Exposure-Response Analysis for Avutometinib in Combination With Defactinib in Low-Grade Serous Ovarian Cancer

Yaofeng Cheng[1], Sarath Nagothu[1], Dinesh Vippala[1], Susana N. Banerjee[2], Rachel N. Grisham[3,4], David M. O'Malley[5], Els Van Nieuwenhuysen[6,7], Udai Banerji[8-10], D. Ross Camidge[11], Joshua E. Reuss[12], Azita Razzaghi[1], Paraneedharan Ramachandran[1], John Hayslip[1], Jonathan A. Pachter[1], Stephanie Lustgarten[1]

[1]Verastem Oncology, Boston, MA; [2]The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, GTG-UK, London, UK; [3]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Weill Cornell Medical College New York, NY, USA; [5]The Ohio State University, James Comprehensive Cancer Center, Columbus, OH; [6]University Hospitals Leuven, Leuven Cancer Institute, BGOG, Leuven, Belgium; [7]Centre Léon BERARD, and University Claude Bernard Lyon I, Lyon, France; [8]Drug Development Unit, The Institute of Cancer Research and The Royal Marsden Hospital NHS Foundation Trust, London, UK; [9]Centre for Cancer Drug Discovery, The Institute of Cancer Research, London, UK; [10]Clinical Pharmacodynamics Biomarker Group, The Institute of Cancer Research, London, UK; [11]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [12]Lombardi Comprehensive Cancer Center, Georgetown University, Washington, DC

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BACKGROUND

- Avutometinib is a first-in-class oral rapidly accelerated fibrosarcoma (RAF)/mitogen-activated extracellular signal-regulated kinase (MEK) clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF.[1,2] Defactinib is a selective inhibitor of focal adhesion kinase (FAK), a key adaptive resistance mechanism to the rat sarcoma virus/mitogen-activated protein kinase pathway.[3,5]
- The efficacy and safety of avutometinib and defactinib combination therapy was initially evaluated in patients with solid tumors, including low-grade serous ovarian cancer (LGSOC), in the phase 1 FRAME study (NCT03875820).[6] In patients with recurrent LGSOC, the combination of avutometinib and defactinib showed an objective response rate (ORR) of 42%. The recommended phase 2 dose is avutometinib 3.2 mg twice weekly (BIW) with defactinib 200 mg twice daily (BID).
- The phase 2 ENGOT-ov60/GOG-3052/RAMP 201 study (NCT04625270) investigated the combination of avutometinib 1.6 mg or 3.2 mg BIW with defactinib 200 mg BID in patients with recurrent LGSOC.[7] The ORR was 31% (Kirsten rat sarcoma virus homologue [*KRAS*] mutant [mt], 44%; *KRAS* wild-type [wt], 17%), median duration of response (DOR) was 31.0 months, and median progression-free survival was 12.9 months (*KRAS* mt, 22.0 months; KRAS wt, 12.8 months).
- The safety profile of avutometinib + defactinib was also evaluated in the phase 2 RAMP 202 study (NCT04620330) in patients with recurrent KRAS mt and v-raf murine sarcoma viral oncogene homolog B1 mt NSCLC.[8]
- The combination of avutometinib (3.2 mg BIW) and defactinib (200 mg BID; AVMAPKI™ FAKZYNJA™ CO-PACK) was approved in the US on May 8, 2025 for the treatment of adult patients with *KRAS* mt recurrent LGSOC who have received prior systemic therapy.
- The phase 3 GOG-3097/ENGOT-ov81/NCRI/RAMP 301 trial evaluating avutometinib + defactinib versus investigators' choice of therapy in patients with recurrent LGSOC is currently ongoing.[9]
- This study characterized the relationship between exposures of avutometinib + defactinib and efficacy and safety endpoints using exposure-response (ER) models to determine the optimal dose selection for treatment of patients with LGSOC.

