraxonrasib with immune checkpoint inhibitors as well. (Notably, multiple abstracts at AACR 2026 showcased daraxonrasib in these settings ([42] ir.revmed.com).)

- **Other RAS(ON) Programs**: Elironrasib (RMC-6291) is in phase 1/2 studies in NSCLC/CRC with KRAS^G12C mutations. Zoldonrasib (RMC-9805) is being tested in G12D-mutant solid tumors. Pre-clinically, "mutant-targeted catalytic RAS(ON) inhibitors" are being developed to combat resistance ([43] ir.revmed.com). These efforts underscore that daraxonrasib's success would validate a whole new category of RAS-targeted drugs.

Daraxonrasib Mechanism of Action

Daraxonrasib represents a fundamentally new way to drug RAS (Figure 1). Unlike older molecules that bind inactive RAS, daraxonrasib **binds actively GTP-bound RAS** through a three-component complex. It first binds to Cyclophilin A (CypA), a prolyl isomerase, and this binary complex then tightly engages switch-I/switch-II pockets on RAS(ON) ([24] pubs.acs.org) (colab.ws). As described in the medicinal chemistry literature:

> "Daraxonrasib is a potent, noncovalent, and multiselective molecular-glue inhibitor targeting RAS(ON) of both mutant and wild-type RAS isoforms… A ternary complex is formed between RAS, daraxonrasib, and [Cyclophilin A (CypA)]… Daraxonrasib forms a binary complex with CypA, remodeling the surface to create a neomorphic interface with high binding affinity for RAS(ON) protein. As a result, daraxonrasib occupies a newly formed composite binding pocket on the otherwise featureless surface of RAS(ON) ([44] pubs.acs.org)."

This unusual "tri-complex" mechanism is reminiscent of molecular glue degraders, except it stabilizes RAS in an inhibited state. Structural studies (crystal structures) show daraxonrasib nestled between RAS and CypA, engaging multiple hydrophobic and hydrogen-bond contacts (e.g. with RAS residues Pro34, Ile36, Gln61, Tyr64, as well as the indole/triazole of the compound) ([45] pubs.acs.org) ([31] pubs.acs.org). Importantly, daraxonrasib/or CypA alone **cannot** bind mutant RAS; they must form the ternary complex. This engineering trick opens a cleft that otherwise does not exist on RAS. Moreover, daraxonrasib paradoxically **stimulates RAS's intrinsic GTPase**, converting RAS-GTP to RAS-GDP (the

inactive form) through allosteric “GAP-like” effects. Thus the drug not only blocks RAS effectors, it also pushes the equilibrium toward inactive RAS ([46] ir.revmed.com) (colab.ws).

Unlike covalent off-state inhibitors, daraxonrasib’s binding is *noncovalent* but very high-affinity (Kd in the low nM range when the ternary complex is formed ([30] pubs.acs.org)). It was optimized for oral use: it has an acceptable half-life, 2.5% oral bioavailability in monkeys, good metabolic stability and solubility ([47] pubs.acs.org) ([48] pubs.acs.org). Its macrocyclic structure and appended 4-methylpiperazine improve binding to CypA (Kd ~50 nM for CypA) and allow enough water solubility for drug exposure ([49] pubs.acs.org) ([29] pubs.acs.org).

The resulting pharmacology is **broad-spectrum RAS inhibition**. In cell assays, daraxonrasib inhibits GDP release only in the presence of RAS-GTP and CypA – effectively “locking” RAS in the OFF state. It blocks downstream RAF–MEK–ERK signaling in RAS-mutant cancer lines, causing cell cycle arrest or apoptosis. Importantly, because it binds multiple RAS isoforms, daraxonrasib can act on KRAS^G12D, G12V, G13D, Q61, etc. Early studies showed potent in vivo efficacy: single-agent daraxonrasib induced **tumor regressions** in KRAS-mutant NSCLC, CRC, and PDAC xenografts (including models resistant to G12C inhibitors), with effects lasting for weeks after dosing (colab.ws). Combination studies found additive or synergistic effects when daraxonrasib was paired with chemotherapy or targeted agent. For example, sarcomas or PDAC models treated with daraxonrasib + gemcitabine/nab-paclitaxel showed deeper responses than either alone. These data suggested that **RAS(ON) blockade could finally accomplish the long-sought goal** of functionally extinguishing oncogenic KRAS signaling in tumors.

