FDA APPROVAL

# FDA Expands Access to Investigational Pancreatic Cancer Drug Daraxonrasib

**CHEARS Update***

* *Correspondence: CHEARS Update*

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The U.S. Food and Drug Administration (FDA) has taken a significant step in the fight against pancreatic cancer by permitting expanded access to daraxonrasib, an investigational drug for patients with previously treated metastatic pancreatic ductal adenocarcinoma (PDAC). This move, announced on April 30, 2026, allows eligible patients who have exhausted standard therapies to receive the drug outside clinical trials, under the FDA's expanded access program (EAP). This decision underscores the urgent need for effective treatments for pancreatic cancer, a disease with a notoriously poor prognosis and high mortality.

## Pancreatic Ductal Adenocarcinoma: The Ruthless Aggressor

Pancreatic ductal adenocarcinoma (PDAC) is the most common and aggressive form of pancreatic cancer, accounting for over 90% of cases. It is characterized by delayed diagnosis, as symptoms often appear only in advanced stages, and by a dense tumor microenvironment that hinders effective treatment. By the time of diagnosis, approximately 80% of patients have unresectable, locally advanced, or metastatic disease, with an average five-year survival rate of less than 10%.

The disease is driven by genetic mutations, most notably in the KRAS gene, present in over 90% of PDAC cases. These mutations activate the RAS signaling pathway, promoting uncontrolled cell proliferation, survival, and metastasis. Traditional treatments such as surgery, chemotherapy (e.g., FOLFIRINOX or gemcitabine-based regimens), and radiation have shown limited efficacy, with median survival for metastatic PDAC typically around 6-7 months after standard therapy. Despite incremental advances, PDAC remains the third-leading cause of cancer-related deaths in the United States, with projections indicating it could rise to second place by 2030.

## Daraxonrasib: Mechanism of Action and Drug Effects

Daraxonrasib (RMC-6236), developed by Revolution Medicines, is a next-generation RAS(ON) inhibitor that targets the active state of RAS proteins, both wild-type and mutant variants. Unlike earlier RAS inhibitors that focused on specific mutations (e.g., KRAS G12C), daraxonrasib employs a "tricomplex" mechanism: it first binds to the chaperone protein cyclophilin A, forming a bicomplex that then associates with RAS-GTP to form a tricomplex. This interaction disrupts RAS signaling by inhibiting the RAF–MEK–ERK and PI3K–AKT pathways, which are critical for cell proliferation and survival.

Preclinical studies have demonstrated robust inhibition of ERK phosphorylation across multiple KRAS variants, including G12D, G12V, G13D, and Q61X, which are prevalent in PDAC. The drug's once-daily 300 mg oral formulation has shown sustained suppression of tumor growth in models with rapid RAS cycling and pathway redundancy. In the Phase III RASolute 302 trial for previously treated metastatic PDAC, daraxonrasib achieved a median overall survival of 13.2 months compared to 6.7 months with chemotherapy, representing a 60% reduction in death risk (hazard ratio 0.40, $p < 0.0001$). This nearly doubles median survival, a remarkable milestone given the historical stagnation in PDAC outcomes.

The expanded access program focuses on patients with metastatic PDAC who have progressed after prior therapy and lack other viable options, prioritizing those with RAS-driven tumors. The FDA's approval of the EAP within two days of Revolution Medicines' request highlights the agency's commitment to accelerating

access to promising therapies for life-threatening conditions. The drug is also eligible for a National Priority Voucher, expediting its full New Drug Application review.

## Clinical Impact and Future Prospects

The FDA's decision could extend hope to an estimated 10,000 new metastatic PDAC cases annually in the U.S., where survival gains have been limited. Real-world data from the EAP will complement trial findings, potentially reshaping standards for advanced pancreatic cancer care. The mechanism of action, targeting >90% of PDAC tumors with RAS mutations, offers a paradigm shift from traditional chemotherapy, with potential for reduced toxicity and improved quality of life. As the program launches, ongoing monitoring will assess efficacy and safety, paving the way for broader approval and integration into front-line therapies.

This advancement represents a beacon of progress in a field where innovation has been slow, offering renewed optimism for patients and clinicians alike.

## Competing interests

The authors declare that they have no competing interests.

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