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Targeting Active-State RAS in Metastatic Pancreatic Ductal Adenocarcinoma

A brief report on RASolute 302 and the emergence of daraxonrasib as a potentially important therapeutic advance in mPDAC

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Resumen

El estudio RASolute 302 sugiere que daraxonrasib, un inhibidor oral multiselectivo de RAS(ON), podría mejorar la supervivencia en pacientes con adenocarcinoma ductal pancreático metastásico (mPDAC) previamente tratados. La magnitud del beneficio observado es notable en esta enfermedad y, de confirmarse en el informe completo revisado por pares, respaldaría a daraxonrasib como una nueva e importante opción terapéutica. Sin embargo, la interpretación dependerá de una descripción más completa de la consistencia entre subgrupos, la heterogeneidad del grupo de control y la tolerabilidad a largo plazo.

Palabras clave

Adenocarcinoma ductal de páncreas metastásico, enfermedad previamente tratada, supervivencia global, daraxonrasib, ensayo aleatorizado de fase 3.

Conflicto de intereses

Este artículo no presenta conflicto de interés.

Summary

RASolute 302 suggests that daraxonrasib, an oral multi-selective RAS(ON) inhibitor, may improve survival in previously treated mPDAC. The reported magnitude of benefit is notable in this disease and, if confirmed in the full peer-reviewed report, would support daraxonrasib as an important new therapeutic option. Interpretation, however, will depend on fuller reporting of subgroup consistency, control-arm heterogeneity, and long-term tolerability.

Key words

Metastatic pancreatic ductal adenocarcinoma, previously treated disease, overall survival, daraxonrasib, randomized phase 3 trial.

Conflict of interests

This article does not present a conflict of interest.

Clinical Context and Trial Overview

mPDAC remains one of the most treatment-refractory solid tumors, with historical median overall survival after progression on first-line therapy of approximately 6 to 7 months.[2] Because most PDACs are driven by KRAS or related RAS signaling, daraxonrasib has a compelling biologic rationale. Daraxonrasib (molecular formula: C44H58N8O5S) is an oral, noncovalent inhibitor that targets GTP-bound RAS across multiple mutant isoforms and wild-type RAS, potentially extending beyond mutation- specific strategies.[3] Mechanistically, daraxonrasib functions as a cyclophilin A– dependent tri-complex inhibitor that binds active, GTP-loaded RAS and sterically impairs RAS–effector interactions, thereby attenuating downstream MAPK signaling (Figure 2).[5] RASolute 302 therefore tested not only a new agent, but also a broader therapeutic proposition: whether inhibition of active-state RAS can improve outcomes in previously treated mPDAC.[1]

Methodological Appraisal

RASolute 302 has several features of a clinically important trial (Figure 1). It was a global, multicenter, open-label, randomized phase 3 study in patients with previously treated mPDAC, with 1:1 assignment to daraxonrasib 300 mg once daily or investigator- choice standard-of-care chemotherapy.[1] Eligibility criteria appear to have been

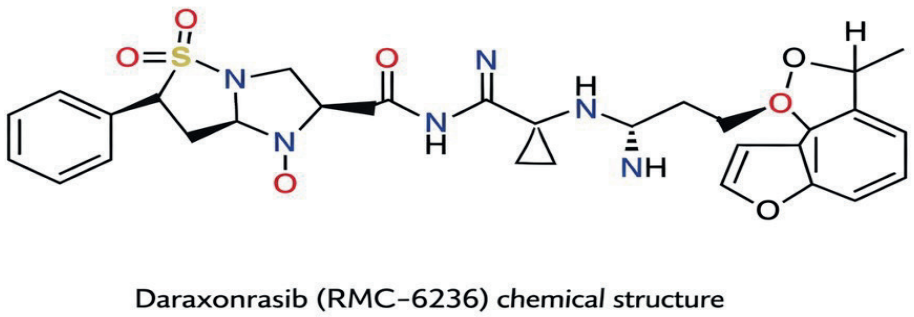

Figure 1. Chemical structure of daraxonrasib (RMC-6236). Original schematic representation included for illustrative purposes.

