Pancreatic ductal adenocarcinoma remains one of the most difficult cancers to treat, with limited progress in drug development over the past decade. At the 2026 ASCO Annual Meeting, the Phase 3 RASolute 302 trial delivered results that stood out against that history.

Brian M. Wolpin's plenary presentation of the RASolute 302 data received a standing ovation from the audience. In pancreatic cancer, where positive Phase 3 results have been rare, the reaction reflected the significance of the findings.

In an exclusive interview with OncoDaily, hosted by Shushan Hovsepyan, Dr. Alan Sandler, Chief Development Officer at Revolution Medicines, discussed the science behind daraxonrasib, the risks taken during its development, and where the program goes from here.

Pancreatic Cancer and the RAS Challenge

Approximately 60,000 patients are diagnosed with pancreatic cancer each year in the United States. Nearly 50,000 die from the disease annually. Most patients present with advanced or metastatic disease. The five-year survival rate for metastatic PDAC is 3% (Siegel RL et al., 2024; Halbrook CJ et al., 2023).

No standard second-line regimen has been established. Fluoropyrimidine- and gemcitabine-based chemotherapy produce median PFS of 3 to 4 months and median OS of 6 to 7 months. Toxicity remains significant across available regimens.

Over 90% of PDAC tumors harbor KRAS mutations. The most common are at codon 12: G12D, G12V, and G12R. PDAC is the most RAS-dependent of all major cancers (Lee JK et al., 2022). These mutations drive constitutive activation of the RAS-MAPK signaling pathway. RAS was identified as an oncogenic driver in 1980 but lacked structural binding pockets for small-molecule inhibition. For decades, it remained beyond therapeutic reach.

The Tri-Complex Approach

Earlier RAS-targeted drugs, such as sotorasib and adagrasib, are covalent KRAS G12C(OFF) inhibitors. They target the inactive, GDP-bound state of a single variant. KRAS G12C is present in only 1 to 2% of PDAC tumors.

Daraxonrasib works through a different mechanism. It binds to cyclophilin A inside the cell, forming a binary complex. That complex then engages the active, GTP-bound state of RAS, known as RAS(ON). The resulting tri-complex blocks RAS from interacting with downstream effectors. This suppresses the RAS-MAPK pathway at its source.

The drug is multi-selective. It inhibits mutant and wild-type KRAS, NRAS, and HRAS across G12, G13, and Q61 variants. This covers the full spectrum of oncogenic RAS mutations found in PDAC.

The therapeutic window rests on a biological difference. In normal cells, RAS exists predominantly in its inactive state. In RAS-mutant cancer cells, RAS is constitutively active. Tumor cells are therefore selectively vulnerable to RAS(ON) inhibition.

RAS also plays a role in normal cell development, which raised early concerns about toxicity. According to Dr. Sandler, the Phase 1 study started at very low doses because of these concerns. Daraxonrasib proved tolerable, with predominantly grade 1 to 2 adverse events. The most common were rash and gastrointestinal effects. Rash is managed with oral antibiotics and topical agents,

following protocols similar to EGFR inhibitor management.

Preclinical data established that sustained RAS pathway suppression of 90% or more is needed for tumor regression. Pharmacokinetic modeling identified 300 mg once daily as the dose to achieve this threshold.

Early Clinical Development

Revolution Medicines was originally founded to develop antifungal therapies. That program did not advance. The company then pivoted to oncology, focusing on RAS-addicted cancers after acquiring Warp Drive Bio in 2018. Daraxonrasib was the first compound to enter the clinic, with first-in-human dosing in 2022.

The Phase 1-2 RMC-6236-001 study enrolled 168 patients with previously treated RAS-mutated PDAC across 16 U.S. sites. Doses ranged from 10 to 400 mg once daily.

At 300 mg in second-line RAS G12-mutated patients (n=26), the study reported an ORR of 35%, disease control rate of 92%, median PFS of 8.5 months, and median OS of 13.1 months. In the broader RAS-mutated group (G12, G13, Q61; n=38), the ORR was 29%, median PFS was 8.1 months, and median OS was 15.6 months (Wolpin BM et al., 2026).

Grade 3 or higher treatment-related adverse events occurred in 30% of patients. No grade 5 events were reported. No patients discontinued treatment due to toxicity at 300 mg.

These figures exceeded historical benchmarks for second-line PDAC chemotherapy. Dr. Sandler noted that during Phase 1 dose-escalation, investigators began reporting scan responses and clinical improvement. This was unusual in pancreatic cancer, where treatment responses are rare. Based on these data, Revolution Medicines bypassed a traditional Phase 2 and advanced directly into a global registrational Phase 3. The development timeline from first-in-human to positive Phase 3 took four years.

RASolute 302

The Phase 3 RASolute 302 trial enrolled 500 patients with previously treated metastatic PDAC across 59 sites in six countries. Patients were randomized 1:1 to daraxonrasib 300 mg daily or investigator’s choice of chemotherapy.

Chemotherapy options included gemcitabine/nab-paclitaxel (56.5%), liposomal irinotecan plus fluorouracil/leucovorin (32.7%), modified FOLFIRINOX (5.6%), and FOLFOX (5.1%). Of enrolled patients, 91.8% had RAS G12 mutations (O’Reilly EM et al., 2026).

The trial met all primary and key secondary endpoints.