METHODS

- Efficacy analyses were performed for patients with LGSOC from 2 clinical studies, and safety analyses included patients with LGSOC and other solid tumors from 3 clinical studies (**Table 1**).
- Efficacy endpoints included ORR and DOR evaluated by an independent review committee (IRC), and best target lesion response (BTLR) evaluated by an investigator (INV; **Table 2**).
- Safety endpoints were treatment-emergent adverse events (TEAEs) of grade ≥2 eye disorders, grade ≥2 gastrointestinal (GI) toxicity, grade ≥2 skin disorders, grade ≥2 liver function test (LFT), and grade ≥3 creatine phosphokinase (CPK) elevation (**Table 2**).
- Exposure metrics for avutometinib and defactinib included steady-state maximum concentration ($C_{max,ss}$), average concentration ($C_{avg,ss}$), and trough concentration ($C_{trough,ss}$), and average concentration until time of event/censoring ($C_{avg,TE}$) derived from population pharmacokinetics model (**Table 2**).
- A list of covariates that may have an impact on the efficacy or safety endpoints were evaluated (**Table 3**).
- Logistic regression, Cox proportional hazard or parametric time-to-event, and nonlinear mixed effects models were utilized to derive the relationship between avutometinib/defactinib exposure and efficacy/safety endpoints

Table 1. Clinical Studies Included in the ER Analysis

Study	Title	Patient	Numbers of patients	Dose levels
IST-VS-6063-003 (FRAME; phase 1)	A Phase 1 Trial of the Combination of Defactinib (VS-6063) (FAK inhibitor) and VS-6766 (a Dual RAF/MEK Inhibitor) in Patients with Advanced Solid Tumors	Solid tumors	91 (LGSOC, n=26)	*Avutometinib + defactinib:* Avutometinib 3.2 mg BIW + defactinib 200 mg BID Avutometinib 4 mg BIW + defactinib 200 mg BID Avutometinib 3.2 mg BIW + defactinib 400 mg BID Avutometinib 4 mg BIW + defactinib 400 mg BID
VS-6766-201 (RAMP 201; phase 2)	A Phase 2 Study of Avutometinib (VS-6766, a Dual RAF/MEK Inhibitor) Alone and in Combination with Defactinib (FAK Inhibitor) in Recurrent Low-Grade Serous Ovarian Cancer (LGSOC)	Recurrent LGSOC	212	*Avutometinib monotherapy:* Avutometinib 4 mg BIW (n=70) *Avutometinib + defactinib:* Avutometinib 3.2 or 1.6 mg BIW + defactinib 200 mg BID (n=142)
VS-6766-202 (RAMP 202; phase 2)	A Phase 2 Study of VS-6766 (Dual RAF/MEK Inhibitor) as a Single Agent and in Combination with Defactinib (FAK Inhibitor) in Recurrent *KRAS*-Mutant (*KRAS* mt) Non-Small Cell Lung Cancer (NSCLC)	Recurrent *KRAS* mt NSCLC	90	*Avutometinib monotherapy:* Avutometinib 4 mg BIW (n=17) *Avutometinib + defactinib:* Avutometinib 3.2 mg BIW + defactinib 200 mg BID (n=73)

Oral dosing for monotherapy and combination therapy was 3 weeks on/1 week off.
Only patients treated with avutometinib and defactinib in combination were included in the ER analysis.

Table 2. Efficacy and Safety Endpoints and Exposure Parameters

Outcome	Measure	Description
Efficacy endpoints	ORR by IRC	The proportion of patients with the best overall tumor response of PR or CR, relative to the total number of patients in the analysis population. Response is assessed according to the RECIST 1.1 criteria
	DOR by IRC	The time from first documentation of objective response of PR or CR to the first documentation of disease progression or death
	BTLR by INV	The largest percentage decrease in sum of target lesion diameters In the case of patients without any decrease, the smallest increase in sum of target lesion diameters is considered
Safety endpoints	Grade ≥2 eye disorders	TEAEs associated with the SOC of eye disorders with a severity of grade ≥2
	Grade ≥2 GI toxicity	TEAEs associated with GI toxicities, including diarrhea, vomiting, and nausea, with a severity of grade ≥2
	Grade ≥2 skin disorders	TEAEs associated with the SOC of skin disorders with a severity of grade ≥2
	Grade ≥2 LFTs	TEAEs associated with LFTs, including ALT, AST, and bilirubin, with a severity of grade ≥2
	Grade ≥3 CPK elevation	TEAEs associated with CPK elevation with a severity of grade ≥3
Exposure parameters	$C_{avg,ss}$	Steady-state average concentration
	$C_{max,ss}$	Steady-state maximum concentration
	$C_{trough,ss}$	Steady-state trough concentration
	$C_{avg,TE}$	Average concentrations until the time of event/censoring