clinically conventional and appropriately restrictive, including metastatic PDAC, measurable disease, an ECOG performance-status score of 0 or 1, documented RAS mutational status, and one prior fluoropyrimidine- or gemcitabine-based regimen in the metastatic setting. [1] The comparator arm was pragmatic and clinically relevant, allowing gemcitabine plus nab-paclitaxel, nal-IRI plus 5-FU and leucovorin, modified FOLFIRINOX, or FOLFOX according to prior therapy and investigator choice, though this flexibility inevitably introduced heterogeneity into the control group.[1]

The efficacy hierarchy appears to have emphasized progression-free and overall survival in the RAS G12-mutant population, with key secondary analyses extending to the overall intention-to-treat population and including objective response and patient-reported outcomes such as pain and global health status or quality of life.[1] That emphasis is methodologically appropriate in PDAC, where radiographic progression may be difficult to adjudicate and modest gains in progression-free survival do not necessarily translate into meaningful clinical benefit. Nevertheless, because the study was open-label, the full report should clarify the randomization schema, prespecified stratification factors, the role of blinded independent central review for progression, subgroup consistency, and the balance of post-protocol therapy between groups.

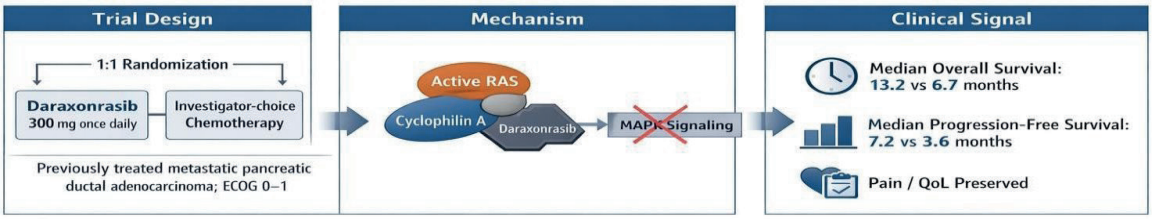

Figure 2. Summary of the RASolute 302 trial and daraxonrasib mechanism. Original schematic summarizing trial design, proposed mechanism of action, and the principal efficacy signal in previously treated metastatic pancreatic ductal adenocarcinoma.

Overall Results and Their Meaning

The reported efficacy is notable by the standards of previously treated mPDAC. Median overall survival was 13.2 months with daraxonrasib and 6.7 months with chemotherapy, with a hazard ratio for death of 0.40; median progression-free survival was 7.2 months and 3.6 months, respectively.[1] If sustained in the full peer-reviewed report, that effect size would exceed what is generally observed with second-line cytotoxic therapy and would support the conclusion that RAS(ON) inhibition can alter the natural history of disease rather than merely delay radiographic progression. The reported preservation of pain control, global health status, and quality of life further strengthens the clinical plausibility of benefit.[1]

Tolerability will remain central to interpretation. In the phase 1–2 study, treatment- related adverse events of any grade occurred in 96% of patients and grade 3 or higher events in 30%; the most common toxic effects were rash, diarrhea, nausea, stomatitis or mucositis, vomiting, and fatigue.[3] These data suggest a toxicity profile that appears manageable but not negligible. The phase 3 report will therefore need to define the frequency of dose reduction, interruption, and discontinuation, as well as the extent to which adverse effects affected treatment exposure and patient-reported function.

