P3.18.65 Trial in Progress - RASolve 301: A Phase 3 Study of Daraxonrasib (RMC-6236) vs. Docetaxel in Patients With Previously Treated RAS-Mutant NSCLC

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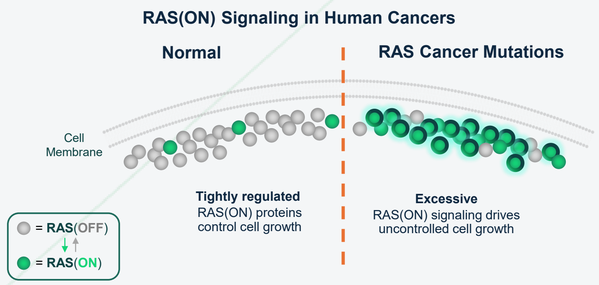
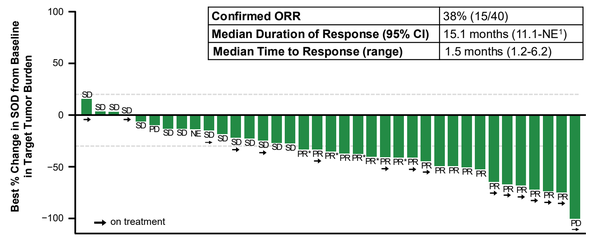
Introduction



- Daraxonrasib (RMC-6236) is a RAS(ON) multi-selective, tri-complex inhibitor designed to directly inhibit uncontrolled RAS(ON) signaling in RAS-driven tumors, including RAS mutant NSCLC
- Significant need exists for improved treatments for patients with previously treated NSCLC
- Reported outcomes for patients with NSCLC receiving docetaxel as 2L+ therapy are:[1–7]
  - Median Overall Survival (OS) is 9.1–11.8 months
  - Median Progression Free Survival (PFS) is 3–4.5 months
  - Objective Response Rate (ORR) is 9.2%–14.7%
  - ~30% of NSCLC tumors harbor an oncogenic RAS mutation[8]
- Current RAS(OFF) G12C therapies have received accelerated approval but not full approval[9]

Daraxonrasib Treatment Resulted in 38% Confirmed ORR and Durable Responses Observed in Patients With RAS G12X NSCLC Treated in 2L/3L at Doses Ranging From 120–220 mg QD[a] [10,11]

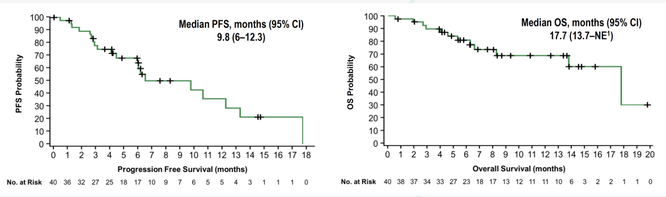


Confirmed ORR	38% (15/40)
Median Duration of Response (95% CI)	15.1 months (11.1-NE[†])
Median Time to Response (range)	1.5 months (1.2-6.2)

- The data included in this graph and the two graphs below is from the 30 Sep 2024 data cutoff
- The population in the Phase 1 study included patients with RAS G12X mutant NSCLC who have received 1 or 2 prior lines of therapy, which must have included prior immunotherapy and platinum chemotherapy administered either concurrently or sequentially and have not received docetaxel previously

Three patients included in the denominator of the ORR analyses are not displayed on waterfall plot 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

Median PFS of 9.8 Months and Median OS of 17.7 Months Observed in Patients With RAS G12X NSCLC Treated in 2L/3L With Daraxonrasib 120–220 mg QD[a] [10,11]



[a]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.

Most Frequent (≥20% in any Grade) TRAEs Observed in Patients With RAS G12X NSCLC Upon Treatment With Daraxonrasib at 120–220 mg[11]

- Rash* (7%) was the only G3 TRAE in ≥5% of patients
- No G4 or G5 TRAEs were observed
- TRAEs were managed by dose modifications and dosing intensity was maintained within this population

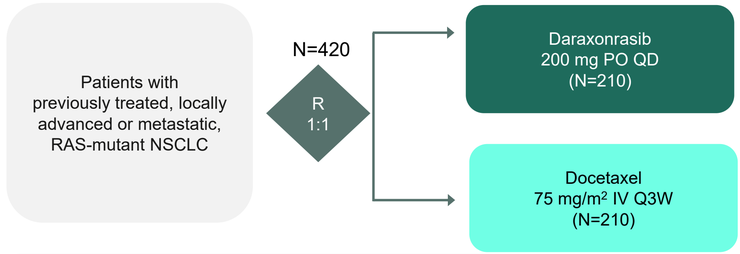
	120–220 mg (N=73)	
	Any Grade	**Grade ≥3**
Any TRAE	71 (97%)	12 (16%)
TRAEs in ≥20% of patients, n (%)		
Rash*	66 (90%)	5 (7%)
Diarrhea	46 (63%)	1 (1%)
Nausea	36 (49%)	0
Vomiting	29 (40%)	2 (3%)
Stomatitis	25 (34%)	0
TRAEs leading to dose modification, n (%)		
Dose interruption	25 (34%)	
Dose reduction	15 (21%)	
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.

