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Safety and Clinical Activity of Daraxonrasib (RMC-6236) in RAS Mutant Non-Small Cell Lung Cancer (NSCLC)

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Disclosures

None

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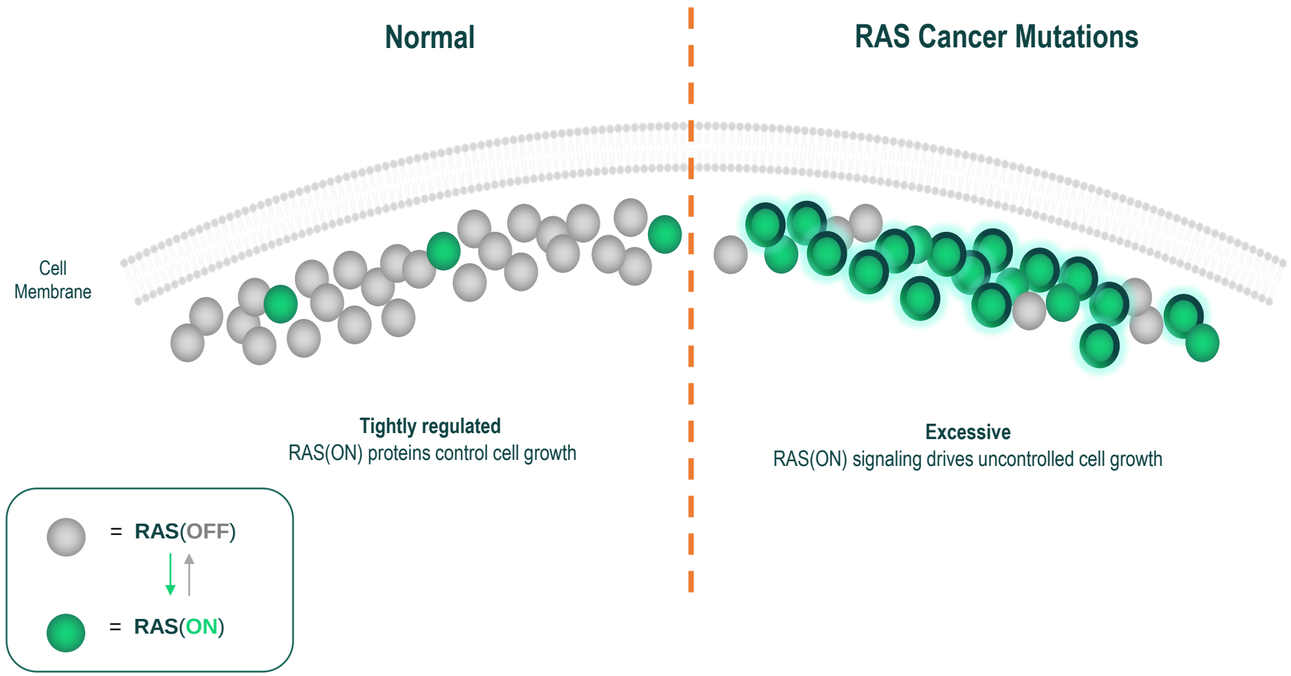
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RAS(ON) Tri-Complex Inhibitors Designed to Deliver Robust and Durable Antitumor Activity

RAS(ON) Signaling in Human Cancers



- 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 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]

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. doi: 10.1200/JCO-24-01544. 7. Mok TS, J Clin Oncol. 2024;42(17_suppl):LBA8509. 8.Estimated using tumor mutation frequencies from Foundation Medicine Insights March 2022.