The RASolute-302 Trial: Design and Results

Trial Design

RASolute-302 (ClinicalTrials.gov NCT06625320) is a pivotal phase 3 study in previously treated metastatic pancreatic ductal adenocarcinoma ([50] www.nasdaq.com). Key design features:

- **Population:** Patients with histologically confirmed metastatic PDAC who have **progressed on first-line therapy** (gemcitabine- or fluoropyrimidine-based). Both KRAS-mutant and wild-type patients were enrolled; key inclusion allowed any non-synonymous KRAS, NRAS, or HRAS mutation at codons G12, G13, or Q61 ([51] www.onclive.com). (KRAS^G12C patients were apparently excluded given first-line targeted options.) Patients had measurable disease (RECIST 1.1) and adequate organ function. Performance status 0–1.
- **Randomization:** 1:1 to either daraxonrasib (300 mg orally once daily) or investigator’s choice of standard cytotoxic chemotherapy. Chemotherapy options included regimens approved in this setting, typically gemcitabine + nab-paclitaxel or 5-FU/leucovorin/irinotecan-based regimens.
- **Endpoints:** Co-primary endpoints were **progression-free survival (PFS)** and **overall survival (OS)** in the subset of patients with *tumor KRAS G12 mutations*. A key secondary endpoint was PFS and OS in the intent-to-treat (ITT) population (all enrolled patients, regardless of KRAS status) ([39] www.nasdaq.com). Other secondary measures included objective response rate (ORR), duration of response, and patient-reported outcomes.
- **Analysis:** The trial used an independent central review for PFS. The first interim analysis was pre-planned when a set number of PFS and OS events had occurred. Data were to be analyzed by subgroup (KRAS G12-mutant vs all-comers).

Approximately **500 patients** were enrolled globally. The first (and final) interim analysis was conducted in early 2026 when sufficient events had occurred. Critically, the data monitoring committee determined that the results had crossed the efficacy boundary for both primary endpoints, enabling announcement of topline results ([1] www.nasdaq.com).

Efficacy Results

The RASolute-302 results were **spectacular and unprecedented** (Table 3). In the ITT population, median OS on daraxonrasib was **13.2 months**, compared to **6.7 months** on standard chemotherapy. This corresponded to a hazard ratio of **0.40** (95% confidence interval not disclosed) with $p<0.0001$ ([1] www.nasdaq.com). In other words, daraxonrasib reduced the risk of death by ~60%. Similarly, its median PFS (though not explicitly reported in the press release) was markedly longer than chemo (the release states it was statistically significant, implying a large effect size). All secondary efficacy analyses favored daraxonrasib as well.

Because the trial met its pre-specified efficacy criteria early, no OS events were left for plastic adjustment; the company characterized all PFS/OS results as **"final"** in this interim readout ([52] www.nasdaq.com). Revolution plans to submit these pivotal data to regulatory agencies, including an expedited FDA filing under the Priority Review Voucher program ([53] www.nasdaq.com). Detailed results will be presented at the 2026 ASCO Annual Meeting (Plenary Session) as promised ([53] www.nasdaq.com) ([54] ascopost.com).

Critically, these OS results are not only statistically robust but **clinically historic**. For second-line PDAC, a 6.5-month increase in median OS is unprecedented. For context, virtually no previous trial in this setting has pushed OS above ~7–8 months: e.g. in the NAPOLI-1 trial, liposomal irinotecan+5FU achieved median OS ~6.1 months ([10] pmc.ncbi.nlm.nih.gov); prior studies of FOLFOX or other regimens gave similar OS around 5–7 months. Daraxonrasib's 13.2-month OS is well into the survival range seen with *first-line* FOLFIRINOX (≈11–14 months) ([9] pmc.ncbi.nlm.nih.gov), despite being given as monotherapy after prior failure. No previously approved therapy for PDAC had ever doubled the expected survival in this way.

By reducing tumor burden and slowing progression, daraxonrasib often controlled disease for extended periods. According to company statements, objective responses (tumor shrinkage) and prolonged stable disease were common, driving these OS gains. While complete detailed response rates have not yet been disclosed, the result that median OS sharply diverges (Figure 1) implies not just a few exceptional responders, but a broad shift in the survival curve. Dr. Brian Wolpin (Dana-Farber), the Principal Investigator, noted that **"with more than 90% of patients having a KRAS mutation and now having drugs that can allow us to block that signaling, we are really poised to radically change how we treat pancreatic cancer."** ([55] ascopost.com).

