Initial efficacy and safety results from ENGOT-ov60/GOG-3052/RAMP 201: A phase 2 study of avutometinib (VS-6766) ± defactinib in recurrent low-grade serous ovarian cancer (LGSOC)

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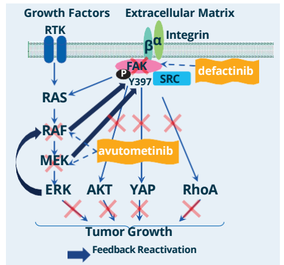
BACKGROUND

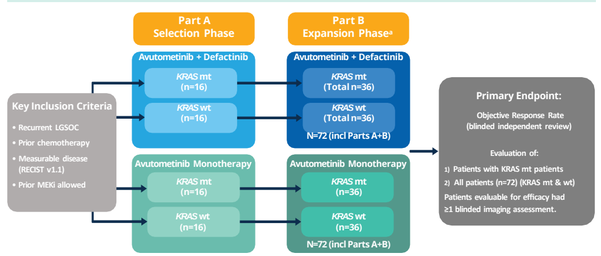
- LGSOC is a RAS/MAPK pathway-driven cancer that constitutes ≤10% of ovarian cancer.[1,2]
- Current treatment options in recurrent LGSOC have shown responses ranging between 0-26%.[3]
- There are no FDA or EMA-approved treatments specifically for LGSOC.
- Avutometinib is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream RAF.[4,5,6,7] (**Figure 1**)
- Defactinib is a selective inhibitor of focal adhesion kinase (FAK), which has been shown to mediate resistance to multiple anticancer agents.[8,9,10,11] (**Figure 1**)
- Avutometinib + defactinib has demonstrated a high rate of confirmed and durable responses (objective response rate [ORR] = 46%; median progression free survival [mPFS] = 23 mo) in recurrent LGSOC (FRAME, NCT03875820), forming the basis for an FDA Breakthrough Therapy Designation and rationale for the ENGOT-ov60/GOG-3052/RAMP 201 study.[12]
- Herein, we present initial efficacy (Part A) and safety (Parts A + B) results from a planned interim analysis of the registration-directed phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (RAMP 201) trial evaluating avutometinib (VS-6766) ± defactinib in LGSOC (NCT04625270).



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

RAMP 201 Study Design



Go-forward regimen selection criteria:
1) Observed ORR is comparatively greater than the other regimen; 2) Observed ORR of the leading regimen is ≥15%.

[a]Final sample size for expansion phase to be adjusted based on adaptive design.
Avutometinib Monotherapy Dosing: Avutometinib 4.0 mg PO 2x/wk 21/28 days.
Avutometinib + Defactinib Dosing: Avutometinib 3.2 mg PO 2x/wk 21/28 days + Defactinib 200 mg PO BID: 21/28 days.
LGSOC, low grade serous ovarian cancer; MEKi, MEK inhibitor; mt, mutant; wt, wild type.

RESULTS

Patient Demographics and Baseline Characteristics

Table 1: Baseline Characteristics of RAMP 201 Part A

	Avutometinib			Avutometinib + Defactinib		
	KRAS mt (n=16)	*KRAS* wt (n=17)	Total (n=33)	*KRAS* mt (n=16)	*KRAS* wt (n=15)	Total (n=31)
Age (yrs), median (min, max)	58 (27, 72)	48 (27, 74)	51 (27, 74)	61 (29, 71)	50 (30, 74)	55 (29, 74)
ECOG PS, n (%)						
0	8 (50)	15 (88)	23 (70)	11 (69)	9 (60)	20 (65)
1	8 (50)	2 (12)	10 (30)	5 (31)	6 (40)	11 (35)
Median number of prior systemic regimens (min, max)	4 (1, 10)	3 (1, 9)	3 (1, 10)	4 (1, 8)	5 (2, 11)	4 (1, 11)
Prior platinum-based chemotherapy, n (%)	15 (94)	17 (100)	32 (97)	16 (100)	15 (100)	31 (100)
Prior MEK inhibitor, n (%)	5 (31)	5 (29)	10 (30)	2 (13)	2 (13)	4 (13)
Prior bevacizumab, n (%)	8 (50)	8 (47)	16 (48)	7 (44)	13 (87)	20 (64)
Prior hormonal therapy, n (%)	11 (69)	13 (76)	24 (73)	15 (94)	13 (87)	28 (90)
Race, n (%)						
White	24 (77)	35 (90)	59 (84)	32 (73)	34 (92)	66 (81)
Black	1 (3)	0	1 (1)	3 (7)	1 (3)	4 (5)
Asian	1 (3)	0	1 (1)	2 (4)	1 (3)	3 (4)
Not reported/Other	5 (31)	4 (24)	9 (27)	7 (16)	1 (3)	8 (26)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; MEK, mitogen-activated protein kinase.

