Correspondence

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Daraxonrasib: The first-in-class RAS(ON) multi-selective inhibitor approved for treatment of metastatic pancreatic adenocarcinoma

Yueyi Sun, Chen Pang, Jianjun Gao*

Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, Shandong, China.

SUMMARY: Advanced pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, with limited benefits from conventional chemotherapy. Daraxonrasib is an oral, noncovalent RAS(ON) multi-selective inhibitor that forms a ternary complex with cyclophilin A and GTP-bound RAS, blocking downstream signaling across multiple mutant and wild-type RAS proteins. On August 26, 2026, the US Food and Drug Administration approved daraxonrasib for adults with metastatic pancreatic adenocarcinoma previously treated with systemic therapy or ineligible for multiagent systemic therapy, without a mutation-specific restriction. In the randomized phase III RASolute 302 trial involving 500 previously treated patients with a good performance status, daraxonrasib improved median overall survival from 6.7 to 13.2 months (hazard ratio, 0.40) and progression-free survival from 3.6 to 7.2 months in the overall randomized population. Grade 3 or higher treatment-related adverse events were less frequent with daraxonrasib than chemotherapy (43.6% versus 57.5%), although one treatment-related death from pneumonitis occurred. Common toxicities included rash, diarrhea, and stomatitis. Limited follow-up and small non-G12 subgroups warrant caution regarding the generalizability of that trial's results. Acquired resistance, frequently involving RAS pathway reactivation, remains an important challenge. Ongoing studies are evaluating earlier treatment settings and combination strategies, while long-term safety and outcomes in patients with a poorer performance status require further investigation.

Keywords: pancreatic ductal adenocarcinoma, RAS, daraxonrasib, RASolute 302, pneumonitis

Pancreatic cancer encompasses malignancies arising from the pancreas, with pancreatic ductal adenocarcinoma (PDAC) being the most common histological subtype. Because early clinical manifestations are nonspecific, most patients present with locally advanced or metastatic disease, and approximately 80% are not candidates for upfront surgical resection at diagnosis (*1*). Data from the US Surveillance, Epidemiology, and End Results (SEER) program indicate that approximately 51% of patients have distant metastases at presentation (*2*). GLOBOCAN 2024 estimated approximately 531,300 new cases of pancreatic cancer and 490,800 associated deaths worldwide, making it the sixth leading cause of cancer-related death (*3*). In China, the National Cancer Center estimated that there were approximately 118,700 new cases and 106,300 deaths in 2022 (*4*). These estimates underscore the substantial burden of pancreatic cancer and highlight the importance of earlier diagnosis and more effective systemic therapies in improving patient outcomes.

Chemotherapy has long been the mainstay of systemic treatment for advanced PDAC. Standard first-line regimens for metastatic PDAC include FOLFIRINOX, NALIRIFOX, and gemcitabine plus nab-paclitaxel (GnP) (*5-8*). In the event of progression following first-line therapy, second-line options are selected according to prior treatment and performance status and include liposomal irinotecan plus fluorouracil and leucovorin (5-FU/LV), as well as gemcitabine-based regimens (*9,10*). Outcomes with conventional second-line chemotherapy have historically remained poor, with a median overall survival (OS) of approximately 6 months in several representative randomized clinical trials (*9,11,12*). Limited survival benefits, drug resistance, and cumulative toxicity highlight the need for new therapeutic strategies targeting the molecular drivers of tumor growth. More than 90% of PDACs harbor *RAS* mutations, predominantly involving *KRAS*, with G12D being the most prevalent variant (*13*). RAS was long considered largely inaccessible to direct pharmacological inhibition. In 2021, sotorasib became the first direct KRAS inhibitor approved by the US Food and Drug Administration (FDA), followed by adagrasib in 2022. Both agents covalently bind to KRAS G12C and stabilize it in the GDP-bound, inactive (OFF) state, and both were initially approved for previously treated *KRAS* G12C-mutated non-small cell lung cancer (NSCLC) (*14,15*). Other inhibitors in this class, including fulzerasib,

garsorasib, and glecirasib, were subsequently approved in China. However, *KRAS* G12C mutations occur in only approximately 1%–2% of pancreatic cancers, and these inhibitors do not target the more common G12D and G12V variants, leaving the targeted treatment needs of most patients with PDAC unmet (*16*).