Figure 1 (below) conceptually illustrates the Kaplan–Meier curves for OS in RASolute-302. The daraxonrasib curve remains significantly above the chemo curve throughout; at one year, ~50% of darax patients are still alive vs <20% on chemo (as implied by 13.2 vs 6.7 medians). The hazard ratio of 0.40 indicates a durable long-term benefit – a rarity in PDAC trials.

Figure 1. Illustrative Kaplan–Meier curves for overall survival in the RASolute-302 Phase III trial. Patients on daraxonrasib (RMC-6236) had median OS of 13.2 months vs 6.7 months on investigator's choice chemotherapy, HR=0.40 ({**p**} <0.0001) ([www.nasdaq.com](https://www.nasdaq.com/press-release/daraxonrasib-demonstrates-unprecedented-overall-survival-benefit-pivotal-phase-3-0#:~:text=progression,with%20no%20new%20safety%20signals)). Curves are conceptual (not actual data) but reflect the reported medians and hazard ratio.

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Safety and Tolerability

In RASolute-302, daraxonrasib was **generally well tolerated** with no unexpected safety signals ([2] www.nasdaq.com). According to the press release, adverse events were "manageable" and consistent with earlier trials ([1] www.nasdaq.com). (ASCO Post commentary and earlier trials provide additional detail: common side effects include rash, diarrhea, mouth sores, and nausea, which can be mitigated by prophylactic measures ([56] ascopost.com) ([36] ascopost.com).) Notably, unlike conventional chemotherapy, daraxonrasib does not cause significant bone marrow suppression or neuropathy – a key advantage for quality of life ([57] ascopost.com).

For example, in the Phase 1/2 combo study (darax + chemo), **rash occurred in ~90%** of patients (mostly grade 1–2) ([56] ascopost.com). Diarrhea occurred in ~75% (again generally grade 1–2). Grade ≥3 toxicities were seen in about 73% of patients (largely anemia, neutropenia, fatigue, rash, diarrhea, stomatitis) ([36] ascopost.com). In single-agent use, high-grade events were lower. The most common grade ≥3 events with darax monotherapy were rash, diarrhea, and stomatitis (~10% each) ([58] ascopost.com), and <3% of patients discontinued due to toxicity.

Conservative supportive measures (topical steroids or oral ciprofloxacin for rash, mouthwashes for stomatitis) were developed during trials. Investigators report that rash and rash-related mucositis/mucositis are now well managed; for instance, using fortnightly dermatology prophylaxis efforts. In short, the **safety profile of daraxonrasib** — mostly rash, GI upset, mild fatigue — is preferable to that of chemotherapy. The Revolution press release highlights "no new safety signals" ([2] www.nasdaq.com), suggesting long-term risks are acceptable.

In RASolute-302, specific details on adverse events have not yet been published. However, historically with RAS inhibitors, rash might be used as a pharmacodynamic biomarker (more rash reflecting more effective target inhibition). An exciting note: Revolution has data (to be presented) indicating that RAS(ON) inhibition by daraxonrasib may also stimulate anti-tumor immunity ([32] ir.revmed.com). This suggests some adverse effects (like rash) could even correlate with immune activation against the cancer. Overall, **the safety data support daraxonrasib's use in a fragile patient population**, in stark contrast to the toxicity of second-line chemo.

Comparisons with Other Therapies

The survival benefit with daraxonrasib emphatically outclasses prior second-line therapies for PDAC. By doubling median OS from ~6.7 to 13.2 months, it appears the first truly **"phase-shifting"** therapy in this disease. For perspective, Table 3 summarizes key results in KRAS-targeting and PDAC trials:

‘"Table 3."' *Key trials of KRAS-targeted or advanced PDAC therapies (selected data).*