Overall survival: 13.2 months with daraxonrasib vs. 6.6 months with chemotherapy in the RAS G12 population (HR 0.40; P<0.001). Overall population: 13.2 vs. 6.7 months (HR 0.40; P<0.001). A 60% reduction in the risk of death.

Progression-free survival: 7.3 vs. 3.5 months in the RAS G12 population (HR 0.45; P<0.001). Overall population: 7.2 vs. 3.6 months (HR 0.49; P<0.001).

Response rate: 33.2% vs. 11.8% in the RAS G12 population.

Patient-reported outcomes: Time to pain deterioration: 9.0 vs. 3.7 months (HR 0.51; P<0.001). Time to deterioration in global health status: 5.6 vs. 2.4 months (HR 0.60; P<0.001). Dr. Sandler noted that quality of life is not always successfully captured in clinical trials. In RASolute 302, patients on daraxonrasib lived longer and reported feeling better for longer.

Safety: Grade 3 or higher adverse events occurred in 61.8% of the daraxonrasib group vs. 69.6% with chemotherapy. Median treatment duration was 6.2 months with daraxonrasib vs. 1.5 to 3.2 months across chemotherapy regimens. Treatment-related discontinuation was 1.2% vs. 11.2%. The most common toxicities were rash (86.3%), diarrhea (67.2%), and stomatitis (54.8%), predominantly grade 1 to 2. One death from treatment-related pneumonitis was reported in the daraxonrasib group. Patients on daraxonrasib maintained high dose intensity. Dr. Sandler noted that patients tended to want to remain on therapy given their clinical benefit.

The chemotherapy arm performed as expected, matching historical benchmarks. This confirmed the observed benefit was genuine. The consistency between Phase 1-2 and Phase 3 results is notable: OS of 13.1 to 13.2 months and ORR of 30 to 35% across both datasets. The 13.2-month second-line OS also surpasses reported first-line medians: 11.1 months with FOLFIRINOX (Conroy et al., 2011), 8.5 months with gemcitabine/nab-paclitaxel (Von Hoff et al., 2013), and 11.1 months with NALIRIFOX (Wainberg et al., 2023).

The ASCO Presentation

The plenary presentation of RASolute 302, delivered by Brian M. Wolpin, became one of the defining moments of the 2026 ASCO meeting.

Dr. Sandler described the magnitude of the result: a doubling of median survival, from 6.6 to 13.2 months, with a hazard ratio of 0.40.

“That being 13.2 months, that’s greater than what had ever been seen in first-line pancreatic cancer. So the magnitude of the effect is really quite dramatic.”— Dr. Alan Sandler

Dr. Sandler previously served as Chief Medical Officer at Mirati Therapeutics, a competitor in the RAS space that was later acquired by Bristol-Myers Squibb. He had followed Revolution Medicines’ science closely and was consistently impressed. He described the company as a patient-centric organization focused on getting effective therapies to patients as rapidly as possible.

Regulatory Path and Ongoing Trials

Revolution Medicines announced topline RASolute 302 results on April 13, 2026 (Revolution Medicines, press release, 2026). A rolling submission to the U.S. FDA is underway. Daraxonrasib holds Breakthrough Therapy Designation, Orphan Drug Designation, and a Commissioner’s National Priority Voucher. An expanded access program is operational in the United States, with daraxonrasib already shipped to at least one site.

The clinical program is expanding into earlier treatment settings. The RASolute 303 trial is evaluating daraxonrasib in first-line metastatic PDAC, randomizing patients 1:1:1 to daraxonrasib monotherapy, daraxonrasib plus gemcitabine/nab-paclitaxel, or gemcitabine/nab-paclitaxel alone. Early-phase data supported this design, with ORR of 47% for monotherapy (n=38) and 55% for the combination (n=31) in newly diagnosed patients (Khachatryan M: 2026, CancerWorld). A separate adjuvant trial is enrolling patients with resected PDAC.

As Dr. Sandler noted in his interview with OncoDaily, the adjuvant setting carries particular

significance — with *“the potential not only extending life, but that may increase the cure rate of patients with resected pancreatic cancer.“*

Beyond daraxonrasib, Revolution Medicines has three additional RAS(ON) selective inhibitors in clinical development: elironrasib (G12C), zoldonrasib (G12D), and RMC-5127 (G12V). Initial combination data are also emerging. In June 2026, Tango Therapeutics reported a 92% ORR when combining vopimetostat, an oral PRMT5 inhibitor selective for MTAP-deleted tumors, with daraxonrasib in previously treated mPDAC (n=12). MTAP deletion is present in approximately 40% of pancreatic cancers. Tango plans to advance the combination into Phase 3 (Tango Therapeutics, press release, 2026).

“This is just the beginning”

The RASolute 302 data represent a clinically meaningful advance in previously treated metastatic PDAC. For Revolution Medicines and the broader field of RAS-targeted therapy, the next chapter is underway.

“We drugged the undruggable. And something that was thought not to be possible became possible in a very, very dramatic way.”

“This is just the beginning. We’re only in maybe the second or third inning.” — Dr. Alan Sandler

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About the Author

Mariam Khachatryan, MD, is Editor-in-Chief of OncoDaily GI, the gastrointestinal oncology platform launched on 7 September 2025. She leads the editorial direction of OncoDaily GI, and on 9 March 2026, launched JocOnDa, its official journal club, bringing structured discussion of new evidence to oncologists working across the GI field.