Abstract TPS4230: Trial in Progress - RASolute 302: A Phase 3, Multicenter, Global, Open-label, Randomized Study of Daraxonrasib (RMC-6236), a RAS(ON) Multi-Selective Inhibitor, versus Standard of Care Chemotherapy in Patients with Previously Treated Metastatic Pancreatic Ductal Adenocarcinoma (PDAC)

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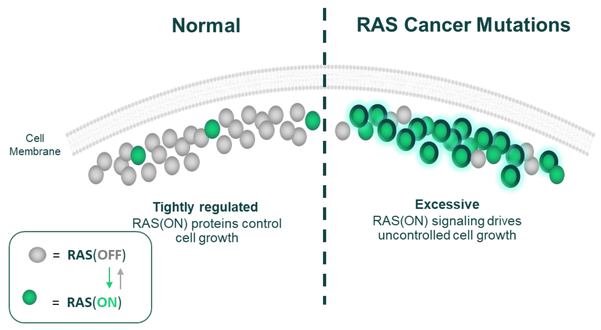
Background

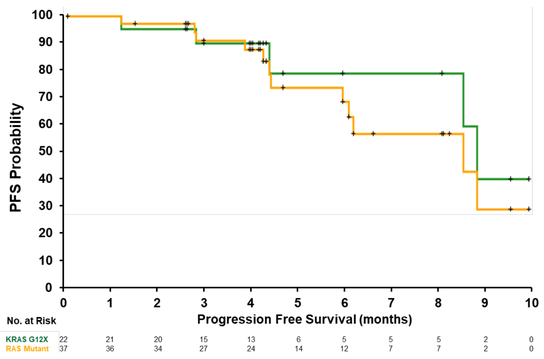
RAS(ON) Multi-Selective Inhibitor Designed to Directly Inhibit Uncontrolled RAS(ON) Signaling in PDAC



- RAS mutations are an oncogenic driver found in >90% of patients with pancreatic ductal adenocarcinoma (PDAC)
- Daraxonrasib (RMC-6236) is an oral, RAS(ON) multi-selective, tri-complex inhibitor of GTP-bound mutant and wild-type RAS[1]

- In the ongoing Phase 1 monotherapy trial (NCT05379985), the Phase 3 dose (300 mg QD) of daraxonrasib exhibited a manageable safety profile with primarily low-grade rash and GI toxicities, and encouraging ORR, PFS and OS in a broad population of previously treated patients with RAS mutant metastatic PDAC[2]
- Reported outcomes for patients with 2L metastatic PDAC treated with standard of care chemotherapy are:
  - Median PFS ~2–3.5 months[3–11]
  - Median OS ~6.1–6.9 months[3–11]

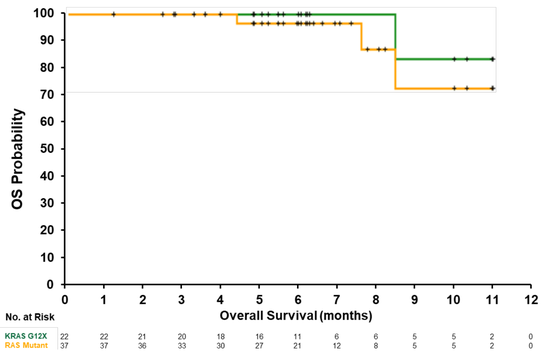
Daraxonrasib Phase I Study (RMC-6236-001): Progression-Free Survival in 2L PDAC[2]



300 mg	KRAS G12X[a] (N = 22)	RAS Mutant[b] (N = 37)
Median PFS, Months (95% CI)	**8.8** (8.5, NE)	**8.5** (5.9, NE)

Data cutoff 23 Jul 2024. 2L in the metastatic setting includes patients who progressed on prior therapy in an earlier setting within 6 months of last dose. Median follow-up was 6.1 months for KRAS G12X and 6.6 months for RAS mutant. [a]KRAS G12X mutations are defined as nonsynonymous mutations in KRAS codon 12 (G12) mutant metastatic PDAC. [b]RAS mutant is defined as patients with G12, G13, or Q61 mutant metastatic PDAC.