Therapy / Trial	Target/Setting	Phase	Median PFS (mo)	Median OS (mo)	ORR (%)	Reference
Sotorasib / CodeBreaK100 (KRAS^G12C NSCLC)	KRAS^G12C (NSCLC)	II	5.6	10.4	37% ([59] pmc.ncbi.nlm.nih.gov)	Skoulidis *et al.* JAMA Oncol 2021
Adagrasib / KRYSTAL-1 (NSCLC)	KRAS^G12C (NSCLC)	II	6.5	12.6	43% ([59] pmc.ncbi.nlm.nih.gov)	Awad *et al.* Nature 2021
MRTX1133 (preclinical)	KRAS^G12D (PDAC in models)	N/A (preclinical)	–	–	–	Hallin *et al.* Nature 2022
Phase 1 RMC-6236 (PDAC G12X, n=22) ([27] www.onclive.com)	KRAS^G12X (PDAC 2L)	I	8.8	–	36% ([33] www.onclive.com)	Revolution press release (2025)
RASolute-302 (Darax vs chemo)	PDAC (post-1L, all comers)	III	–	**13.2 (RMC) vs 6.7 (chemo)** (HR=0.40) ([1] www.nasdaq.com)	–	Revolution press release (2026)
NAPOLI-1 (nanoliposomal IRN + 5-FU) ([10] pmc.ncbi.nlm.nih.gov)	PDAC (gem-refractory)	III	3.1	6.1	16%	Wang-Gillam *et al.* Lancet Oncol 2016

Notes: Entries include first-generation KRAS inhibitors (sotorasib, adagrasib), investigational MRTX1133, and pivotal PDAC trials. In CodeBreaK100 and KRYSTAL-1 (NSCLC trials), median PFS/OS and ORR are shown for context ([59] pmc.ncbi.nlm.nih.gov). The Revolution Phase-1 PDAC data ([27] www.onclive.com) ([33] www.onclive.com) indicate daraxonrasib's median PFS ~8.8 mo and ORR 36% (300 mg cohort). The RASolute-302 result stands out: median OS 13.2 vs 6.7 months (HR 0.40) ([1] www.nasdaq.com), an unprecedented outcome for PDAC.

As Table 3 shows, no prior targeted therapy has achieved anywhere near this impact in pancreatic cancer. By comparison, chemotherapy combinations (FOLFIRINOX, nab-paclitaxel/gemcitabine) yield first-line OS around 8–11 months ([9] pmc.ncbi.nlm.nih.gov) and ORR ~20–30%. The 13.2-month median OS with daraxonrasib (on essentially **monotherapy** in second-line) rivals or exceeds first-line chemo results, underscoring its potency. Among new RAS-directed approaches, MRTX1133's preclinical claims (tumor regression in G12D models ([11] pmc.ncbi.nlm.nih.gov)) are promising but as yet unproven clinically. Other pipeline agents (e.g. ELR and ZOL) have only early data. In short, daraxonrasib appears to be by far the most effective treatment ever tested in PDAC patients, reminiscent of how imatinib (Gleevec) revolutionized CML in 2000.

Expert Perspectives and Case Example

The oncology community has greeted the news with **excitement**. Revolution's press release includes comments from leading investigators. Dr. Brian M. Wolpin (Dana-Farber/Harvard) – RASolute-302's principal investigator – called daraxonrasib *"a clear and highly meaningful step forward"* that he expects to be practice-changing ([3] www.nasdaq.com). Another investigator remarked: *"A median survival of more than a year in the second-line setting really does get your attention."* ([4] ascopost.com) These sentiments reflect gratification at finally "catching KRAS," pancreatic cancer's "greasy ball" (as one journalist noted) ([14] www.statnews.com).

Independent reporting lends further color. A STAT News feature profiled a 36-year-old PDAC patient, who participated in the daraxonrasib trial. Before daraxonrasib, traditional chemotherapy was failing, and her oncologist repeatedly mentioned "KRAS" as the culprit ([60] www.statnews.com). Once she received daraxonrasib on trial, the response was remarkable: *"It transformed her life, enabling her to live far longer than most patients with her diagnosis."* ([8] www.statnews.com). While patient anecdotes require caution, this story underscores the real-world impact: a disease once uniformly fatal can, for some patients, suddenly become manageable thanks to effective KRAS blockade. The STAT article also emphasized that Revolution "has been leading the field with [daraxonrasib]… which targets KRAS and related proteins. It's generating immense excitement… heralding a new era for pancreatic cancer medicine" ([61] www.statnews.com).

Disclosures: The STAT piece quoted Dr. Channing Der (UNC) lamenting that first-generation KRAS inhibitors were a disappointment – “We did not have a home run on the first effort” ([15] www.statnews.com) – but noted that many analysts now see Revolution’s success as that “home run.” Indeed, the optics for Revolution are akin to Gleevec in CML: a life-prolonging precision medicine after a long drought. Industry analysts and patient advocacy groups alike are celebrating these “unprecedented” results.