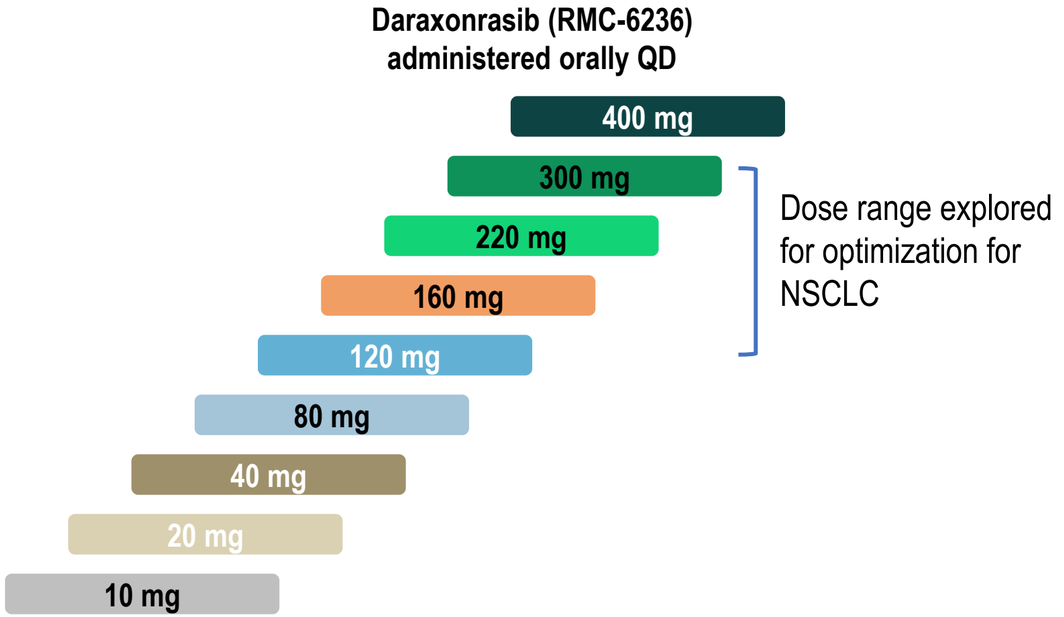
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NSCLC, non-small cell lung cancer; 2L+, treatment in second line or as a later line of therapy

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RMC-6236-001 First-In-Human Study

Dose Escalation



Study enrolled patients with tumors harboring RAS mutations in KRAS, HRAS, and NRAS at codon 12 (RAS G12X), codon 13 (G13) or codon 61 (Q61), including patients with NSCLC; no NSCLC patients with KRAS G12C mutations were enrolled

Baseline Characteristics of Patients with RAS Mutant NSCLC

Baseline Characteristics	120–300 mg N = 124*	120–220 mg N = 73
Age, years, median (range)	67 (31, 89)	68 (36, 89)
Male, n (%)	49 (40%)	28 (38%)
ECOG PS 1, n (%)	100 (81%)	59 (81%)
Number of prior anti-cancer therapies, median (range)	2 (1, 6)	2 (1, 6)
Smoking current/past, n (%)	94 (76%)	53 (73%)
Brain metastases at baseline, n (%)	36 (29%)	19 (26%)
Metastatic at diagnosis [stage IV], n (%)	70 (57%)	37 (51%)

All data included in this presentation is from the data cutoff of 30 Sep 2024
* Additional 7 patients were treated at doses from 20-80 mg daily and 1 patient treated at 400mg daily

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ECOG PS, Eastern Cooperative Oncology Group Performance Status; NSCLC, non-small cell lung cancer

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Daraxonrasib (RMC-6236) Treatment-Related Adverse Events (TRAEs) in Patients with NSCLC

	120–300 mg (N = 124)		120–220 mg (N = 73)		300 mg (N = 51)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TRAE	121 (98%)	33 (27%)	71 (97%)	12 (16%)	50 (98%)	21 (41%)
TRAEs in ≥ 10% of patients, n (%)						
Rash*	110 (89%)	9 (7%)	66 (90%)	5 (7%)	44 (86%)	4 (8%)
Diarrhea	87 (70%)	10 (8%)	46 (63%)	1 (1%)	41 (80%)	9 (18%)
Nausea	68 (55%)	0	36 (49%)	0	32 (63%)	0
Vomiting	55 (44%)	3 (2%)	29 (40%)	2 (3%)	26 (51%)	1 (2%)
Stomatitis	47 (38%)	3 (2%)	25 (34%)	0	22 (43%)	3 (6%)
Paronychia	26 (21%)	0	14 (19%)	0	12 (24%)	0
Fatigue	20 (16%)	0	8 (11%)	0	12 (24%)	0
Dry skin	19 (15%)	0	9 (12%)	0	10 (20%)	0
AST increased	17 (14%)	2 (1.6%)	11 (15%)	0	6 (12%)	2 (4%)
ALT increased	15 (12%)	3 (2.4%)	10 (14%)	0	5 (10%)	3 (6%)
Decreased appetite	14 (11%)	0	4 (6%)	0	10 (20%)	0
Dysgeusia	12 (10%)	0	3 (4%)	0	9 (18%)	0
Other select TRAEs, n (%)						
Anemia	9 (7%)	3 (2%)	4 (6%)	2 (3%)	5 (10%)	1 (2%)

