Early Reduction in Circulating Tumor DNA (ctDNA) is Associated with Clinical Activity of Daraxonrasib (RMC-6236) in RAS Mutant Non-Small Cell Lung Cancer (NSCLC)

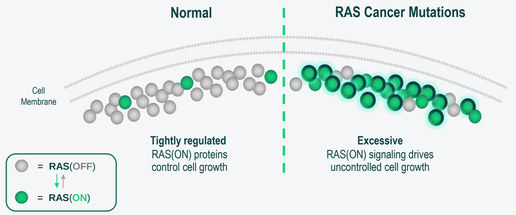
Jia Luo[1], Salman R Punekar[2], Kathryn C Arbour[3], Melissa Johnson[4], Alex Spira[5], Ignacio Garrido-Laguna[6], Jonathan W Goldman[7], Benjamin Herzberg[8], Sai-Hong Ignatius Ou[9], Dae Won Kim[10], Lijia Wang[11], Li Cheng[11], Vidya Seshadri[11], Sumit Kar[11], Minoti Hiremath[11], David S Hong[12]

[1]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA; [2]New York University Langone Health, Perlmutter Cancer Center, New York, NY; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]Sarah Cannon Research Institute, Nashville, TN; [5]NEXT Oncology Virginia, Virginia Cancer Specialists Research Institute, Fairfax, VA; [6]University of Utah, Huntsman Cancer Institute, Salt Lake City, UT; [7]UCLA Health Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, Los Angeles, CA; [8]Columbia University Irving Medical Center, Medical Oncology, New York, NY; [9]University of California Irvine School of Medicine, Orange, CA; [10]Moffitt Cancer Center, Tampa, FL; [11]Revolution Medicines, Redwood City, CA; [12]The University of Texas MD Anderson Cancer Center, Department of Investigational Therapeutics, Houston, TX

Introduction and Background

- Daraxonrasib (RMC-6236) is a RAS(ON) multi-selective, tri-complex inhibitor designed to directly inhibit uncontrolled RAS(ON) signaling in RAS-driven tumors, including RAS mutant NSCLC
- There is a significant unmet medical need for improved treatments for patients with previously treated NSCLC
- Clinical outcomes for patients with 2L+ NSCLC receiving docetaxel result in ORR of 9-15%, PFS of 3-4.5 months and OS of 9.1-11.8 months[1-7]
- Collectively, RAS mutations are present in approximately 30% of NSCLC cases.[8] 60% of RAS mutant NSCLC are non-KRAS G12C including KRAS G12X, G13X, and Q61 and have no approved targeted therapies
- 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[9-11]

RAS(ON) Signaling in Human Cancers



Materials and Methods

- Phase 1 monotherapy study in patients with advanced RAS mutant tumors (NCT05379985)
- Patients received daraxonrasib orally in 21-day cycles
- Study enrolled patients with tumors harboring RAS mutations in KRAS, HRAS, and NRAS at codon 12 (RAS G12X), codon 13 (RAS G13X) or codon 61 (RAS Q61X), including patients with NSCLC. No patients with KRAS G12C mutant NSCLC were enrolled in the study. Enrollment was based on identification of RAS mutation by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory or equivalent local laboratory
- Objectives included assessment of safety/tolerability, antitumor activity, pharmacokinetics, and pharmacodynamic changes in ctDNA
- ctDNA testing was performed on paired plasma samples (C1D1 and C2D1 or C1D1 and C3D1 using the Guardant Health Infinity assay

All data included in this presentation is from the data cutoff of 30 Sep 2024

1. Baseline Characteristics of Patients with RAS Mutant NSCLC

Baseline Characteristics	120–220 mg N = 73
Age, years, median (range)	68 (36, 89)
Male, n (%)	28 (38%)
ECOG PS 1, n (%)	59 (81%)
Number of prior anti-cancer therapies, median (range)	2 (1, 6)
Prior checkpoint inhibitor therapy, n (%)	72 (99%)
Prior platinum doublet chemotherapy, n (%)	72 (99%)
Prior docetaxel, n (%)	14 (19%)
Smoking current/past, n (%)	53 (73%)
Brain metastasis at baseline, n (%)	19 (26%)
Metastatic at diagnosis [stage IV], n (%)	37 (51%)