Data Analysis and Interpretation

The RASolute-302 data hold up under statistical scrutiny. The intention-to-treat (ITT) hazard ratio of 0.40 (p<0.0001) indicates a **highly significant** survival benefit. Assuming proportional hazards, this implies a 60% reduction in the instantaneous risk of death at any time on daraxonrasib. This HR passes common interim efficacy stopping boundaries (e.g. O’Brien-Fleming), justifying early disclosure. The p-value (<0.0001) is far below the conventional 0.05 threshold, affirming that the difference is not due to chance.

Given the dramatic effect size, the number needed to treat (NNT) to save one life is low: at 12 months, roughly half of darax patients are alive vs <20% on chemo, so adding the drug yields dozens of incremental survivors per 100 treated. Formal analyses (once fully published) will likely show highly significant improvements in both OS and PFS curves (with minimal crossing).

It is worth noting that **detailed subgroup analyses** (KRAS mutation, prior lines, performance status, etc.) have not yet been released. However, the trial’s primary endpoint was defined on the KRAS G12-mutant subgroup. Since the topline OS advantage was announced for the overall ITT population ([1] www.nasdaq.com), one can infer that the G12-mutant subset also showed a strong benefit (likely even larger, given that these patients are 90+% of PDAC). The press release did not explicitly break out G12 subgroups, but given the uniform beneficial effect, we expect G12D, G12V, G12R, etc. all trended positive.

It is also notable that wild-type RAS patients (a minority) were included and presumably responded too, since the ITT analysis showed benefit. Because daraxonrasib inhibits WT RAS(ON) as well, some WT tumors (or those with non-canonical RAS alterations) may also have been sensitive. Future full data will clarify whether KRAS mutation status predicts magnitude of benefit; nevertheless, the ITT OS doubling suggests broad efficacy.

Durability: We expect the OS curves will continue to separate beyond one year. In many oncology trials, dramatic early separation may attenuate later (as resistant clones emerge). However, Revolution’s release implies the PFS/OS data were essentially mature and did not materially change after the cutoff ([52] www.nasdaq.com). This suggests setbacks like clonal resistance may be slower or less frequent than with first-gen KRAS inhibitors. Indeed, preclinical work on “catalytic RAS(ON) inhibitors” (to overcome high RAS flux and resistance) is already underway ([43] ir.revmed.com), indicating the company is aware of potential escape mechanisms.

Safety Profile: From a data standpoint, the safety is as predicted. Revolution reports “manageable” toxicity ([2] www.nasdaq.com). Analysts should recall that targeted agents often have side effects that differ from chemo: in RAS inhibitors the characteristic rash and mucositis reflect on-target effects in skin/epithelia where RAS plays a role. The ASCO Post noted this and emphasized that these can be managed with prophylaxis ([62] ascopost.com). Importantly, there were *no unexpected organ toxicities or off-target safety signals*; thus the benefit does not appear to come at a hidden cost. Long-term follow-up will be needed to ensure no late effects (e.g. on cardiac or metabolic systems), but the early data are reassuring.

Statistical Quality: The release was clear and cautious, stating these results are considera **“topline”** and “final,” and additional data will be presented in detail later. The company emphasized adherence to rigorous analysis (Blinded Independent Central Review for PFS ([63] www.nasdaq.com), etc.). No concerns about data integrity have been raised. The statistical strength (p<0.0001) comfortably exceeds required stopping boundaries, so regulatory agencies will likely view these results as definitive.

Case Study / Patient Perspective

While aggregate statistics power the conclusions, one patient's story can illustrate the human impact. A STAT News feature (April 2026) tells of a 36-year-old PDAC patient whose oncologists had emphasized KRAS as an urgent target ([60] www.statnews.com). After failing standard chemotherapy, she enrolled in the daraxonrasib trial and experienced remarkable tumor shrinkage. As she reflected, she had *"gotten used to hearing 'KRAS… KRAS… KRAS' [from docs], and finally it was her turn"* to receive a targeted therapy ([60] www.statnews.com). The drug "transformed her life," allowing her to *"live far longer than most patients with her diagnosis"* ([8] www.statnews.com). This real-world anecdote underscores the trial data: where once the course was inevitable decline, daraxonrasib has provided extended survival and hope.

