Efficacy of Avutometinib and Defactinib vs Conventional Care in Low-Grade Serous Ovarian Cancer: An External Control Arm Analysis

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Background

- LGSOC is a rare and distinct subtype of epithelial ovarian cancer, commonly driven by alterations in the MAPK pathway, including *KRAS* mutations[1-3]
- The phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (NCT04625270) study evaluated avutometinib (RAF/MEK clamp) + defactinib (FAK inhibitor) in patients with recurrent LGSOC[4]
  - ORR was 31% (44% in *KRAS* mt and 17% in *KRAS* wt)[4]
  - These promising results led to FDA-accelerated approval of the combination in *KRAS*-mt recurrent LGSOC[5]
- GOG 281 (NCT02101788) was a phase 2/3 study that evaluated trametinib vs physician's choice standard of care in patients with recurrent LGSOC[6]
- The purpose of this analysis was to construct an external control arm to contextualize the clinical benefit of avutometinib + defactinib compared with conventional care in patients with recurrent LGSOC

Methods

- Data from RAMP 201 (N=115; data cutoff: August 12, 2025) and GOG 281 (N=130; data cutoff: July 16, 2019; external control arm) in patients with recurrent LGSOC were included
- Patients in RAMP 201 received avutometinib 3.2 mg twice weekly and defactinib 200 mg twice daily for 3 weeks followed by 1 week off (4-week cycle)
- Patients in GOG 281 received physician's choice conventional care
  - Conventional care included letrozole, tamoxifen, paclitaxel, pegylated liposomal doxorubicin, or topotecan
- Study designs of each of the respective studies have been published previously.[4,6] To ensure a comparable and clinically relevant study population, patients from each study met a set of inclusion criteria (**Table 1**)
- Key population differences in GOG 281 vs RAMP 201 included:
  - Prior MEK inhibitor treatment not permitted
  - *KRAS* mutational status not collected prospectively
  - Prior bevacizumab use not specified but anticipated to be low due to timing of study
- *KRAS* mutation status was captured for all patients in RAMP 201 and in 49% in GOG 281
- A matching approach was used to reweight patient-level data to adjust for differences in key baseline characteristics including age, performance status, stage at diagnosis, number of prior therapies, prior hormonal or chemotherapy, prior MEK inhibitor therapy, and *KRAS* mutational status across both studies
- Outcomes included ORR and PFS per RECIST v1.1 as assessed by the investigator
  - ORR was estimated using a weighted logistic regression estimated model to determine odds ratios and 95% CIs
  - PFS was estimated using a weighted Cox proportional hazards model to determine hazard ratios and 95% CIs

Table 1. Key inclusion criteria

Key inclusion criteria of RAMP 201 and GOG 281 studies
• Adult female patients (≥18 years) with histologically confirmed recurrent LGSOC
• Patients must have measurable disease per RECIST v1.1
• Received prior systemic/platinum-based therapy with disease recurrence
• Baseline performance status of 0 or 1 (ECOG or GOG)
• Adequate organ function including hematologic, renal, hepatic, and cardiac parameters
• Baseline QTc interval within acceptable range
• Agreement to use highly effective contraception
• Recovery from prior treatment toxicities
• *KRAS* mutational status must be known (RAMP 201 only)

ECOG, Eastern Cooperative Oncology Group; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; QTc, corrected QT interval; RECIST v1.1, Response Evaluation Criteria in Solid Tumors - Version 1.1.

Results

- After weighting, the RAMP 201 and GOG 281 cohorts were well balanced across all measured characteristics, as evidenced by negligible SMDs and matching weighted covariate distributions (**Table 2**)
  - Effective sample size after propensity score weighting was 64.5 for avutometinib + defactinib and 53.6 for conventional care
- Weighted ORR was higher in patients treated with avutometinib + defactinib compared with conventional care, regardless of *KRAS* mutation status (38.7% vs 0% in *KRAS* mt; 22.7% vs 7.9% in *KRAS* wt) (**Table 3**)
- Avutometinib + defactinib showed significant improvements in PFS over conventional care, irrespective of *KRAS* mutation status (*KRAS* mt: HR 0.29; *KRAS* wt: HR 0.58) (**Table 3** and **Figure 1**)

Abbreviations:

FAK, focal adhesion kinase; FDA, Food and Drug Administration; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase; mt, mutant; ORR, overall response rate; PFS, progression-free survival; RAF, rapidly accelerated fibrosarcoma; RECIST v1.1, Response Evaluation Criteria in Solid Tumors - Version 1.1; SMD, standardized mean difference; wt, wild-type.

