# Safety, Efficacy, and On-Treatment Circulating Tumor DNA (ctDNA) Changes from a Phase 1 Study of Daraxonrasib (RMC-6236), a RAS(ON) Multi-Selective, Tri-Complex Inhibitor, in Patients with RAS Mutant Pancreatic Ductal Adenocarcinoma (PDAC)

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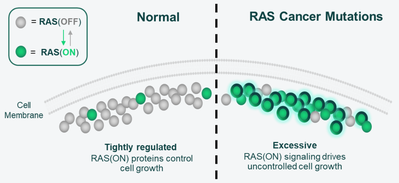
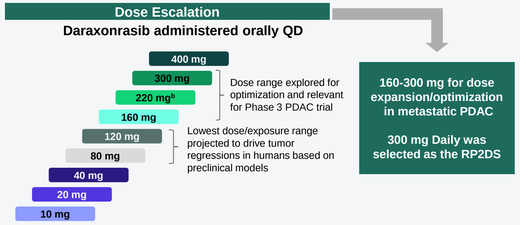
## Introduction




- Daraxonrasib (RMC-6236) is a RAS(ON) multi-selective, tri-complex inhibitor designed to directly inhibit uncontrolled RAS(ON) signaling
- Unmet need in PDAC is significant, given high mortality rate
- Outcomes for patients with 2L PDAC treated with standard of care chemotherapy are:
  - Median PFS ~2-3.5 months[1-9]
  - Median OS ~6.1-6.9 months[1-9]
- >90% of PDAC tumors harbor an oncogenic RAS mutation
- Molecular response (on-treatment reductions in circulating tumor DNA [ctDNA]) has been shown to predict anti-tumor activity and is complementary to RECIST in select solid tumors[10-12]

## Materials and Methods

- Daraxonrasib is being investigated in an ongoing Phase 1 monotherapy study in patients with advanced RAS mutant tumors (NCT05379985)
- Eligible patients were ≥18 years old with ECOG PS 0-1 and advanced solid tumors with KRAS G12X mutations[a] (initially excluding KRAS G12C), who had received prior standard therapy appropriate for tumor type and stage, and who had no active brain metastases
- Objectives included assessment of safety/tolerability, pharmacokinetics, pharmacodynamic changes in ctDNA, and antitumor activity
- Plasma samples at baseline and on-treatment (C2D1 or C3D1) were analyzed for changes in RAS variant allele frequency (in ctDNA) by Guardant Health




Date cutoff 23 Jul 2024.
[a]KRAS G12X mutations are defined by nonsynonymous mutations in KRAS codon 12 (G12). RAS mutant includes patients with G12, G13, or Q61 mutant metastatic PDAC. [b]220 mg cleared DLT evaluation and a dose of 200 mg was selected for further expansion/optimization.

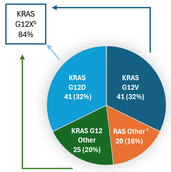
## Key Results

### Demographics and Baseline Characteristics for Patients with PDAC

| | 160-300 mg (N=127) | 300 mg (N=76) |
|---|---|---|
| **Age, years, median (range)** | 64 (30-86) | 65 (31-83) |
| **Male, n (%)** | 71 (56%) | 44 (58%) |
| **ECOG PS 1, n (%)** | 81 (64%) | 50 (66%) |
| **Number of prior anticancer therapies, median (range)** | 2 (1-11) | 2 (1-7) |
| **Number of prior anticancer therapies in metastatic setting, n (%)[a]** | | |
| 0 | 2 (1%) | 0 (0%) |
| 1 | 57 (45%) | 37 (49%) |
| 2+ | 68 (54%) | 39 (51%) |
| **Liver metastases at baseline, n (%)** | 85 (67%) | 51 (67%) |
| **Metastatic at diagnosis [stage IV], n (%)** | 66 (52%) | 41 (54%) |

Data cutoff 23 Jul 2024.
[a]Patients with locally advanced or metastatic PDAC; 1 prior line of therapy in the metastatic setting included patients who progressed on prior therapy in an earlier setting within 6 months of last dose.
[b]KRAS G12X mutations are defined by nonsynonymous mutations in KRAS codon 12 (G12).
[c]RAS Other includes mutations in KRAS G13X, KRAS Q61X, or mutations in HRAS or NRAS at codons G12X, G13X, or Q61X.