Table 2: RAMP 201 Part A Patient Disposition[a]

	Avutometinib			Avutometinib + Defactinib		
Patient Disposition	*KRAS*mt	*KRAS*wt	Total	*KRAS*mt	*KRAS*wt	Total
Patients randomized, n	16	17	33	16	15	31
Patients treated, n	16	17	33	16	15	31
Patients on treatment, n	6	3	9	8	5	13
Patients that discontinued due to AE, n	2	5	7	0	3	3

[a]Minimum follow-up: 12 months.
AE, adverse event.

Efficacy

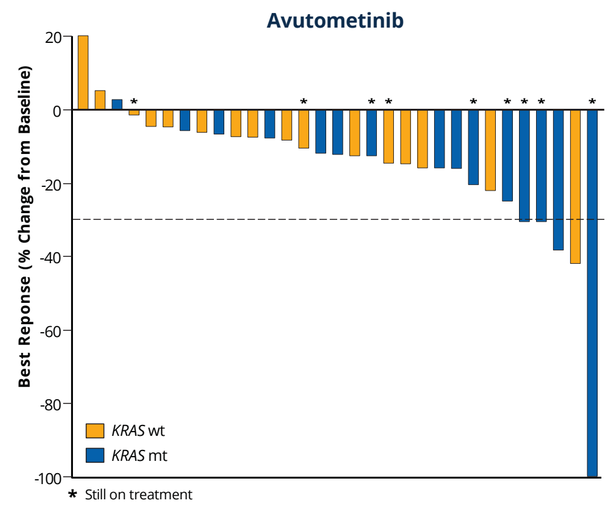
- Confirmed ORRs of 45% (13/29; 95% CI: 26%, 64%) and 10% (3/30; 95% CI: 2%, 24%) were observed on the combination and monotherapy arms, respectively.
  - *KRAS* mt responses: 60% (9/15) for avutometinib + defactinib, 13% (2/15) for avutometinib.
  - *KRAS* wt responses: 29% (4/14) for avutometinib + defactinib, 6% (1/16) for avutometinib.
- Tumor shrinkage was observed in the vast majority of patients on the on the combination and monotherapy arms, 86% (25/29) and 90% (28/31), respectively.
- Responses observed in 3/4 patients who received prior MEK inhibition therapy in combination arm (1/10 in monotherapy arm).
- Median time to response in combination arm: 5.5 months (range: 1.6-14.7 months) and monotherapy arm: 7.3 months (range 2.1-11 months).
- Median duration of response and progression-free survival have not been reached.

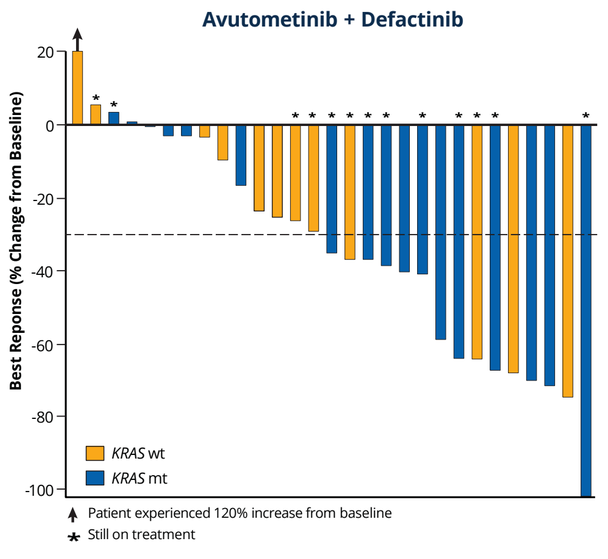
Table 3: RAMP 201 Part A Efficacy Results per BICR (Efficacy Evaluable Patient Population[a])

