RAMP 202: A phase 2 study of avutometinib (VS-6766) ± defactinib in patients with advanced KRAS G12V mutant non–small cell lung cancer (NSCLC)

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ABSTRACT # 9100

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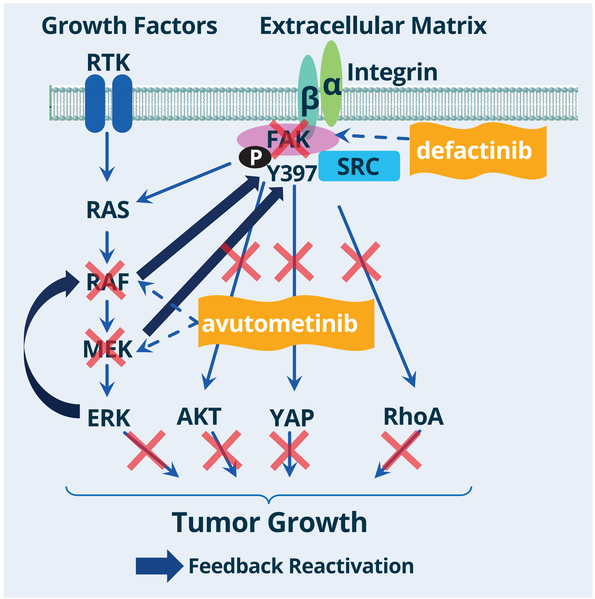
BACKGROUND

- *KRAS* mutations (mt) occur in ~30% of lung adenocarcinomas, among which G12C is most common (40%), followed by G12V (19%) and G12D (15%).[1]
- Approved treatments for advanced *KRAS* mt NSCLC (excluding G12C) are limited to chemotherapy and immune checkpoint inhibitors.
- Avutometinib is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream RAF.[2,3,4,5] (**Figure 1**)
- Defactinib is a selective inhibitor of focal adhesion kinase (FAK), which has been shown to mediate resistance to multiple anticancer agents.[6,7,8,9] (**Figure 1**)
- Herein, we present efficacy and safety results of the randomized, phase 2, adaptive, multicenter, open-label RAMP 202 trial evaluating avutometinib ± defactinib in previously-treated *KRAS* mt NSCLC (NCT04620330).

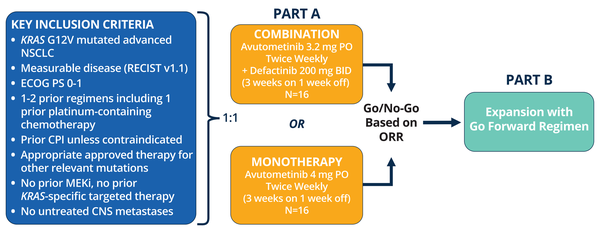


ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; MEK, mitogen-activated protein kinase; RAF, rapidly accelerated fibrosarcoma; RTK, receptor tyrosine kinase; YAP, yes-associated protein.

Figure 1. Avutometinib + Defactinib Mechanism of Action

RESULTS

RAMP 202 Study Design



BID, twice daily; CNS, central nervous system; CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; MEKi, MEK inhibitor; ORR, overall response rate; PO, by mouth.

Endpoints

PRIMARY

Parts A and B
- Confirmed ORR per RECIST v1.1 as assessed by BICR

SECONDARY

Parts A and B
- Safety and tolerability
- Additional efficacy data: DoR, ORR, DCR, PFS, OS
- Pharmacokinetics

EXPLORATORY
- Mutations, gene expression levels, and protein levels and/or activity related to RAS/RAF/MEK pathway and other markers
- ORR in *KRAS*-other (non-G12V) NSCLC

BICR, blinded indepedent central review; DCR, disease control rate; DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Baseline Characteristics

	Avutometinib (n=16)	Avutometinib + Defactinib (n=19)
Age, median, yrs (range)	66.5 (57, 85)	68.0 (34,79)
Male sex, n (%)	7 (43.8)	7 (36.8)
ECOG PS, n (%)		
0	4 (25)	6 (31.6)
1	12 (75)	13 (68.4)
Number of prior systemic regimens, median (min, max)	2.0 (1, 4)	2.0 (1,5)
Prior platinum-based chemotherapy, n (%)	15 (93.8)	19 (100)
Prior ICI, n (%)	14 (87.5)	16 (84.2)
Prior bevacizumab, n (%)	1 (6.3)	1 (5.3)
Other, n (%)	2 (12.5)	3 (15.8)
Time since most recent treatment (months), median (min, max)	2.0 (0.6, 49.3)	2.5 (1.1, 47.9)
Best response to most recent treatment in metastatic/recurrent setting, n (%)		
CR	0	0
PR	4 (25.0)	4 (21.1)
SD	4 (25.0)	6 (31.6)
PD	6 (37.5)	8 (42.1)
NE	1 (6.3)	0
Unknown	1 (6.3)	1 (5.3)

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ICI, immune checkpoint inhibitor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Efficacy

- Limited clinical activity was observed in both monotherapy and combination treatment arms.
- Current data do not meet protocol criteria to proceed with the expansion phase.