Materials and Methods

RASolve 301 Study Design (NCT06881784)

- RASolve 301 is a global, randomized, open-label, Phase 3 study designed to evaluate the efficacy and safety of daraxonrasib compared to docetaxel in patients with previously treated, locally advanced or metastatic, RAS-mutant NSCLC



Dual Primary Endpoints

PFS[a] and OS (RAS G12X-C population)

Key Secondary Endpoints

PFS[a], OS (RAS [MUT] population)

ORR[a] (RAS G12X-C and RAS [MUT] population)

Other Secondary Endpoints[b]

ORR[c], PFS[c], DOR[a,c], TTR[a,c],

QoL[d], safety/tolerability, PK profile

[a]Per RECIST v1.1 as assessed by investigator; [b]In the RAS G12X-C and RAS (MUT) population; [c]RECIST v1.1 as assessed by BICR; [d]Using EORTC QLQ-LC13 or EORTC QLQ-C30

Key Inclusion Criteria

- Histologically confirmed locally advanced or metastatic NSCLC
- ≥18 years of age
- Measurable disease per RECIST v1.1
- ECOG PS 0 or 1
- Adequate organ function (bone, marrow, liver, kidney, coagulation)
- One to two prior lines of therapy including an anti-PD1/PD-L1 agent and platinum-based chemotherapy.

Prior therapy with any RAS inhibitor, including a KRAS G12C inhibitor, is prohibited

- Documented RAS mutation status based on local testing. Eligible RAS mutations are defined as nonsynonymous mutations in KRAS, NRAS, or HRAS at codons 12, 13, or 61 (G12, G13, or Q61)

Key Exclusion Criteria

- Untreated CNS metastases
- Prior RAS-directed therapy or docetaxel
- Presence of an actionable driver mutation for which approved targeted therapy is available
- Medically significant comorbidities (eg significant CVD, lung disease, impaired GI function)
- Ongoing anticancer therapy
- Pregnant and/or breastfeeding

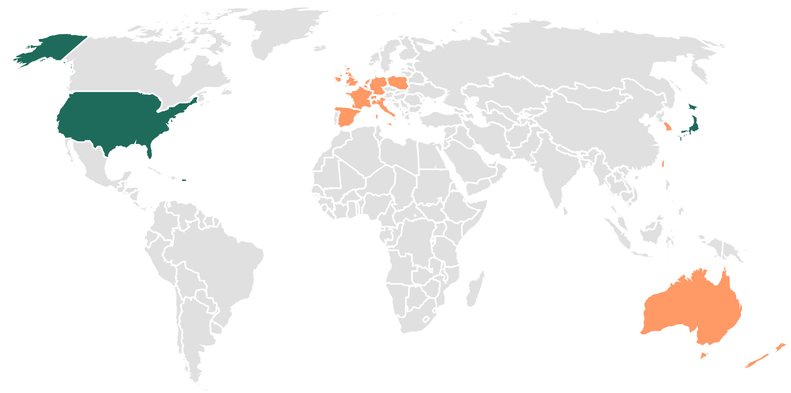
RASolve 301 Participating Countries[†]

Study locations currently recruiting

- Japan
- Puerto Rico
- United States

Other planned locations

- Australia
- Belgium
- France
- Germany
- Hong Kong
- Italy
- Ireland
- Netherlands
- New Zealand
- Poland
- Singapore
- South Korea
- Spain
- Switzerland
- Taiwan
- UK



[†]As of August 27th, 2025.

Study enrollment commenced in May 2025 and is ongoing

Abbreviations

2L, second-line; 2L+, second-line and beyond; 3L, third-line; BICR, blinded independent central review; CNS, central nervous system; CVD, cardiovascular disease; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer quality of life questionnaire-lung cancer 13; G3, Grade 3; GI, gastrointestinal; G12C, glycine 12 to cysteine mutation; HRAS, Harvey rat sarcoma virus; IV, intravenous; KRAS, Kirsten rat sarcoma virus; MUT, mutant; NE, not estimable; NRAS, neuroblastoma RAS viral oncogene homolog; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; pK, pharmacokinetics; PO, by mouth; PR, partial response; Q3W, every 3 weeks; Q61, glutamine at codon 61; QD, once daily; QoL, quality of life; R, randomization; RAS, rat sarcoma viral oncogene homolog; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SOD, sum of diameters; TTR, time to response; TRAE, treatment-related adverse event

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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:JCO2401544.
7. Mok T, et al. *J Clin Oncol*. 2024;42(11):1252-1264.
8. Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022.
9. FDA grants accelerated approval to adagrasib for KRAS G12C-mutated NSCLC. U.S. Food & Drug Administration. Updated December 12, 2022. Accessed July 21, 2025. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-adagrasib-kras-g12c-mutated-nsclc.
10. Punekar AR, et al. *J Thoracic Onc*. 2025; 20(351) S10_6MO.
11. Luo J, et al. *Cancer Res*. 2025; 85(8_Supplement_2):LB218.