	Avutometinib			Avutometinib + Defactinib		
	KRAS mt (n=15)	*KRAS* wt (n=16)	Total (n=31)	*KRAS* mt (n=15)	*KRAS* wt (n=14)	Total (n=29)
Confirmed ORR, n (%)	2 (13)	1 (6)	3 (10)	9 (60)	4 (29)	13 (45)
CR, n (%)	1 (7)	0	1 (3)	0	0	0
PR, n (%)	1 (7)	1 (6)	2 (7)	9[b](60)	4 (29)	13 (45)
SD, n (%)	12 (80)	13 (81)	25 (83)	6 (40)	7 (50)	13 (45)
Disease control rate[c] , n (%)	14 (93)	14 (88)	28 (93)	15 (100)	11 (79)	26 (90)
PD, n (%)	1 (7)	2 (13)	3 (10)	0	3 (21)	3 (10)
Confirmed + unconfirmed ORR, n (%)	2 (13)	1 (6)	3 (10)	11 (73)	4 (29)	15 (52)

Data cutoff: April 6, 2023
[a]Evaluable for efficacy: At least one blinded imaging assessment in 31 of 33 and 29 of 31 patients enrolled in monotherapy and combination arms, respectively. [b]One patient deepened to CR at last assessment; CR not yet confirmed.
[c]Disease control rate (SD + PR + CR) at 8 weeks.
BICR, blinded independent central review; mt, mutant; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; wt, wild type.

Percent Change in Baseline Tumor Assessment





Safety

- Dose reductions at data cutoff date (safety population):
  - Avutometinib: 20/70 (29%)
  - Avutometinib + defactinib: 14/81 (17%)
- Few discontinuations were due to adverse events in the combination arm (safety population):
  - 12.3% (10/81) discontinued avutometinib or defactinib due to ≥ 1 TEAE, 4.9% (4/81) due to elevated blood CPK.
- Relative dose intensity:
  - Avutometinib: 80% ± 20% (Part A); 81% ± 21% (all patients)
  - Avutometinib + defactinib: 83% ± 20% (Part A); 79% ± 23% (all patients)

Table 4: Most Common TRAEs (>20%) in All Treated Patients

TRAE	Avutometinib (n=70)		Avutometinib + Defactinib (n=81)	
	Any Grade (%)	Grade ≥3 (%)	Any Grade (%)	Grade ≥3 (%)
Nausea, n (%)	39 (55.7)	3 (4.3)	50 (61.7)	0
Diarrhea, n (%)	50 (71.4)	3 (4.3)	40 (49.4)	3 (3.7)
Blood CPK increased, n (%)	35 (50.0)	16 (22.9)	39 (48.1)	15 (18.5)
Oedema peripheral, n (%)	34 (48.6)	0	34 (42.0)	1 (1.2)
Vomiting, n (%)	28 (40.0)	4 (5.7)	30 (37.0)	0
Vision blurred, n (%)	29 (41.4)	1 (1.4)	29 (35.8)	0
Dermatitis acneiform, n (%)	27 (38.6)	6 (8.6)	28 (34.6)	2 (2.5)
Fatigue, n (%)	27 (38.6)	2 (2.9)	27 (33.3)	3 (3.7)
Rash, n (%)	26 (37.1)	1 (1.4)	25 (30.9)	2 (2.5)
Dry skin, n (%)	23 (32.9)	0	18 (22.2)	0
Anaemia, n (%)	19 (27.1)	8 (11.4)	14 (17.3)	3 (3.7)

CPK, creatine phosphokinase; TRAE, treatment-related adverse event.

CONCLUSIONS

- Key objectives for Part A of the ENGOT-ov60/GOG-3052/RAMP 201 study were achieved:
  - Avutometinib (3.2 mg PO twice weekly 21/28 days) + defactinib (200 mg PO BID 21/28 days) has been selected as the go-forward regimen in patients with recurrent LGSOC.
- The combination of avutometinib + defactinib demonstrated exceptionally high responses in heavily-pretreated recurrent LGSOC, regardless of *KRAS* status.
  - Confirmed ORR: 45% (60% in *KRAS* mt, 29% in *KRAS* wt).
  - Confirmed + unconfirmed ORR: 52% (73% in *KRAS* mt, 29% in *KRAS* wt).
- Tumor shrinkage was observed in the vast majority of patients in both monotherapy (90%) and combination (86%) arms.
- The safety profile was consistent with previously reported safety results for avutometinib ± defactinib.
  - Majority of AEs were grade 1-2.
  - Limited number of patients experienced dose reductions or discontinuations.
- Enrollment in combination arm of the ENGOT-ov60/GOG-3052/RAMP 201 study continues in all patients with recurrent LGSOC, irrespective of *KRAS* mutation status.

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