Table 3. Covariates

Covariate	Efficacy	Safety
KRAS mutation status	✓	✓
Number of prior regimens (1-3 vs ≥4)	✓	✓
Age at baseline	✓	✓
ECOG preformance status (0 vs 1)	✓	✓
Stage of cancer at baseline	✓	
Target lesion size at baseline	✓	
Cancer type (LGSOC vs other)		✓
Sex		✓

RESULTS

Efficacy and Safety Data Exploration

- A total of 158 patients with LGSOC from the FRAME and RAMP 201 studies were included in the ORR analysis. Among these patients, 46 with a confirmed complete (CR) or partial response (PR) were included in the DOR analysis. The BTLR analysis included 164 patients. In the RAMP 201 study, only 1 of 23 patients who received avutometinib 1.6 mg BIW had a PR or CR, while 34 of 109 patients who received avutometinib 3.2 mg BIW had a PR or CR (**Table 4**).
- A total of 303 patients treated with avutometinib + defactinib (FRAME, n=88; RAMP 201, n=142; RAMP 202, n=73) were included in the safety analysis (**Table 5**). Of the 5 TEAEs of interest, the most frequent was grade ≥2 skin disorders (39.9%; n=121), followed by grade ≥2 GI toxicity (34.0%; n=103), grade ≥2 LFTs (25.1%; n=76), and grade ≥3 CPK elevation (14.5%; n=44). The least frequent TEAE of interest was grade ≥2 eye disorders (8.9%; n=27).

Table 4. Summary of Efficacy Results by Studies

Study and cohort	ORR				DOR			BTLR	
	n	PR/CR, n (%)	SD/PD, n (%)	Missing/ unknown, n (%)	n	Disease progression, n (%)	No disease	n	Percent change, mean (range)
FRAME									
Avutometinib 3.2 mg BIW + defactinib 200 mg BID	20	10 (50.0)	10 (50.0)	0	10	7 (70.0)	3 (30.0)	-	-
Avutometinib 3.2 mg BIW + defactinib 400 mg BID	1	0	1 (100)	0	-	-	-	1	-4.7 (NA)
Avutometinib 4 mg BIW + defactinib 200 mg BID	5	1 (20.0)	4 (80.0)	0	1	1 (100)	0	5	-24.2 (-56.2, -8.1)
RAMP 201									
Avutometinib 1.6 mg BIW + defactinib 200 mg BID	23	1 (4.3)	20 (87.0)	2 (8.7)	1	0	1 (100	26	-9.1 (-72.1, 75.0)
Avutometinib 3.2 mg BIW + defactinib 200 mg BID	109	34 (31.2)	71 (65.1)	4 (3.7)	34	8 (23.5)	26 (76.5)	132	-25.2 (-100, 103)
All data	158	46 (29.1)	106 (67.1)	6 (3.8)	46	16 (34.8)	30 (65.2)	164	-22.5 (-100, 103)

Table 5. Summary of Safety Results by Studies

TEAE of interest, n (%)	FRAME (n=88)		RAMP 201 (n=142)		RAMP 202 (n=73)	
	No	Yes	No	Yes	No	Yes
Grade ≥2 eye disorders	86 (97.7)	2 (2.3)	124 (87.3)	18 (12.7)	66 (90.4)	7 (9.6)
Grade ≥2 GI toxicity	69 (78.4)	19 (21.6)	85 (59.9)	57 (40.1)	46 (63.0)	27 (37.0)
Grade ≥2 skin disorders	48 (54.5)	40 (45.5)	81 (57.0)	61 (43.0)	53 (72.6)	20 (27.4)
Grade ≥2 LFTs	61 (69.3)	27 (30.7)	101 (71.1)	41 (28.9)	65 (89.0)	8 (11.0)
Grade ≥3 CPK elevation	80 (90.9)	8 (9.1)	112 (78.9)	30 (21.1)	67 (91.8)	6 (8.2)