Data reported at clinically relevant dose ranges of 120-220 mg QD

2. Daraxonrasib Treatment-Related Adverse Events (TRAEs) in Patients with NSCLC

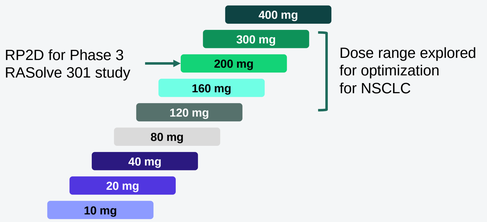
	120–220 mg (N = 73)	
	Any Grade	**Grade ≥3**
Any TRAE	71 (97%)	12 (16%)
TRAEs in ≥ 10% of patients, n (%)		
Rash*	66 (90%)	5 (7%)
Diarrhea	46 (63%)	1 (1%)
Nausea	36 (49%)	0
Vomiting	29 (40%)	2 (3%)
Stomatitis	25 (34%)	0
Paronychia	14 (19%)	0
AST increased	11 (15%)	0
ALT increased	10 (14%)	0
Dry skin	9 (12%)	0
Fatigue	8 (11%)	0
Other select TRAEs, n (%)		
Anemia	4 (6%)	2 (3%)

- Rash (7%) was the only G3 TRAE in ≥5% of patients
- No G4 or G5 TRAEs were observed
- TRAEs led to dose interruption in 34%, dose reduction in 21% of patients, and dose discontinuation in 4% of patients
- Mean dose intensity = 91%

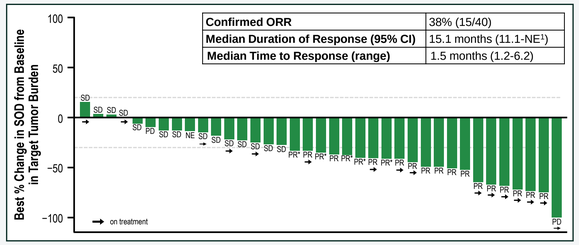
*Includes preferred terms of Rash pustular, Rash maculo-papular, Rash, Erythema, and Dermatitis acneiform. Multiple types of rash may have occurred in the same patient

Dose Escalation

Daraxonrasib administered orally QD



3. Confirmed Objective Response Rate and Duration of Response in Patients with RAS G12X NSCLC Treated in 2L/3L with Daraxonrasib at 120-220 mg QD

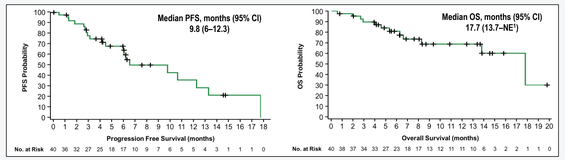


Confirmed ORR	38% (15/40)
Median Duration of Response (95% CI)	15.1 months (11.1-NE[1])
Median Time to Response (range)	1.5 months (1.2-6.2)

Clinical activity (ORR by RECIST v1.1) assessed in patients with NSCLC (N = 40) that
- All patients who received first dose of daraxonrasib at least 14 weeks prior to data cutoff date (to allow 2 potential scans)
- Harbor RAS G12X mutations
- Have received 1 or 2 prior lines of therapy* (prior immunotherapy and platinum chemotherapy)
- Have not received docetaxel previously

Three patients included in the denominator of the ORR analyses are not displayed on waterfall due to lack of post-baseline target lesion assessment (2 due to patient request to withdraw from treatment, and 1 due to patient withdrawal of consent). Unconfirmed PRs (PR*) with treatment discontinued (will never confirm) were not considered responders but remained in the denominator. Patient with 100% reduction in SOD from baseline was deemed as PD due to new lesion, treatment is ongoing post progression as treatment beyond progression was permitted if protocol specified criteria were met. *Adjuvant therapy or multimodal therapy with curative intent is considered prior therapy if disease progression occurred on treatment or within 6 months of treatment completion. Median duration of response estimated using the Kaplan-Meier method. Median follow-up is 10.8 months.

4. Progression-Free Survival and Overall Survival in Patients with RAS G12X NSCLC treated in 2L/3L with daraxonrasib 120-220 mg QD

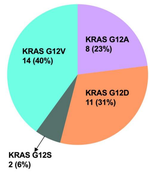


Population includes patients with RAS G12X mutant NSCLC who have received 1 or 2 prior lines of therapy which must include prior immunotherapy and platinum chemotherapy administered either concurrently or sequentially and have not received docetaxel previously. Adjuvant therapy or multimodal therapy with curative intent is considered prior therapy if disease progression occurred on treatment or within 6 months of treatment completion. Median follow-up is 10.8 months.

