Preliminary Safety, Antitumor Activity, and Circulating Tumor DNA (ctDNA) Changes with Zoldonrasib (RMC-9805), an Oral, RAS(ON) G12D-Selective, Tri-Complex Inhibitor in Patients with KRAS G12D Pancreatic Ductal Adenocarcinoma (PDAC) from a Phase 1 Study in Advanced Solid Tumors

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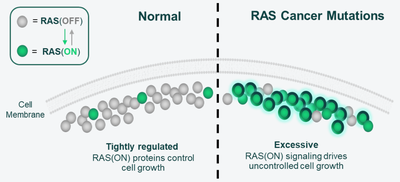
Introduction



- Zoldonrasib (RMC-9805) is a potent, orally bioavailable RAS(ON) G12D-selective covalent 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]
- PDAC is a RAS-driven disease
  - 40% of PDAC harbor a RAS G12D mutation[10]
- 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[11-13]

Materials and Methods

Part 1: Dose Escalation

- 1200 mg QD
- 600 mg BID
- 900 mg QD
- 450 mg BID
- 600 mg QD
- 300 mg BID
- 300 mg QD
- 150 mg QD

Part 2: Expansion and Dose Optimization in PDAC

- Zoldonrasib (with or without daraxonrasib [RMC-6236]) is being investigated in an ongoing Phase 1 study (NCT06040541)
- Eligible patients were ≥18 years old with ECOG PS 0 or 1 and advanced solid tumors with KRAS G12D mutations, who had received prior standard therapy appropriate for tumor type and stage and had no active brain metastases
- Patients received zoldonrasib orally QD (150-1200 mg) or BID (300-600 mg) on a 21-day treatment cycle
- Objectives included assessment of safety/tolerability, pharmacokinetics, pharmacodynamic changes in ctDNA, and anti-tumor activity
- Plasma samples at baseline and on-treatment (C2D1 or C3D1) were analyzed for changes in KRAS G12D variant allele frequency (in ctDNA) by Guardant Health

Key Results

Key Demographics and Baseline Characteristics

	All Histologies[a] (N = 179)	All PDAC (N = 104)
Age, years, median (range)	62 (25-86)	65 (30-86)
Male, n (%)	98 (55%)	57 (55%)
ECOG PS 1, n (%)	125 (70%)	74 (71%)
Number of prior anticancer therapies, median (range)	2 (0-9)	2 (0-6)
Liver metastases at baseline, n (%)	135 (75%)	89 (86%)
Metastatic at diagnosis [stage IV], n (%)	106 (59%)	59 (57%)

[a] Includes the following tumor types: pancreatic ductal adenocarcinoma, colorectal cancer, non-small cell lung cancer, sinonasal adenocarcinoma, melanoma of the vulva, metastatic small bowel carcinoma, ovarian cancer, uterine adenocarcinoma, high grade mucinous carcinoma peritonei, ampullary cancer, duodenal, signet ring gastric carcinoma, uterine, appendiceal.

Zoldonrasib Treatment Related Adverse Events (TRAEs)

Maximum severity of TRAEs	Grade 1	Grade 2	Grade 3	Any Grade
	All Patients Treated with Zoldonrasib (N = 179)			
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	48 (27%)	5 (3%)	0	53 (30%)
Diarrhea	24 (13%)	5 (3%)	0	29 (16%)
Vomiting	20 (11%)	6 (3%)	0	26 (15%)
Other select TRAEs, n (%)				
ALT increased	12 (7%)	0	1 (1%)	13 (7%)
AST increased	10 (6%)	1 (1%)	0	11 (6%)
Rash[a]	11 (6%)	0	0	11 (6%)
Stomatitis	0	0	0	0
TRAEs leading to dose reduction, n (%)	5 (3%)	0	0	5 (3%)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	0
	Patients Treated with Zoldonrasib 1200 mg Daily (1200 mg QD, N = 60 or 600 mg BID, N = 39)			
TRAEs occurring in ≥10% of patients, n (%)				
Nausea	23 (23%)	4 (4%)	0	27 (27%)
Diarrhea	16 (16%)	4 (4%)	0	20 (20%)
Vomiting	13 (13%)	2 (2%)	0	15 (15%)
Rash[a]	10 (10%)	0	0	10 (10%)
Other select TRAEs, n (%)				
ALT increased	5 (5%)	0	1 (1%)	6 (6%)
AST increased	3 (3%)	1 (1%)	0	4 (4%)
Stomatitis	0	0	0	0
TRAEs leading to dose reduction, n (%)	4 (4%)	0	0	4 (4%)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	0

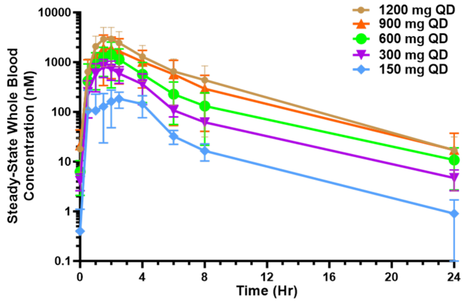
No treatment-related Grade 4 or 5 AEs or SAEs were reported

Maximum Tolerated Dose (MTD) was not reached.
Data cutoff date 02 Sep 2024. Median time on treatment was 2.8 months (range: 0.1-8.9) for all treated patients; Median time on treatment was 2.8 months (range: 0.2-6.7) for 1200 mg Daily treated patients.
[a]Includes preferred terms of dermatitis, dermatitis acneiform, dermatitis psoriasiform, eczema, erythema, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, and rash pustular.