Key Findings From Model Analysis

Efficacy Evaluation

- In patients with LGSOC, a positive ER relationship was observed, with higher avutometinib exposure significantly associated with improved ORR, longer DOR, and increased BTLR across both *KRAS* mt and *KRAS* wt populations.
- Defactinib exposure was not significantly correlated with efficacy within the tested range.
- *KRAS* mutation status was the only identified covariate and patients with *KRAS* mt LGSOC tumors demonstrated better efficacy compared with those with *KRAS* wt tumors.

Safety Evaluation

- All analyzed TEAEs were associated with avutometinib exposure. This finding was with $C_{avg,TE}$ as the best avutometinib exposure parameter to describe the relationship.
- Only grade ≥2 LFTs were associated with defactinib exposure. This finding was predominately increased blood bilirubin and only contributed minimally by elevated ALT and AST. This increased blood bilirubin is believed to be primarily due to interruption of bilirubin metabolism and circulation by defactinib rather than hepatocyte injury.
- Patients with LGSOC were estimated to have higher probabilities of all analyzed TEAEs compared to those with other cancer types. This is likely attributable to the longer treatment duration observed in patients with LGSOC.
- *KRAS* mutation status was identified as a significant covariate for grade ≥2 eye disorders, likely reflecting the longer treatment duration observed among patients with *KRAS* mt LGSOC compared with those with *KRAS* wt LGSOC.

Table 6. Summary of ER Analysis by Efficacy and Safety Endpoints

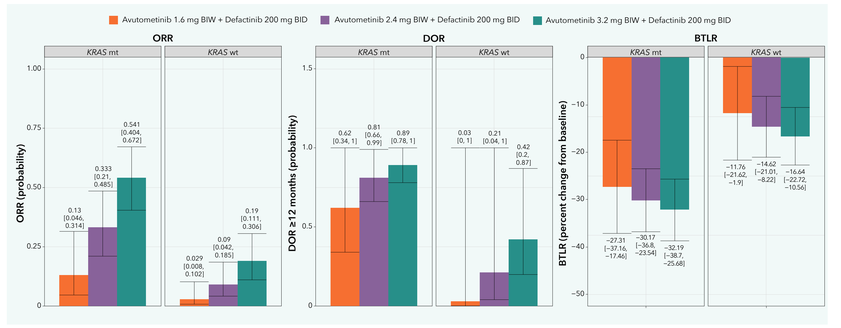
Endpoint	Exposure metrics and response relationship		Significant covariate
	Avutometinib	Defactinib	
ORR (by IRC)	$C_{avg,TE}$ Significant (+)	NA	*KRAS* mutation status
DOR (by IRC)	$C_{avg,TE}$ Significant (+)	NA	*KRAS* mutation status
BTLR (by INV)	$C_{avg,ss}$ Significant (-)	NA	*KRAS* mutation status
Grade ≥2 eye disorders	$C_{avg,TE}$ Significant (+)	NA	Cancer type *KRAS* mutation status
Grade ≥2 GI toxicity	$C_{avg,TE}$ Significant (+)	$C_{avg,ss}$ (*P*=0.052)	Cancer type
Grade ≥2 skin disorders	$C_{avg,TE}$ Significant (+)	NA	Cancer type
Grade ≥2 LFTs	$C_{avg,TE}$ Significant (+)	$C_{avg,TE}$ Significant (+)	Cancer type
Grade ≥3 CPK elevation	$C_{avg,TE}$ Significant (+)	NA	Cancer type

Significance defined as p-value < 0.05.
A positive (+) sign indicates a positive correlation, and a negative (-) sign indicates a negative correlation.