Table 2. Baseline characteristics pre- and post-weighting

Characteristic	Pre-weighting			Post-weighting (95% trimmed weight)		
	Avutometinib + defactinib	Conventional care	SMD	Avutometinib + defactinib	Conventional care	SMD
Age, years						
Mean (SD)	53.7 (14.7)	53.9 (14.0)	0.016	52.7 (14.1)	52.7 (14.4)	0.001
Median (IQR)	54.0 (42.5, 66.0)	55.3 (42.5, 65.5)		51.0 (42.5, 66.0)	53.7 (41.9, 64.4)	
Cancer stage at diagnosis, %						
I	6.1	6.2		4.3	4.3	
II	7.0	8.5		5.4	5.4	
III	61.7	71.5	0.308	74.8	74.8	0.001
IV	24.3	13.8		15.5	15.5	
Unknown	0.9	0		0	0	
ECOG PS, %						
0	67.8	71.5	0.081	73.0	73.0	0.001
1	32.2	28.5		27.0	27.0	
No. of prior systemic regimens						
Mean (SD)	3.4 (1.9)	2.9 (1.7)	0.272	3.2 (1.8)	3.2 (1.9)	0.001
Median (IQR)	3 (2, 5)	3 (2, 4)		3 (2, 4)	3 (2, 4)	
Prior chemotherapy, %	99.1	100.0	0.132	100.0	100.0	0.001
Prior hormonal therapy, %	86.1	56.9	0.683	69.3	69.3	0.001
Prior MEK inhibitor therapy, %	21.7	0	0.745	0	0	0.001
Mutational status, %						
KRAS mt	49.6	10.8		32.1	32.1	
KRAS wt[a]	50.4	38.5	1.588	67.9	67.9	0.001
Unknown	0	50.8		0	0	