**RAS Genotypes Among Patients with PDAC 160-300 mg (N=127)**




### Daraxonrasib Treatment-Related Adverse Events (TRAEs) in Patients with PDAC

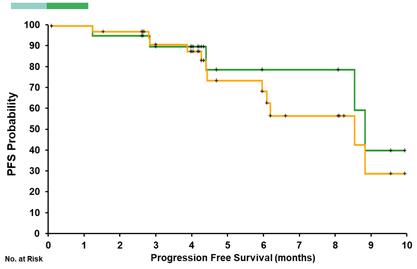
| Maximum severity of TRAEs | 160-300 mg (N=127) | | 300 mg (N=76) | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| **Any TRAE** | 124 (98%) | 37 (29%) | 73 (96%) | 26 (34%) |
| **TRAEs occurring in ≥10% of patients, n (%)** | | | | |
| Rash[a] | 115 (91%) | 10 (8%) | 69 (91%) | 6 (8%) |
| Diarrhea | 61 (48%) | 3 (2%) | 40 (53%) | 3 (4%) |
| Nausea[b] | 54 (43%) | 0 (0%) | 29 (38%) | 0 (0%) |
| Vomiting[b] | 39 (31%) | 0 (0%) | 27 (36%) | 0 (0%) |
| Stomatitis | 39 (31%) | 4 (3%) | 26 (34%) | 3 (4%) |
| Fatigue | 25 (20%) | 1 (1%) | 12 (16%) | 1 (1%) |
| Paronychia | 17 (13%) | 0 (0%) | 10 (13%) | 0 (0%) |
| Mucosal inflammation | 16 (13%) | 1 (1%) | 13 (17%) | 1 (1%) |
| Decreased appetite | 14 (11%) | 1 (1%) | 10 (13%) | 0 (0%) |
| Oedema peripheral | 13 (10%) | 0 (0%) | 10 (13%) | 0 (0%) |
| Platelet count decreased | 12 (9%) | 3 (2%) | 8 (11%) | 3 (4%) |
| Dry skin | 11 (9%) | 0 (0%) | 8 (11%) | 0 (0%) |
| **Other select TRAEs, n (%)** | | | | |
| Anemia | 11 (9%) | 7 (6%) | 6 (8%) | 5 (7%) |
| ALT increased | 10 (8%) | 3 (2%) | 5 (7%) | 3 (4%) |
| AST increased | 9 (7%) | 2 (2%) | 4 (5%) | 1 (1%) |
| Neutrophil count decreased | 7 (6%) | 2 (2%) | 5 (7%) | 2 (3%) |
| **TRAEs leading to dose modification, n (%)** | 45 (35%) | | 32 (42%) | |
| Dose interruption | 43 (34%) | | 30 (40%) | |
| Dose reduction | 24 (19%) | | 19 (25%) | |
| Dose discontinuation | 0 (0%) | | 0 (0%) | |
| **Specific TRAEs leading to dose reduction in >10% patients, n (%)** | | | | |
| Rash[a] | 14 (11%) | | 10 (13%) | |
| **Median/Mean dose intensity** | 99%/92% | | 97%/89% | |

One Grade 4 TRAE observed (platelet count decreased) at 300 mg dose level; no Grade 5 TRAEs
300 mg QD was selected as the Phase 3 dose for monotherapy daraxonrasib in 2L PDAC

Data cutoff 23 Jul 2024. Median duration of treatment was 5.3 months in 160-300 mg population, 5.2 months in 300 mg population.
[a]Includes preferred terms of dermatitis, dermatitis acneiform, eczema, erythema, rash, rash erythematous, rash maculopapular, rash pruritic and rash pustular; multiple types of rash may have occurred in the same patient. [b]No prophylaxis for nausea or vomiting was administered.

### Daraxonrasib Progression-Free Survival in Patients with 2L PDAC

*Efficacy plotted for 300 mg, data for 160-300 mg shown in table for comparison*

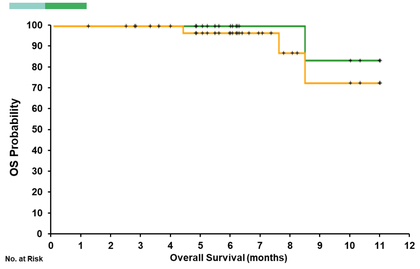



| 300 mg | KRAS G12X[a] (N = 22) | RAS Mutant[b] (N = 37) |
|---|---|---|
| **Median PFS, Months (95% CI)** | **8.8** (8.5, NE) | **8.5** (5.9, NE) |
| **160-300 mg** | **KRAS G12X[a] (N = 42)** | **RAS Mutant[b] (N = 57)** |
| **Median PFS, Months (95% CI)** | **8.5** (5.3, 11.7) | **7.6** (5.9, 11.1) |

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 for 300 mg. Median follow-up was 6.2 months for KRAS G12X and 6.6 months for RAS mutant for 160-300 mg.
[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 Overall Survival in Patients with 2L PDAC