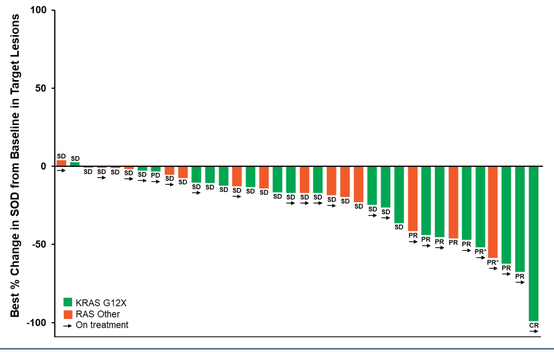
Daraxonrasib Phase I Study (RMC-6236-001): Overall Survival in 2L PDAC[2]



300 mg	KRAS G12X[a] (N = 22)	RAS Mutant[b] (N = 37)
Median OS, Months (95% CI)	**NE** (NE, NE)	**NE** (8.5, NE)
OS Rate at 6 months, % (95% CI)[c]	**100** (100, 100)	**97** (79, 100)

Data cutoff 23 Jul 2024. Median follow-up was 6.1 months for KRAS G12X and 6.6 months for RAS mutant. [a]KRAS G12X mutations are defined as nonsynonymous mutations in KRAS codon 12 (G12). [b]RAS mutant is defined as patients with G12, G13, or Q61 mutant metastatic PDAC. [c]OS rate at 6 months and 95% CI are from Kaplan-Meier analysis.

Daraxonrasib Phase I Study (RMC-6236-001): Best Response in 2L PDAC[2]



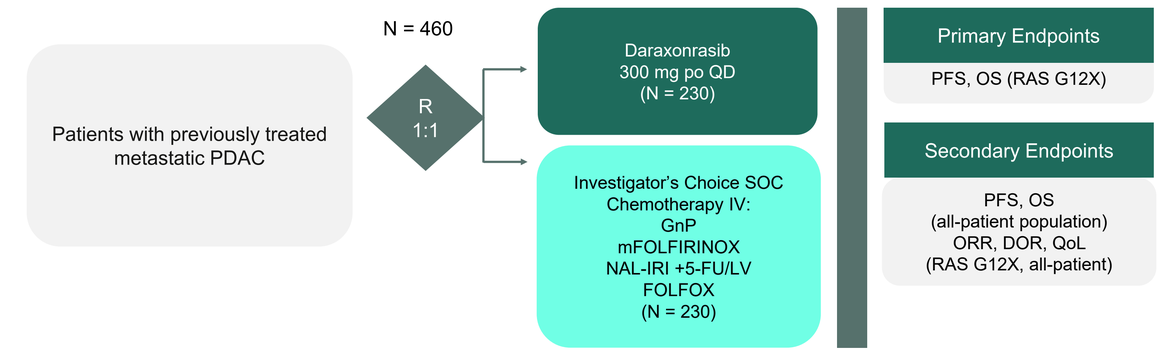
300 mg	KRAS G12X[a] (N = 22)	RAS Mutant (N = 37)
ORR[b]	36%	27%
DCR[b]	91%	95%

Data cutoff 23 Jul 2024. Among patients with a response (confirmed or unconfirmed), 46% of first response occurred within 2 months of daraxonrasib treatment at 300mg. [a]KRAS G12X mutations are defined as nonsynonymous mutations in KRAS codon 12 (G12). RAS Other includes mutations in KRAS G13X, KRAS Q61X, or mutations in HRAS or NRAS at codons G12X, G13X, or Q61X. [b]ORR and DCR analyses included all patients who received first dose of daraxonrasib at least 14 weeks prior to data cutoff date (to allow 2 potential scans). Unconfirmed PRs (PR*) with treatment discontinued (will never confirm) were not considered responders but remained in the denominator; ORR (by RECIST v1.1) included confirmed CRs/PRs and unconfirmed CRs/PRs who were still on treatment and may yet be confirmed; 2L in the metastatic setting included patients who progressed on prior therapy in an earlier setting within 6 months of last dose.