At 120–220 mg: Rash (7%) was the only G3 TRAE in ≥ 5% patients; no G4 or 5 TRAEs were observed

At 300 mg: One Grade 4 TRAE observed (pneumonitis) with patient recovering; no Grade 5 TRAEs

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

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ALT, alanine transaminase; AST, aspartate transferase; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; TRAE, treatment-related adverse event

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Daraxonrasib (RMC-6236) Dose Intensity

TRAEs Leading to Dose Modifications

	120–300 mg (N = 124)	120–220 mg (N = 73)	300 mg (N = 51)
TRAEs leading to dose modification, n (%)	64 (52%)	30 (41%)	34 (67%)
Dose interruption	59 (48%)	25 (34%)	34 (67%)
Dose reduction	34 (27%)	15 (21%)	19 (37%)
TRAEs leading to dose discontinuation, n (%)	7 (6%)	3 (4%)	4 (8%)
Mean dose intensity	86%	91%	78%

For the 120–220 mg cohort,

- Median treatment duration was 5.5 months
- Median cumulative duration of dose interruption was 8.5 days

Rash Prophylaxis at 120-220 mg

	Without Prophylaxis for Rash (N = 58)	With Prophylaxis for Rash (N = 15)
Treatment related rash		
Grade ≥ 3	5 (9%)	0 (0%)
Dose modification due to treatment related rash		
Grade ≥ 3	4 (7%)	0 (0%)

Based on the overall benefit-risk, 200 mg was selected for evaluation in the Phase 3 study

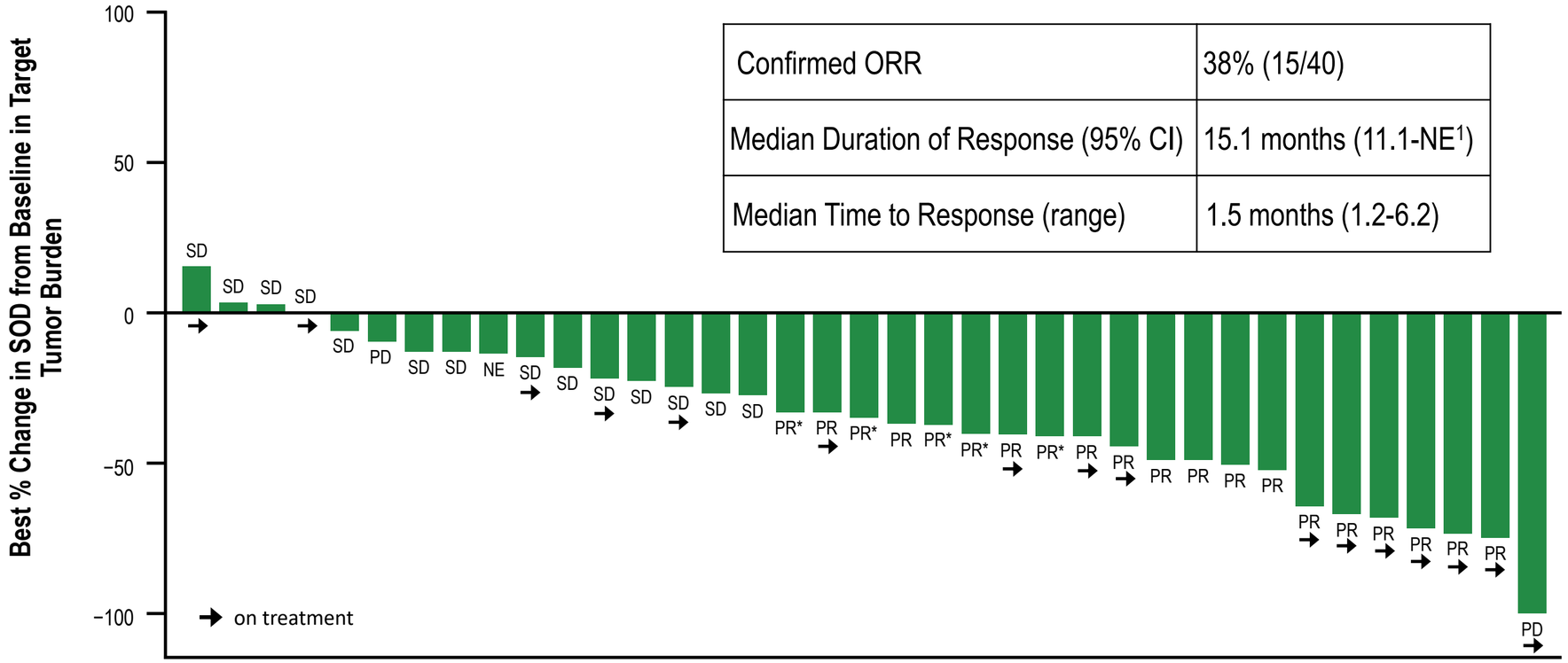
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TRAE, treatment-related adverse event