*Efficacy plotted for 300 mg, data for 160-300 mg shown in table for comparison*

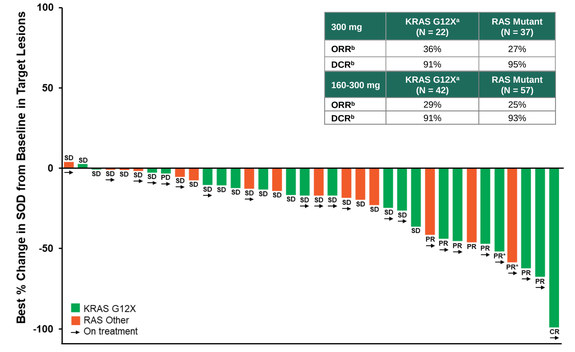



| 300 mg | KRAS G12X[a] (N = 22) | RAS Mutant[b] (N = 37) |
|---|---|---|
| **Median OS, Months (95% CI)** | **NE** (NE, NE) | **NE** (8.5, NE) |
| **OS Rate at 6 months, % (95% CI)[c]** | **100** (100, 100) | **97** (79, 100) |
| **160-300 mg** | **KRAS G12X[a] (N = 42)** | **RAS Mutant[b] (N = 57)** |
| **Median OS, Months (95% CI)** | **14.5** (8.8, NE) | **14.5** (8.8, NE) |
| **OS Rate at 6 months, % (95% CI)[c]** | **89** (70, 97) | **91** (77, 96) |

Data cutoff 23 Jul 2024.
Median follow-up was 6.1 months for KRAS G12X and 6.6 months for RAS mutant for 300 mg. Median follow-up was 6.2 months for KRAS G12X and 6.6 months for RAS mutant for 160-300 mg.
[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 Best Response in Patients with 2L PDAC

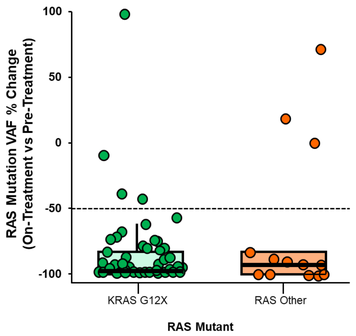
*Efficacy plotted for 300 mg, data for 160-300 mg shown in table for comparison*




| 300 mg | KRAS G12X[a] (N = 22) | RAS Mutant (N = 37) |
|---|---|---|
| **ORR[b]** | 36% | 27% |
| **DCR[b]** | 91% | 95% |
| **160-300 mg** | **KRAS G12X[a] (N = 42)** | **RAS Mutant (N = 57)** |
| **ORR[b]** | 29% | 25% |
| **DCR[b]** | 91% | 93% |

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.

### On-Treatment Reduction in RAS Variant Allele Frequency (VAF) in ctDNA




- 73 patients with 2L+ PDAC treated at 160-300 mg QD were evaluable for changes in RAS VAF on-treatment
- Marked reduction in RAS VAF in ctDNA in both RAS G12X and RAS Other tumors

| | KRAS G12X[a] (N = 60) | RAS Mutant[b] (N = 73) |
|---|---|---|
| **>50% RAS VAF decrease from pre-treatment, n (%)** | 56 (93%) | 66 (90%) |
| **100% RAS VAF decrease from pre-treatment, n (%)** | 29 (48%) | 33 (45%) |

[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]RAS mutant is defined as patients with G12, G13, or Q61 mutant metastatic PDAC.

Line inside box plots indicate median value; whiskers indicate largest or smallest value (at most ±1.5x the interquartile range).

## Conclusions

- Daraxonrasib is the first investigational targeted agent designed to directly inhibit all major forms of oncogenic RAS(ON), the common drivers of PDAC
- At the Phase 3 dose of 300 mg QD, daraxonrasib exhibited a manageable safety profile, favorable dose intensity and encouraging ORR, PFS and OS
- Marked reduction in RAS VAF in ctDNA observed in PDAC patients treated with daraxonrasib 160-300 mg QD indicates inhibition of all major forms of oncogenic RAS
- These results support the ongoing RASolute 302 study, a global, randomized, Phase 3 clinical trial of daraxonrasib as 2L treatment versus chemotherapy in patients with previously treated metastatic PDAC (ClinicalTrials.gov Identifier: NCT06625320)

## Acknowledgements

- We thank all patients who participated in this study, their families who supported them, and the clinical investigators and research staff who cared for them
- This study was sponsored by Revolution Medicines, Inc. (ClinicalTrials.gov identifier: NCT05379985)

**References**
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**Abbreviations**
2L, second line; AE, adverse event; ALT, alanine transaminase; AST, aspartate transferase; C1D1, cycle 1 day 1; C2D1, cycle 2 day 1; C3D1, cycle 3 day 1; CR, complete response; ctDNA, circulating tumor DNA; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PR, partial response; PR*, unconfirmed PR; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOD, sum of diameters; TRAE, treatment-related adverse event; VAF, variant allele frequency