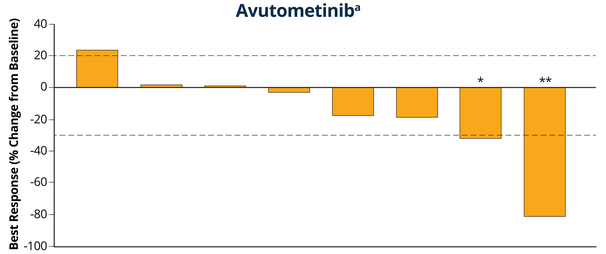
	Avutometinib (n=16)	Avutometinib + Defactinib (n=19)
Confirmed ORR, n (%)	0 (0)	2 (11)
PR	0 (0)	2 (11)
SD	7 (44)	5 (26)
PD	1 (6)	8 (42)
NE[a]	8 (50)	4 (21)
Disease control rate (SD + PR)	7 (44)	7 (37)

[a]NE includes patients for whom not all target lesions were evaluated, as well as those who did not undergo a follow-up assessment at the time of the data cut-off.

NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

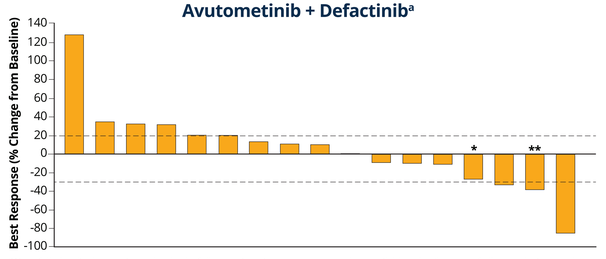
Percent Change from Baseline Sum of Target Lesions as Assessed by BICR

Avutometinib[a]



[a]Waterfall plot displays patients that had a follow-up imaging assessment and an available value for sum of all target lesions at the time of data cut.
*Patient experienced a best percentage change of -32.4% but was not classified as PR because patient discontinued after initial assessment of PR.
**Patient experienced a best percentage change of -81.3% but was not classified as PR because patient discontinued after initial assessment of PR.

Avutometinib + Defactinib[a]



[a]Waterfall plot displays patients that had a follow-up imaging assessment and an available value for sum of all target lesions at the time of data cut.
*Patient experienced a best percentage change of -27.3% but was not classified as SD due to worsening nontarget peritoneal disease.
**Patient experienced a best percentage change of -38.8%. Patient had PR in target lesions but was classified as a PD due to a new lesion at same assessment.

Safety

	Avutometinib (n=16)		Avutometinib + Defactinib (n=19)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any AE, n (%)	15 (93.8)	7 (43.8)	19 (100)	7 (36.8)
Nausea	3 (18.8)	-	10 (52.6)	-
Diarrhea	4 (25.0)	0	6 (31.6)	1 (5.3)
Peripheral edema	4 (25.0)	1 (6.3)	6 (31.6)	1 (5.3)
Rash	4 (25.0)	1 (6.3)	2 (10.5)	0
Blood CPK increased	4 (25.0)	3 (18.8)	5 (26.3)	0
Dermatitis acneiform	3 (18.8)	-	2 (10.5)	-
Fatigue	2 (12.5)	1 (6.3)	4 (21.1)	1 (5.3)
AST increased	2 (12.5)	-	4 (21.1)	-
Vomiting	0	0	5 (26.3)	1 (5.3)
Blood bilirubin increased	0	0	4 (21.1)	1 (5.3)

AE, adverse event; AST, aspartate aminotransferase; CPK, creatine phosphokinase.

CONCLUSIONS

- In this pretreated population of patients with *KRAS-G12V* mt NSCLC, limited clinical activity was observed with avutometinib monotherapy and avutometinib + defactinib combination therapy.
- While no new safety signals were identified, criteria to proceed to part B were not met, and further evaluation of avutometinib ± defactinib in *KRAS-G12V* mt NSCLC will not be pursued.
  - Enrollment in the *BRAF* mt cohort of RAMP 202 is ongoing.
- Additional trials evaluating rational avutometinib monotherapy and rational avutometinib combinations (sotorasib [NCT05074810], adagrasib [NCT05375994], everolimus [NCT02407509]) are ongoing in patients with *KRAS* mt NSCLC.

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