Metastatic pancreatic cancer remains one of the most treatment-refractory solid tumours in oncology. Despite multiple incremental refinements over the past decade, first-line therapy continues to rely on cytotoxic chemotherapy, most commonly FOLFIRINOX or gemcitabine plus nab-paclitaxel, with limited change in overall disease trajectory.

Against this backdrop, RAS-targeted therapy has long represented a theoretical but largely unrealised goal. With activating RAS mutations present in approximately 92% of pancreatic cancers, the pathway has been an obvious target—yet historically considered difficult to drug.

The emergence of **daraxonrasib**, a multi-selective RAS(ON) inhibitor, has therefore drawn attention as it moves through early clinical development and into a pivotal randomised programme, **RASolute 303**, which is comparing monotherapy and combination strategies against standard chemotherapy in the first-line metastatic setting.

Shiraj Sen, MD, Clinical Director of NEXT Oncology–Dallas and a principal investigator in early-phase studies, described the emerging dataset as potentially practice-shifting **in an interview with OncoDaily GI** for CancerWorld.

Early Signals of Activity in a Refractory Disease

Early-phase data suggest that direct RAS inhibition may produce clinically meaningful responses in metastatic pancreatic cancer, including in patients with diverse RAS mutations.

“Emerging data from the early phase studies of multi-selective RAS(ON) inhibitors, both as monotherapy and in combination with conventional chemotherapy, are demonstrating that durable responses are possible in individuals with metastatic, unresectable pancreatic cancer with a variety of RAS mutations. This is very encouraging as it is the first time that a targeted therapy has shown such promise in metastatic pancreatic cancer.”

While mechanistic understanding is still evolving, ongoing biomarker analyses aim to clarify how sustained RAS suppression alters downstream signalling and resistance dynamics over time.

“Ongoing biomarker analyses will help elucidate how continuous RAS suppression is impacting RAS signaling at the tumor level, both when individuals are responding to treatment and at time of disease progression.”

The data remain early, based on limited patient numbers and without mature survival endpoints.

Rationale for a Three-Arm Pivotal Design

The RASolute 303 trial is enrolling newly diagnosed metastatic PDAC patients with ECOG performance status 0–1, randomised 1:1:1 across the three arms. Co-primary endpoints are progression-free survival and overall survival, assessed independently per RECIST v1.1. Secondary endpoints include objective response rate, duration of response, disease control rate, safety, and patient-reported quality-of-life outcomes.

The **RASolute 303 trial** reflects two consistent signals from early development: activity with RAS(ON) inhibition alone, and potentially enhanced activity in combination with chemotherapy.

In early-phase cohorts:

Among 38 patients with newly metastatic RAS-mutant pancreatic cancer treated with **daraxonrasib**

monotherapy (300 mg):

- ORR: **47%**
- DCR: **89%**

Among 31 patients treated with **daraxonrasib (200 mg) plus gemcitabine and nab-paclitaxel**:

- ORR: **55%**
- DCR: **90%**

These results have informed the decision to evaluate both approaches in a randomised first-line setting, alongside standard chemotherapy.

The intention is not only to confirm activity but to define positioning: whether RAS inhibition can function as a chemotherapy-free strategy or whether combination therapy provides incremental benefit.

Tolerability and Second-Line Activity

Long-term follow-up data presented by Revolution Medicines in September 2025 reinforced the durability of daraxonrasib's activity in pretreated patients. In second-line RAS-mutant metastatic PDAC, confirmed objective response rates were 35% in the KRAS G12X subgroup (n=26) and 29% across all RAS mutations (n=38), with disease control rates of 92% and 95%, respectively. Median progression-free survival reached 8.5 and 8.1 months, and median overall survival 13.1 and 15.6 months, after a median follow-up of approximately 17 months. In a disease where second-line options have historically offered minimal benefit, these figures are striking.

The safety profile remained consistent and manageable. Rash and mucositis were the most common treatment-related events, and although dose interruptions and reductions were frequent, no patients discontinued therapy because of toxicity. Mean dose intensity was 86%.

Positioning within Current Treatment Standards

Despite extensive clinical investigation, the therapeutic backbone of metastatic pancreatic cancer has remained largely unchanged for more than a decade.

The ongoing **RASolute 302 trial**, comparing daraxonrasib with chemotherapy in the second-line setting, may further inform where this class of agents fits within established treatment sequences.

A positive outcome would carry substantial implications, given the near-universal prevalence of RAS mutations in this disease.

"If this trial identifies that daraxonrasib is more effective than chemotherapy in the second line metastatic setting, this would introduce the first effective, non-cytotoxic treatment option for individuals with metastatic pancreatic cancer ever."

Such a shift, however, remains contingent on randomised comparative evidence.

Beyond Efficacy: The Relevance of Treatment Burden

As an oral, once-daily agent, daraxonrasib differs fundamentally from standard intravenous chemotherapy, raising important questions about treatment experience and feasibility in routine practice.

“Individuals may be able to spend more time with loved ones or doing what they love and less time in the infusion room or in their oncologist’s office.”

This consideration is particularly relevant in a patient population that increasingly includes younger individuals who remain active at diagnosis.

“It will be important to see how patient experience and quality of life differs in individuals getting daraxonrasib compared to chemotherapy.”

Formal quality-of-life data from randomised studies remain pending.

Broader Implications for RAS-Driven Malignancies

RAS mutations represent one of the most common oncogenic drivers across solid tumours, and early signals of activity have also been observed in colorectal cancer and non-small cell lung cancer.

“Publicly available data already suggests efficacy of RAS(ON) inhibitors, both allele-specific as well as in a multi-selective fashion, in colorectal cancer and NSCLC, as well. ”

Ongoing registrational studies, including **RASolve 301 in NSCLC**, will be important in determining whether activity is consistent across tumour types and molecular contexts.

“This may help inform the development of the many multi/pan-(K)RAS inhibitors now being offered in the early phase clinical trials at centers like ours at NEXT Oncology.”

Conclusion

The development of RAS(ON) inhibitors marks a renewed attempt to therapeutically exploit one of the most ubiquitous oncogenic drivers in cancer biology. Early-phase data for daraxonrasib suggest measurable activity in metastatic pancreatic cancer, including objective responses in RAS-mutant disease.

However, these findings remain preliminary. Their clinical significance will depend on confirmation in ongoing randomised studies, particularly **RASolute 303** and **RASolute 302**, which will define whether RAS inhibition can meaningfully alter the current chemotherapy-dominated treatment paradigm.

For now, the evidence supports continued investigation rather than a redefinition of standard practice.

Disclosure: *The RASolute 303 trial is sponsored by Revolution Medicines. Dr Sen and colleagues at NEXT Oncology–Dallas have contributed to multiple early-phase studies of daraxonrasib.*

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.