No single case fully represents a population, but the consistency of benefit in RASolute-302 suggests many patients will have experiences like this. Patient advocates, who have campaigned for KRAS-targeted drugs for years, viewed the news as vindication. One group noted that this may be "the first effective targeted therapy we've seen for pancreatic cancer" (paraphrased from advocacy commentary).

Implications and Future Directions

The implications of RASolute-302 are profound. For patients, daraxonrasib could **become a new standard of care** after first-line therapy. If FDA-approved (Revolution plans an NDA submission under accelerated programs ([53] www.nasdaq.com)), oncologists will likely use it routinely for any metastatic PDAC that has progressed. The impact on global health could be substantial given the incidence of PDAC. Even if available only by specialist referral initially, the pressure will mount to test all PDAC tumors for KRAS (done almost universally already) and to prescribe daraxonrasib as soon as progression occurs.

Because the trial included all RAS types, the drug could be broadly indicated for **"RAS-mutant PDAC"** similar to how EGFR inhibitors are used in EGFR-mutant NSCLC. Curiously, even some RAS wild-type patients were enrolled, which suggests the label might not absolutely require a mutation (although the emphasis will be on G12X). This would still cover most cases, as >90% are KRAS-mutant ([5] www.nasdaq.com).

In the immediate future, doctors will incorporate this data. ASCO 2026 (June) will feature the results in the Plenary Session, and detailed data (survival curves, subgroup analyses, adverse events) will be scrutinized by the community. If the full data confirm the press release, **guidelines will be updated promptly**. Pancreatic cancer treatment is likely to shift from "head-on war with chemo" to a precision approach: use chemotherapy to debulk and sensitize, then switch to daraxonrasib to control RAS-driven growth. Conceptually, it resembles the paradigm in CML or CLL.

Revolution's pipeline beyond PDAC also gains momentum. The positive PDAC data bolster daraxonrasib's use in other RAS-driven tumors: for example, the **RASolute-301 trial in previously treated KRAS-mutant NSCLC** is due to report soon (already enrolls KRAS-mutant patients and will test daraxonrasib vs docetaxel ([42] ir.revmed.com)). If daraxonrasib proves superior in lung cancer as well, it could challenge the current standard (dol-lur). Colorectal cancer might also benefit, either alone or in combination with other agents (e.g. anti-EGFR therapies).

From a mechanistic standpoint, these results validate the *RAS(ON)* approach. It is likely that **other RAS(ON) inhibitors** will progress. For instance, elironrasib (G12C) and zoldonrasib (G12D) may follow similar paths in their respective indications. There is also the intriguing possibility of combining RAS(ON) and RAS(OFF) inhibitors for synergy: Revolution scientists have data suggesting that multiselective RAS(ON) inhibitors actually promote GTP hydrolysis, effectively increasing the pool of GDP-bound RAS and potentially **sensitizing tumors to G12C OFF-state drugs** ([46] ir.revmed.com). Combination trials of daraxonrasib with sotorasib/adagrasib (or for example with MEK inhibitors) are logical next steps in research.

On the regulatory side, stool rotation: The FDA has already given daraxonrasib Breakthrough Therapy and Orphan Drug designations for PDAC ([64] www.nasdaq.com) ([34] www.onclive.com), and the company will use a **Commissioner's Priority Review Voucher** to expedite the NDA. Global filings (EMA, Japan, etc.) will likely follow. Given the magnitude of the effect, regulatory approval seems likely, though full reading of the data (including any safety issues) will be needed. It is conceivable the FDA even grants an "accelerated approval" based on these results, requiring confirmatory trials post-approval.

Beyond PDAC, the impact on RAS biology is huge. Researchers will study mechanisms of daraxonrasib resistance (emergent RAS mutations, bypass tracks) to design combo treatments. Several "catalytic" RAS(ON) inhibitors (e.g. newer molecules that maintain potency even as RAS flux increases) are already in preclinical development ([43] ir.revmed.com). Academic labs will also explore if RAS(ON) inhibitors can clear minimal residual disease or be used in the neoadjuvant setting (with surgery after tumor shrinkage). In short, a positive Wolrd War on RAS(ON) is underway.

Finally, the revelations here may encourage genomic testing and RAS biomarker programs. PDAC patients (or at least their tumors) might be sequenced to confirm RAS status to match therapy. Even though RAS is the overwhelming driver, now knowing a RAS(ON) inhibitor works, there will be renewed interest in pinpointing which codons matter, how to detect RAS addiction by gene expression, etc.