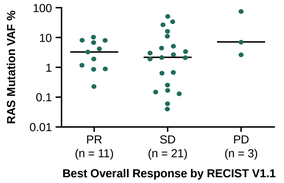
Key Results

5. Baseline ctDNA in 2L+ Patients with RAS G12X NSCLC and Response to Daraxonrasib at 120-220 mg QD

Distribution of Baseline RAS G12X Mutations in ctDNA (N = 35)

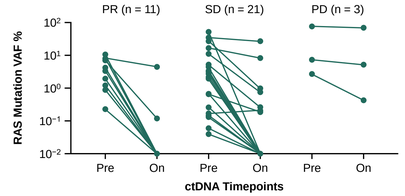


Relationship of Tumor Response to Baseline RAS Mutant VAF



- ctDNA testing was performed in 56 patients with 2L+ RAS G12X NSCLC with paired plasma samples collected (C1D1 and C2D1 (n = 49) or C1D1 and C3D1 (n = 7))
- A RAS G12X mutation was detected in baseline ctDNA in 63% (35/56) of the patients and were evaluable for ctDNA response
- Partial response (PR) or stable disease (SD) was observed across a wide range of baseline RAS mutant variant allele frequencies (VAFs) (0.04-52.05% VAF)

6. ctDNA Response in 2L+ Patients with RAS G12X NSCLC Treated with Daraxonrasib Associates with Clinical Response



- Complete ctDNA clearance (100% RAS VAF decrease from pre-treatment) was seen in 66% (23/35) of patients with 2L+ RAS G12X NSCLC with a detectable RAS G12X mutation in baseline ctDNA and associates with radiographic response
- Additionally, ctDNA clearance was seen across all RAS G12X mutations (KRAS G12D, KRAS G12V, KRAS G12A, KRAS G12S) and across the wide range of VAFs detected in baseline ctDNA
- Similar rate of complete ctDNA clearance was observed in the 2L/3L RAS G12X NSCLC population

Confirmed Best Overall Response by RECIST v1.1	Complete ctDNA Clearance (100% RAS VAF decrease from pre-treatment)	Incomplete ctDNA Clearance (<100% RAS VAF decrease from pre-treatment)
PR	82% (9/11)	18% (2/11)
SD	67% (14/21)	33% (7/21)
PD	0% (0/3)	100% (3/3)

Freeman Halton Fisher Exact test *P*=0.033

Population includes patients with RAS G12X mutant NSCLC who have received 1 or more prior lines of therapy which must include prior immunotherapy and platinum chemotherapy administered either concurrently or sequentially and have not received docetaxel previously.

Conclusions

- In the first in human study, daraxonrasib exhibited encouraging clinical activity as assessed by overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) in patients with RAS mutant non-small cell lung cancer (NSCLC). Clinical activity was accompanied by manageable safety and an acceptable tolerability profile
- Clinical response to daraxonrasib in NSCLC was observed irrespective of the baseline RAS mutant variant allele frequency (VAF) in circulating tumor DNA (ctDNA)
- Clinical response to daraxonrasib was associated with early on-treatment complete clearance of ctDNA across multiple RAS G12X mutations in NSCLC
- A global, randomized Phase 3 study (RASolve 301, NCT06881784) of daraxonrasib versus docetaxel in patients with previously treated, locally advanced or metastatic RAS mutant NSCLC has been initiated

Revolution Medicines

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HRAS, Harvey rat sarcoma viral oncogene homolog; KRAS, Kirsten rat sarcoma viral oncogene homolog; mg, milligrams; N, number; NE, not evaluable; NE[1], not estimatable; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease, PFS, progression free survival; PR, partial response; QD, once daily; RAS, rat sarcoma viral oncogene homolog; RECIST, Response Evaluation Criteria in Solid Tumors; SOD, sum of diameters; SD, stable disease; TRAEs, treatment-related adverse events; VAF, variant allele frequency

References:
1. Garon EB, et al. Lancet 2014;384:665-673.
2. Borghaei H, et al. N Engl J Med 2015; 373:1627-1639.
3. Rittmeyer A, et al. Lancet 2017;389:255-265.
4. Fehrenbacher L, et al. Lancet 2016;387:1837-1846.
5. de Langen AJ, et al. Lancet 2023;401:733-746.
6. Ahn MJ, J Clin Oncol. 2024 Sep 9:JCO2401544.
7. Mok TS, J Clin Oncol. 2024;42(17_suppl):LBA8509.
8. Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022.
9. Murciano-Goroff YR, et al. Cancer Res. 2023;83(7_Suppl):Abstract nr 1144.
10. Paweletz, CP et al. Clin Can Res. 2023; 29(16):3074-3080.
11. Sacher A, et al. N Engl J Med. 2023;389:710-721.

AACR
April 26-30, Chicago Abstract LB218

Contact: Minoti Hiremath (mhiremath@revmed.com)

We thank all the patients who participated in this study, their families who supported them, and the clinical investigators, advanced practice providers, and research staff who cared for them

This study was sponsored by Revolution Medicines, Inc. (ClinicalTrials.gov identifier: NCT05379985)