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Confirmed Objective Response Rate and Duration of Response

in 2L/3L Patients with RAS G12X NSCLC Treated with Daraxonrasib (RMC-6236) at 120-220 mg Daily



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 assessed in patients with NSCLC (n=40) that

- Harbor RAS G12X mutations
- Have received 1 or 2 prior lines of therapy (prior immunotherapy and platinum chemotherapy)
- Have not received docetaxel previously

ORR analyses included all patients who received first dose of daraxonrasib at least 14 weeks prior to data cutoff date (to allow 2 potential scans). ORR (by RECIST v1.1). 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. Population includes patients with RAS G12X mutant NSCLC who have received 1 or 2 prior lines of therapy which 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 or treatment completion was within 6 months of first dose of RMC-6236. Median duration of response estimated using the Kaplan-Meier method. Median follow-up is 10.8 months.

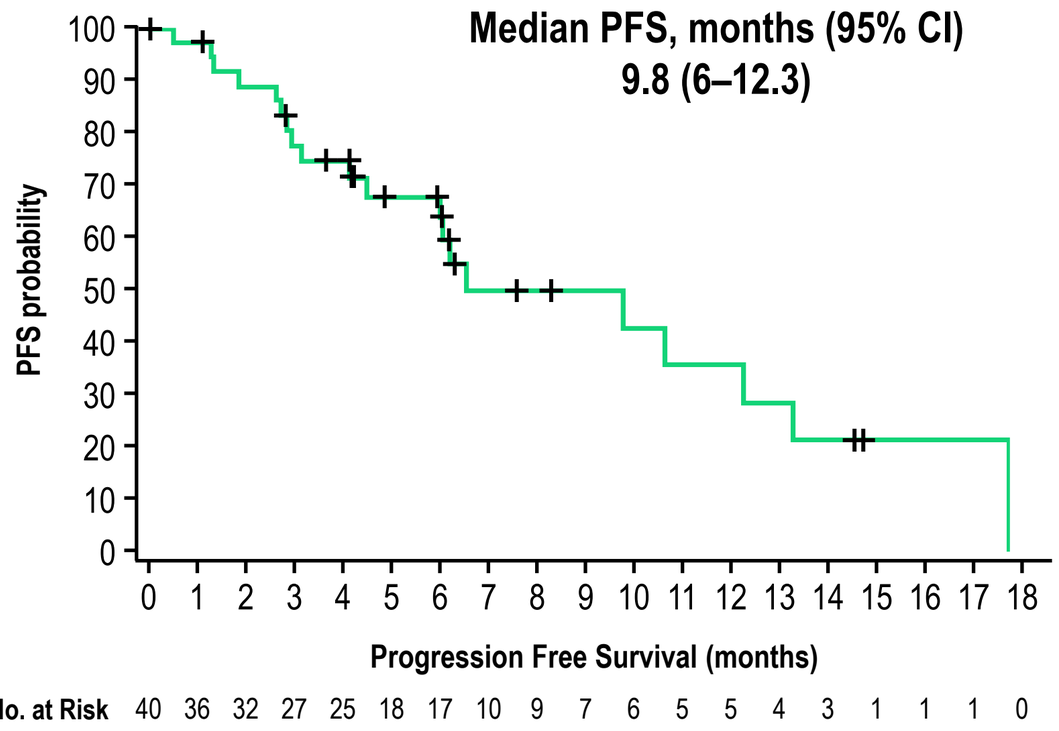
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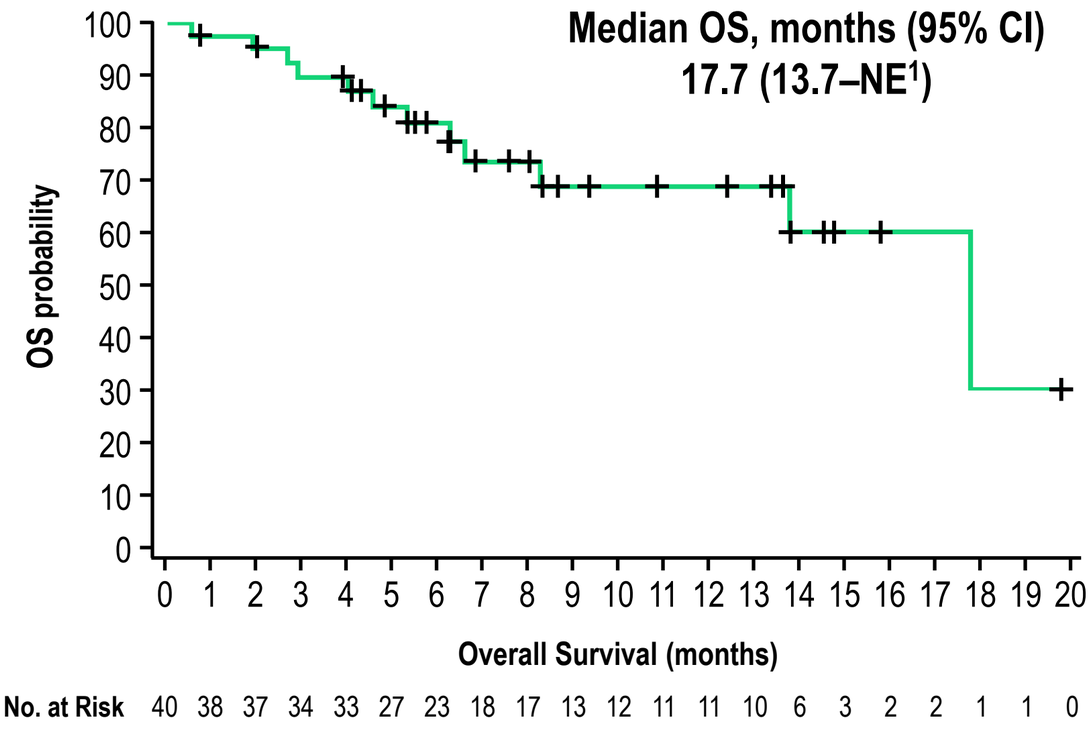
NE, not evaluable; NE[1], Not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; SOD, sum of diameter.

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Median Progression Free Survival and Interim Overall Survival

in 2L/3L Patients with RAS G12X NSCLC Treated with Daraxonrasib (RMC-6236) at 120–220 mg Daily





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 or treatment completion was within 6 months of first dose of daraxonrasib. Median follow-up is 10.8 months.

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2L, second line; 3L, third line; CI, confidence interval; NE[1], not estimable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

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Conclusions

In the first in human study, daraxonrasib (RMC-6236) demonstrated encouraging clinical activity as measured by ORR, PFS, and OS in patients NSCLC with a manageable safety and tolerability profile and favorable dose intensity

A randomized Phase 3 study (RASolve 301) of daraxonrasib versus docetaxel in patients with previously treated, locally advanced or metastatic RAS mutant NSCLC has been initiated based on these data

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