Methods

- RASolute 302 is a global, randomized, open-label, Phase 3 study designed to evaluate whether treatment with daraxonrasib will improve progression free survival (PFS), or overall survival (OS) compared to Investigator's choice of standard of care chemotherapy in patients with metastatic PDAC who were previously treated with one prior line of therapy with 5-fluorouracil (5-FU) based or gemcitabine-based regimen

RASolute 302 Study Design (NCT06625320)



Key Inclusion Criteria	Key Exclusion Criteria
• Confirmed PDAC with metastatic disease	• History of or known CNS metastatic disease
• 1 prior line of therapy (either 5-fluorouracil-based or gemcitabine-based regimen) in the metastatic setting	• Prior therapy with direct RAS-targeted therapy (e.g. degraders and/or inhibitors)
• Documented disease progression on prior therapy	• Any conditions that may affect the ability to take or absorb study treatment
• Measurable disease per RECIST v1.1	• Major surgery within 4 weeks prior to randomization
• ECOG PS 0-1	• Patient is unable or unwilling to comply with protocol-required study visits or procedures
• Documented RAS mutation status (mutant or wild-type)[a]	

[a]Eligible RAS mutations are defined as nonsynonymous mutations in KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61). Patients with tumors that are RAS wild-type and received appropriate approved targeted therapy for actionable mutations are also eligible.

- Patients continue to receive treatment until unacceptable toxicity or disease progression, or withdrawal of consent
- For patients randomized to daraxonrasib, recommended prophylactic measures for rash include oral antibiotics and topical corticosteroids
- Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) tumor assessments will be performed every 8 weeks until disease progression, withdrawal of consent, lost to follow up, or death, whichever occurs first
- Dual primary endpoints are progression-free survival (PFS) as assessed by blinded independent central review and overall survival (OS) in the RAS G12X-mutant population
- PFS and OS in the all-patient population are included as key secondary endpoints, along with objective response and quality of life measures in both RAS G12X-mutant and all-patient population
- Quality of Life measures include evaluation of time to deterioration using EORTC-QLQ-PAN26 and EORTC-QLQ-C30 questionnaires

RASolute 302 Participating Countries

Enrollment for the trial commenced in October 2024 and is ongoing

References and Acknowledgements

Abbreviations

5-FU, 5-fluorouracil; CI, confidence interval; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC-QLQ-C30, European Organisation for Research and Treatment of Cancer core quality of life questionnaire; EORTC-QLQ-PAN26, European Organisation for Research and Treatment of Cancer pancreatic cancer-specific quality of life questionnaire; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; GI, gastrointestinal; KRAS, Kirsten rat sarcoma virus; mFOLFIRINOX, modified fluorouracil, irinotecan, leucovorin, oxaliplatin; NAL-IRI, liposomal irinotecan; NE, not evaluable; NRAS, neuroblastoma RAS viral oncogene homolog; ORR, objective response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; po, oral administration; QD, once daily; QoL, quality of life; RECIST v1.1, response evaluation criteria in solid tumors version 1.1; SOC, standard of care; WT, wild-type

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References

1. Jiang J, et al. *Cancer Discov* 2024;14:994–1017.
2. Garrido-Laguna I, et al. *J Clin Oncol* 2025; 43:722.
3. Onivyde USPI.
4. Chiorean EG, et al. *Clin Cancer Res* 2021;27:6314–33.
5. Chung V, et al. *JAMA Oncol* 2017;3:516–22.
6. Hecht JR, et al. *J Clin Oncol* 2021;39:1108–18.
7. Huffman BM, et al. *JAMA Network Open* 2023;6:e2249720.
8. Hammel P, et al. *ASCO GI* 2022.
9. Fouchardiere C, et al. *J Clin Oncol* 2024;42:1055–1066.
10. Gupta A, et al. *Frontiers Oncol* 2023;3:1250136.
11. Enzler T, et al. *Eur J Cancer* 2024;113950.

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