Discussion

Strength of Evidence

The case for daraxonrasib is built on a solid foundation of scientific and clinical evidence. The Phase 3 result is the central pillar: an unprecedented OS benefit with a p-value orders of magnitude below significance. Supporting that, phase 1 studies and AACR 2026 abstracts have shown consistent anti-tumor activity in PDAC (monotherapy and combination), high tumor control rates (≥90% disease control in many cohorts ([65] ascopost.com)), and manageable safety. The mechanistic basis is rational and reproducible: we have crystallographic structures, biochemical potency, and in vivo efficacy data.

From a reproducibility perspective, Revolution has multiple ongoing trials testing the same drug (e.g. in other indications, combinations). If those independently confirm benefit, the case only strengthens. We anticipate BLA (Biologics License Application) submission late 2026, first expected review by Spring 2027. If regulators accept that positive data are robust, it could lead to a review under an FDA Advisory Committee (given it's a novel class).

One consideration is that the announced data are topline and interim. Full publication of RASolute-302 (peer-reviewed or as a conference poster) is needed. We must be alert for any nuances: e.g. was the chemo arm "investigator's choice" standardized? Was there any imbalance in baseline prognostic factors? Did wild-type RAS patients do as well as mutants? At the press time, we have no reason to doubt the company, but independent confirmation (from FDA documents or journals) will solidify trust.

Comparative Perspectives

Revolution's own statements understandably highlight the positives. As one would expect, the PR and management emphasize how this validates their fifteen-year research investment ([20] www.nasdaq.com). From a competitor's viewpoint, Mirati (which is developing MRTX1133) must be tracking this closely. MRTX1133's Phase 1 is expected to start in 2026; had those trials produced data by now, Revolution would likely have mentioned them. The Mirati approach is also GTP-bound RAS (they call it "ON-state inhibitor"), but it is allele-specific and formed from a different chemistry (a

phosphonamide that disrupts switch regions ([66] pmc.ncbi.nlm.nih.gov)). Early lab results for MRTX1133 were remarkable (complete regressions in mouse PDAC xenografts ([11] pmc.ncbi.nlm.nih.gov)), and first-human data are keenly awaited.

From the academic perspective, Darax's success suggests any potent KRAS/NRAS inhibitor is worth pursuing. Researchers will examine existing RAS(OFF) inhibitors and SHP2/SOS1 inhibitors to see if they can now be combined with daraxonrasib. Also, cancer metronomy: since 90% of PDAC is RAS-driven, one might ask: is there a subset of PDAC that is not RAS-addicted (e.g. via other drivers)? The darax trial included these "KRAS wild-type" patients (though rare), hinting that maybe some wild-type tumors still rely on RAS signaling (perhaps via upstream RTKs). Further exploration of RAS independence vs addiction is warranted.

Clinically, the debate will shift to sequencing: *Should daraxonrasib be used as soon as possible, or saved for post-chemo?* Revolution is testing it after one line, but if a patient is frail or chemo-intolerant, could daraxonrasib be moved earlier? The RASolute-303 first-line trial will provide guidance. Some oncologists may even consider using daraxonrasib off-trial in borderline first-line cases (though without data yet).

Safety and Quality of Life

An important aspect is patient quality of life (QoL). Chemotherapy's side effects often severely impair PDAC patients' well-being. In contrast, if daraxonrasib's adverse effects are mostly skin and GI, these can sometimes be tolerated relatively well. For example, the ASCO Post reports that rash is now prophylaxable and not as crippling as neuropathy or cytopenias ([57] ascopost.com). Revolution mentioned that QoL questionnaires were part of RASolute-302; it will be imperative to see if patients on daraxonrasib report better functioning and symptom control than those on chemo. If so, that will strengthen the case for its use even in frailer patients (e.g. ECOG 2) who might not handle chemo.

Economic and Access Considerations

A novel targeted drug will be expensive. The economics of revolution medicines (RVMD) hinge on pricing and coverage. If daraxonrasib is priced like other targeted therapies (e.g. >$100,000/year), the value proposition must be weighed by payers. However, in oncology, overall survival is king. A >6-month OS improvement in a high-mortality cancer justifies a premium from a health-economics standpoint. Also, daraxonrasib is oral, potentially reducing infusion center costs relative to chemo. That said, payers may demand biomarker testing (to ensure KRAS mutation status), and governments may push cost-effectiveness studies.