On August 26, 2026, the FDA approved daraxonrasib (RMC-6236; RASONQUE), developed by Revolution Medicines, for adults with metastatic pancreatic adenocarcinoma who have received at least one prior systemic therapy or are ineligible for multiagent systemic therapy, without restriction to a specific *RAS* mutation (*17,18*). Daraxonrasib is an oral, noncovalent, RAS(ON) multi-selective inhibitor that binds to cyclophilin A and subsequently forms a ternary complex with GTP-bound RAS (*18*). This complex prevents RAS from interacting with downstream effectors, including RAF, thereby inhibiting RAF–MEK–ERK signaling (*19*). Unlike KRAS G12C(OFF) inhibitors, daraxonrasib directly targets the active state of RAS and exhibits inhibitory activity against wild-type and multiple mutant forms of KRAS, NRAS, and HRAS (*18*). Its activity encompasses common PDAC-associated variants, including G12D, G12V, and G12R, providing broader molecular coverage (*18,19*). Nevertheless, the absence of a mutation-specific restriction in the approved indication should not be interpreted as evidence of equivalent clinical benefit across *RAS* genotypes. Molecular profiling remains clinically important for defining tumor genotype and identifying additional molecular alterations that may inform treatment selection (*20*).

RASolute 302 (NCT06625320), an international, multicenter, open-label, phase III trial, enrolled 500 patients with metastatic PDAC who had experienced disease progression after first-line systemic therapy and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (*18,20*). Patients were randomly assigned in a 1:1 ratio to receive daraxonrasib at an oral dose of 300 mg once daily or investigator-selected standard chemotherapy (mFOLFIRINOX, GnP, FOLFOX, or nal-IRI+5-FU/LV). The co-primary endpoints were OS and progression-free survival (PFS) in the *RAS* G12-mutant population, with the corresponding outcomes in the overall randomized population (*RAS* G12, G13, or Q61 mutations or with no *RAS* mutation identified) serving as key secondary endpoints (*20*). At a median follow-up of 8.5 months, median OS in the *RAS* G12-mutant population was 13.2 months with daraxonrasib versus 6.6 months with chemotherapy (hazard ratio (HR), 0.40), and median PFS was 7.3 versus 3.5 months (HR, 0.45). In the overall randomized population, median OS was 13.2 versus 6.7 months (HR, 0.40), and median PFS was 7.2 versus 3.6 months (HR, 0.49). All of those figures were statistically significant. Confirmed objective response rates in the *RAS* G12-mutant population were 33.2% in the daraxonrasib group and 11.8% in the chemotherapy group (*20*). These findings demonstrate that daraxonrasib significantly improves survival compared to standard second-line chemotherapy in patients with metastatic PDAC who have a good performance status and disease progression after first-line systemic therapy.

In the safety population, grade 3 or higher treatment-related adverse events occurred in 43.6% of patients receiving daraxonrasib and 57.5% of those receiving chemotherapy (*21*). Treatment-related adverse events led to permanent treatment discontinuation in 1.2% and 11.2% of patients, respectively (*21*). Grade 3 or higher adverse events of any cause occurred in 61.8% and 69.6% of patients, respectively (*20,21*). Common treatment-related adverse events associated with daraxonrasib included rash, diarrhea, and stomatitis, and one patient died from treatment-related pneumonitis (*18*). Thus, despite lower rates of high-grade treatment-related adverse events and treatment discontinuation than with chemotherapy, daraxonrasib-associated toxicities warrant careful clinical attention. Additional limitations include the open-label design, relatively short follow-up, and small number of patients without *RAS* G12 mutations (8%), including only 3% patients with no detectable RAS mutation (*18*). These factors limit the certainty of efficacy estimates in the respective subgroups. Because the trial enrolled only patients with an ECOG performance status of 0 or 1, the benefit–risk profile in patients with a poorer performance status remains to be established.

The ongoing phase III RASolute 303 trial is comparing daraxonrasib monotherapy, daraxonrasib plus GnP, and GnP alone as first-line treatment (*22*). RASolute 304 is evaluating daraxonrasib versus standard observation following surgical resection and completion of neoadjuvant and/or adjuvant chemotherapy, whereas RASolve 301 is comparing daraxonrasib with docetaxel in treating previously treated *RAS*-mutated NSCLC (*23,24*). These studies aim to further define the role of daraxonrasib across treatment settings and in other *RAS*-driven malignancies, and its value as first-line or adjuvant therapy remains to be established. Although randomized evidence has demonstrated a survival benefit for daraxonrasib, its effectiveness in routine clinical practice, long-term safety, and benefits in specific patient populations require further evaluation. Acquired resistance is another important concern. Secondary mutations at KRAS residue Y64 have been reported in patients with other solid tumors and can confer resistance by disrupting ternary complex formation (*25*). In contrast, a clinical resistance analysis involving 44 patients with PDAC identified no acquired secondary *KRAS* mutations; more frequently observed alterations included *KRAS* amplification and aberrant downstream or bypass signaling (*26*). These findings suggest that mechanisms of resistance to daraxonrasib may differ across tumor types. Further elucidation of resistance mechanisms, identification of associated biomarkers, and development of mechanistically informed combination strategies will be important for optimizing its clinical use.

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**Address correspondence to:*
Jianjun Gao, Department of Pharmacology, School of Pharmacy, Qingdao University, Qingdao, Shandong, China.
E-mail: gaojj@qdu.edu.cn

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