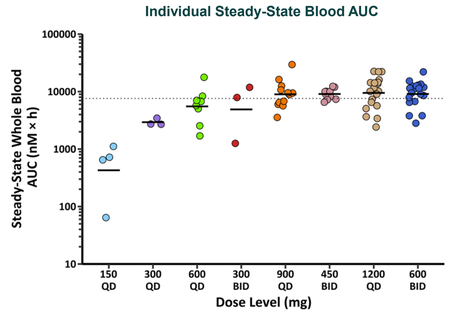
Zoldonrasib Steady-State Pharmacokinetics

- Zoldonrasib exposure showed dose-dependent increases and achieved levels predicted to induce tumor regressions based on preclinical data
- 1200 mg QD identified as a candidate RP2DS in PDAC

Mean Steady-State Blood PK Profiles



Individual Steady-State Blood AUC

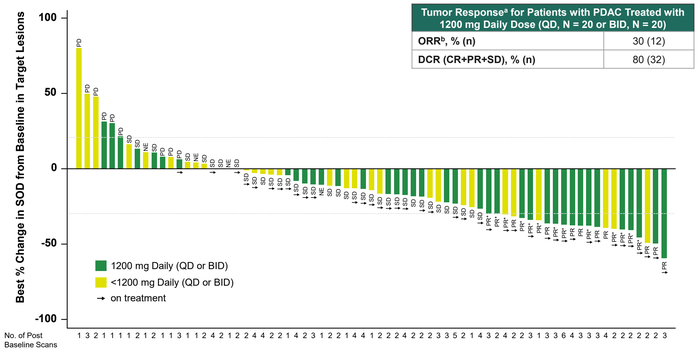


Exposure in mice at 100 mg/kg
- Dose that induces tumor regressions in majority of KRAS G12D PDAC preclinical models

PK data as of 16 Jul 2024; Left: steady-state concentrations from Cycle 1 Day 15; Error bars represent standard deviation; Right: steady-state AUC in Cycle 1 Day 15; Each circle represents an individual patient AUC

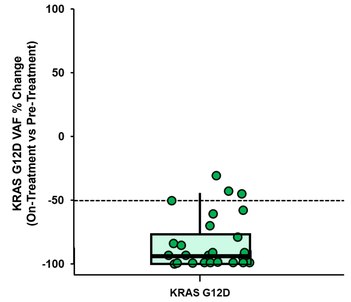
ORR and DCR in Patients with KRAS G12D PDAC Receiving Zoldonrasib

Tumor Response[a] for Patients with PDAC Treated with 1200 mg Daily Dose (QD, N = 20 or BID, N = 20)	
ORR[b], % (n)	30 (12)
DCR (CR+PR+SD), % (n)	80 (32)



Data cutoff date 02 Sep 2024.
All treated patients with PDAC who received a first daily dose at least 14 weeks prior to data cutoff date (applies to waterfall plot and ORR table); 3 additional patients (n = 2 at 1200 mg daily; n = 1 at <1200 mg daily) are not displayed on the waterfall plot due to withdrawal of consent or clinical progression; 2 patients progressed after initial PR without a confirmation and remained on treatment at the data cut-off date. Among patients with a response (confirmed or unconfirmed), 55% of first responses occurred after 2 months of RMC-9805 treatment (all dose levels).
[a]Per RECIST v1.1. [b]Includes confirmed PRs and unconfirmed PRs who were still on treatment and may yet be confirmed.

On-Treatment Reduction in KRAS G12D Variant Allele Frequency (VAF) in ctDNA



- 28 patients with PDAC treated at 1200 mg Daily were evaluable for changes in KRAS G12D VAF on-treatment
- Marked reduction in KRAS G12D VAF in ctDNA in patients with PDAC

	KRAS G12D (N = 28)
>50% KRAS G12D VAF decrease from pre-treatment, n (%)	24 (86%)
100% KRAS G12D VAF decrease from pre-treatment, n (%)	11 (39%)

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

Conclusions

- Zoldonrasib is a potent RAS(ON) G12D-selective covalent tri-complex inhibitor
- Zoldonrasib is orally bioavailable and demonstrates dose-dependent blood PK reaching exposures consistent with those inducing tumor regressions in KRAS G12D PDAC preclinical models
- Zoldonrasib was well tolerated, with manageable and primarily Grade 1 treatment-related adverse events
- Zoldonrasib demonstrated encouraging preliminary antitumor activity in patients with KRAS G12D PDAC based on ORR at 1200 mg QD, a candidate RP2DS for PDAC, with follow-up ongoing for durability assessment
- Marked reduction in KRAS G12D VAF in ctDNA observed in majority of patients treated at 1200 mg Daily
- Preliminary safety and clinical activity data support the ongoing development of zoldonrasib as a single agent and in combination with other therapies, including the RAS(ON) multi-selective inhibitor daraxonrasib

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Abbreviations

2L, second line; ALT, alanine transaminase; AST, aspartate transferase; AUC, area under the curve; BID, twice daily; CR, complete response; ctDNA, circulating tumor DNA; DCR, disease control rate; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group Performance Status; MTD, maximum tolerated dose; NE, not evaluable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PK, Pharmacokinetics; PR, partial response; PR*, unconfirmed PR; QD, once daily; RECIST, response evaluation criteria in solid tumors; RP2DS, recommended phase 2 dose and schedule; SD, stable disease; SOD, sum of diameters; TRAE, treatment-related adverse event; VAF, variant allele frequency.