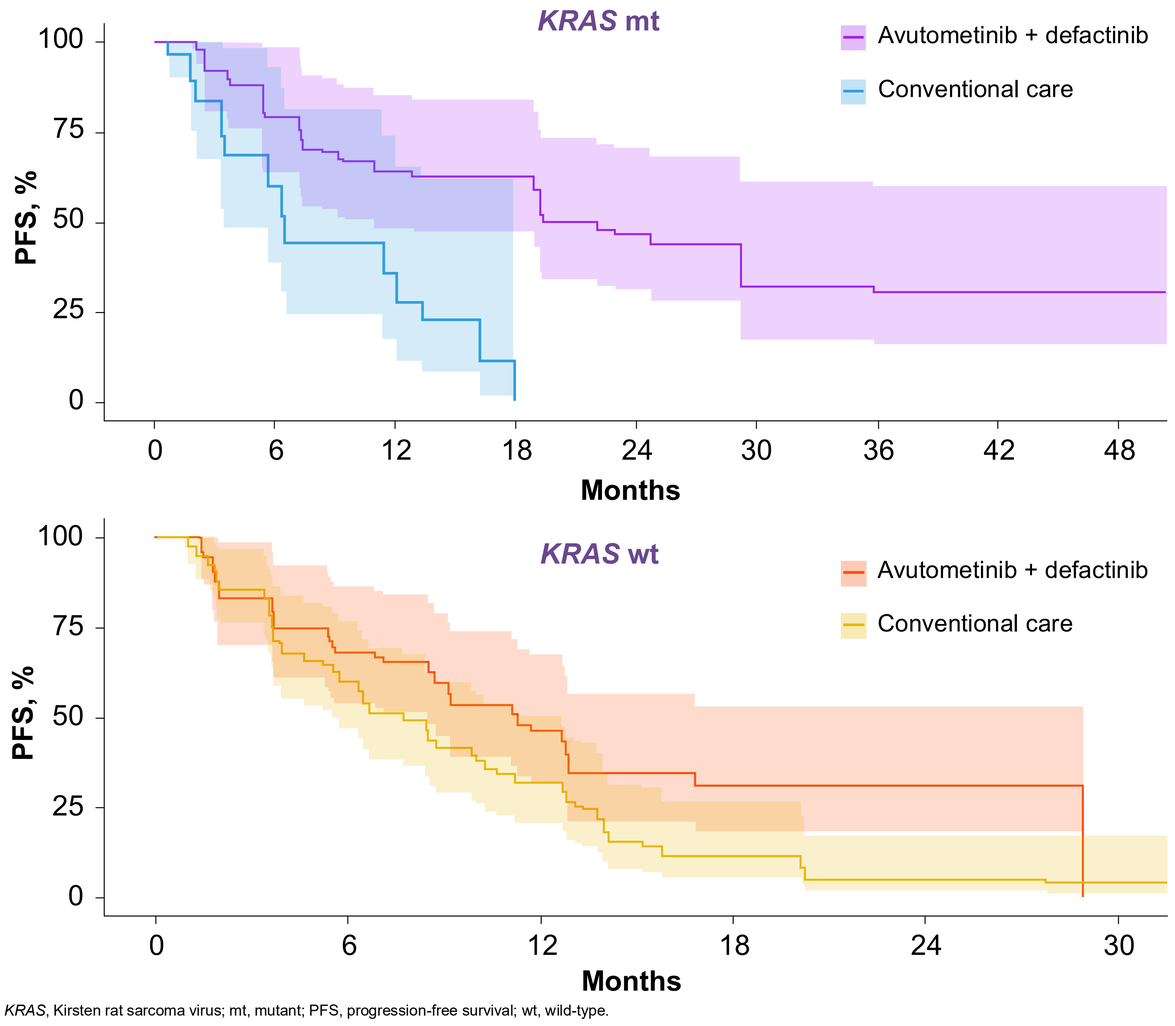
[a]Included *NRAS* and *BRAF* mutations.
BRAF, B-rapidly accelerated fibrosarcoma protein; ECOG PS, Eastern Cooperative Oncology Group performance stage; IQR, interquartile range; *KRAS*, Kirsten rat sarcoma virus; MEK, mitogen-activated protein kinase; mt, mutant; *NRAS*, N-rat sarcoma protein; SMD, standardized mean difference; wt, wild-type.

Table 3. Weighted ORR and PFS by investigator assessment

Parameter	*KRAS* mt		*KRAS* wt	
	Avutometinib + defactinib	Conventional care	Avutometinib + defactinib	Conventional care
Weighted ORR, % (95% CI)	38.7 (22.4–55.0)	0	22.7 (8.8–36.5)	7.9 (0.7–15.0)
Median weighted PFS, months (95% CI)	22.1 (10.9–NR)	6.5 (3.5–NR)	11.3 (8.5–NR)	7.7 (5.6–12.7)
Weighted PFS HR (95% CI)	0.29 (0.15–0.56)		0.58 (0.34–0.98)	

HR, hazard ratio; *KRAS*, Kirsten rat sarcoma virus; mt, mutant; NR, not reached; ORR, overall response rate; PFS, progression-free survival; wt, wild-type.

Figure 1. PFS by investigator assessment: *KRAS* mt and *KRAS* wt



KRAS, Kirsten rat sarcoma virus; mt, mutant; PFS, progression-free survival; wt, wild-type.

Conclusions

- These findings, adjusted for the evaluated baseline characteristics, demonstrate favorable ORR and PFS for avutometinib + defactinib compared with conventional care, irrespective of *KRAS* mutation status, in patients with recurrent LGSOC
- This analysis contextualizes and further supports the clinical benefit of avutometinib + defactinib observed in RAMP 201

References:

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