Model Predictions of Efficacy and Safety

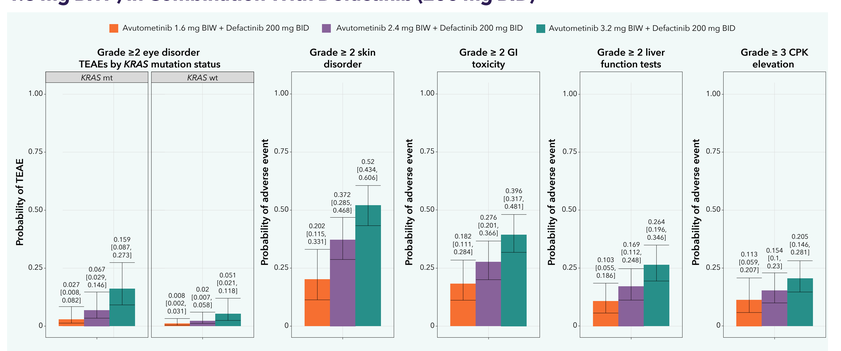
- Avutometinib 3.2 mg BIW + defactinib 200 mg BID was estimated to have greater ORR, higher DOR ≥12 months, and greater BTLR for patients with LGSOC compared to lower avutometinib doses (eg, 2.4 or 1.6 mg BIW). Patients with KRAS mt LGSOC generally exhibited better efficacy compared to those with KRAS wt LGSOC (**Figure 1**)
- TEAEs included in this analysis were improved with lower doses of avutometinib (**Figure 2**).

Figure 1. Predicted Efficacy for Patients With *KRAS* mt or *KRAS* wt LGSOC Following Avutometinib (3.2, 2.4, and 1.6 mg BIW) in Combination With Defactinib (200 mg BID)



Error bars indicate 95% CIs.

Figure 2. Predicted Safety for Patients With LGSOC Following Avutometinib (3.2, 2.4, and 1.6 mg BIW) in Combination With Defactinib (200 mg BID)



Error bars indicate 95% CIs.

CONCLUSIONS

- In patients with LGSOC, higher avutometinib exposure was significantly associated with improved ORR, longer DOR, and better BTLR in patients with both *KRAS* mt and wt tumors. No relationship was identified for defactinib over the exposure range tested.
- For the ER safety analysis, a dose response was established between avutometinib exposures and all 5 safety endpoints analyzed.
- A dose response was also confirmed between defactinib and grade ≥2 LFTs. However, these TEAEs, which were predominately increased blood bilirubin, may be due to interruption of bilirubin metabolism and circulation by defactinib rather than hepatocyte injury.
- All efficacy endpoints, including ORR, DOR and BTLR, suggest the best therapeutic effect at avutometinib 3.2 mg BIW + defactinib 200 mg BID. While a lower avutometinib dose (eg, 2.4 mg or 1.6 mg) may mitigate TEAEs, it may also compromise the efficacy observed at 3.2 mg. Further, the TEAEs described here can be monitored and managed with dose interruptions.
- Overall, results of these ER efficacy and safety analyses demonstrate a favorable risk-benefit profile for the combination of avutometinib 3.2 mg BIW with defactinib 200 mg BID.

References

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Abbreviations

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; BIW, twice weekly; BTLR, best target lesion response; $C_{avg,ss}$, steady-state average concentration; $C_{avg,TE}$, average concentration until time of event/censoring; $C_{max,ss}$, steady-state maximum concentration; $C_{trough,ss}$, steady-state trough concentration; CI, confidence interval; CPK, creatine phosphokinase; CR, complete response; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; ER, exposure-response; FAK, focal adhesion kinase; GI, gastrointestinal; INV, investigator; IRC, independent review committee; *KRAS*, Kirsten rat sarcoma virus homolog; LFT, liver function test; LGSOC, low-grade serous ovarian cancer; MEK, mitogen-activated extracellular signal-regulated kinase; mt, mutant; NA, not applicable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RAF, rapidly accelerated fibrosarcoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; SOC, system organ class; TEAEs, treatment emergent adverse events; wt, wild-type."