On equity: PDAC has a high mortality especially among lower-income and minority populations. Ensuring fair access (perhaps via patient assistance or broader insurance coverage) will be important. Revolution may need to work with foundations (e.g. Pancreatic Cancer Action Network) to educate about the new therapy and help enroll underrepresented patients in trials or access programs.

Research Directions

Beyond the immediate clinical implications, RASolute-302 opens many research avenues. Key future questions include:

- **Resistance mechanisms:** Which secondary mutations or bypass pathways emerge in daraxonrasib-treated tumors? In sotorasib trials, bypass through EGFR or MET activation was seen. Similar studies (sequencing post-progression biopsies from darax patients) will be done to inform next-gen therapies. Revolution's work on "catalytic RAS(ON)" agents suggests they aim to pre-empt resistance by developing molecules that maintain potency under high RAS flux ([43] ir.revmed.com).

- **Biomarker studies:** Are there genomic or proteomic predictors of response? For instance, co-mutations in tumor suppressors (TP53, SMAD4), or RAS allele variant (G12D vs G12V vs G12R), might correlate with outcomes. Circulating tumor DNA (ctDNA) was monitored in trials: nearly all patients had substantial drops in RAS VAF on therapy ([67] ascopost.com). Could ctDNA clearance be used as an early efficacy marker or to tailor duration of therapy? Research will exploit these blood biomarkers longitudinally.
- **Combination therapy:** We already mentioned combos with chemo and immunotherapy. DARAX + immune checkpoint inhibitors (PD-1/PD-L1) is logical, given PDAC's low baseline immunogenicity. Preclinically, RAS inhibition can increase tumor antigen presentation. Several early-phase trials combining RAS inhibitors with PD-1 blockade are likely to launch. Additionally, combining daraxonrasib with other new agents (e.g. PARP inhibitors in BRCA-mutant PDAC, or with MEK inhibitors) could be explored. Safety of combos will need to be assessed (e.g. overlapping diarrhea rash with ICI).
- **Earlier use:** Should daraxonrasib be tested in adjuvant (post-surgery) or neoadjuvant (pre-surgery) settings for resectable PDAC with RAS mutations? If it truly controls micrometastatic disease, it might improve cure rates for a minority of PDAC. Imagine giving daraxonrasib after surgery instead of waiting for recurrence. These would require carefully designed trials (likely in high-risk, node-positive patients).

Conclusion

The **DARAXONRASIB RASolute-302 Phase 3 trial results (April 2026)** represent a monumental breakthrough in oncology. For the first time, a targeted therapy has delivered a clear, statistically robust survival benefit in metastatic pancreatic cancer – one of the toughest cancers. Daraxonrasib, a first-in-class **RAS(ON) inhibitor**, doubled median overall survival compared to chemotherapy in pretreated PDAC patients ([1] www.nasdaq.com). This "unprecedented OS benefit" ([1] www.nasdaq.com) was heralded by leading investigators as likely practice-changing ([3] www.nasdaq.com) ([4] ascopost.com).

This outcome comes on the heels of decades of research that slowly chipped away at KRAS's "undruggable" reputation ([13] pubs.acs.org). Revolution Medicines' RAS(ON) program, rooted in deep medicinal chemistry and structural biology (colab.ws) ([7] pubs.acs.org), has now reached fruition with an approved drug in hand (pending regulatory review). Moreover, the strategy is validated: a new class of RAS inhibitors (multi-selective molecular glues) can indeed shut down oncogenic RAS in patients. The implications extend beyond PDAC: every RAS-driven cancer is a potential frontier for RAS(ON) therapy.

Moving forward, the focus will be on bringing daraxonrasib to patients worldwide (through FDA/EMA approval and commercialization), studying it in combination and earlier lines, and exploring related agents. The success of daraxonrasib will spur intense scientific and clinical activity to conquer the remaining challenges: identifying resistance mutations, optimizing combination strategies, and perhaps developing even more potent RAS(ON) molecules.

Pancreatic cancer, sadly, has remained a harbinger of poor outcomes. At long last, the field has something tangible to celebrate – a new treatment that **truly extends life** in this devastating disease. If the RASolute-302 results hold true, we have entered a **new era in pancreatic cancer** – one in which the once impossible target "KRAS" is turning into a vulnerable Achilles' heel. The "greasy ball" of KRAS might finally be snagged, with daraxonrasib leading the way, and many patients with PDAC reaping the reward of this innovation.

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