Strengths, Limitations, and Scientific Implications

The principal strength of RASolute 302 is that it appears to convert a long-standing biologic rationale into a randomized survival benefit in a disease with profound unmet need.[1] More broadly, it suggests that multi-selective inhibition of active-state RAS may have therapeutic relevance beyond mutation-restricted strategies.[1,3] The limitations are equally important. The control arm was clinically appropriate but heterogeneous; the study was open-label; and the durability, subgroup consistency, and treatment effect after subsequent therapy remain incompletely defined in the absence of the full report.[1] Thus, even if clinically influential, RASolute 302 should also be understood as a translational turning point, one that intensifies the need to define predictive biomarkers, mechanisms of resistance, and rational sequencing or combination strategies.[1,3]

Where the Field Should Go Next

The next priorities are to define predictive biomarkers, characterize mechanisms of acquired resistance, and test daraxonrasib in earlier lines of therapy and in rational combinations. Because mPDAC is biologically heterogeneous and rapidly adaptive, durable disease control will probably require combination strategies rather than single- agent therapy alone. Even so, RASolute 302 may provide important proof of principle that active-state RAS inhibition can yield a meaningful survival benefit in this disease.[1,3]

Conclusion

RASolute 302 appears to represent an important step forward in mPDAC. If the full report confirms the publicly presented findings, daraxonrasib may warrant serious consideration as an important new therapeutic option for previously treated

disease. More broadly, the study suggests that mechanism-based inhibition of active-state RAS may be moving from aspiration toward therapeutic consequence in mPDAC.[1,3]

Disclosure: The author declares no conflicts of interest related to this editorial.

Note: The molecular formula of daraxonrasib is C44H58N8O5S, the CAS number is 2765081-21-6, the molecular weight is 811.05 g/mol, the PubChem CID is 164726578, the UNII is B6T47Y2UAP, the InChIKey is FVICRBSEYSH-KFY-JYQNNKODSA-N, and a

shortened IUPAC designation is trans-(1S,2S)-N-[(7S,13S)-21-ethyl-20-[2-[(1S)-1- methoxyethyl]-5-(4-methylpiperazin-1-yl)-3-pyridinyl]-17,17-dimethyl-8,14-dioxo-15-oxa-4-thia-9,21,27,28-tetrazapentacyclo[...] octacosa-hexaen-7-yl]-2- methylcyclopropane-1-carboxamide.[4]

Box. Daraxonrasib identifiers	
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Mechanism: Daraxonrasib is an oral, noncovalent, multi-selective RAS(ON) inhibitor that forms a tri-complex with cyclophilin A and GTP-bound RAS, thereby blocking effector engagement and downstream oncogenic signaling.[5]

Referencias

1. Wolpin BM, Park W, Garrido-Laguna I, Spira A, Starodub A, Sommerhalder D, et al. RASolute 302: daraxonrasib versus investigator-choice chemotherapy in previously treated metastatic pancreatic ductal adenocarcinoma. N Engl J Med. 2026 May 31. doi:10.1056/NEJMoa2605555.
2. Wang-Gillam A, Hubner RA, Siveke JT, et al. NAPOLI-1 phase 3 study of liposomal irinotecan in metastatic pancreatic cancer: final overall survival analysis and characteristics of long-term survivors. Eur J Cancer. 2019;108:78-87.
3. Wolpin BM, Park W, Garrido-Laguna I, Spira A, Starodub A, Sommerhalder D, et al. Daraxonrasib in previously treated advanced RAS-mutated pancreatic cancer. N Engl J Med. 2026;394:1790-1802. doi:10.1056/NEJMoa2505783.
4. PubChem. Daraxonrasib; CID 164726578. Bethesda (MD): National Library of Medicine; accessed 2026 Jun 2.
5. Cregg J, Edwards AV, Chang S, Lee BJ, Knox JE, Tomlinson AC, et al. Discovery of daraxonrasib (RMC-6236), a potent and orally bioavailable RAS(ON) multi-selective, noncovalent tri-complex inhibitor for the treatment of patients with multiple RAS- addicted cancers. J Med Chem. 2025;68(5):4650-4674.