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)

European Network of

European Network of

Company of the standard of care*

European Network of Standard of Care*

European Network of







ABSTRACT # 5515

Quick Response (QR) Code are for personal use only and may not be reproduced without permission from

ASCO® or the author of this poster.

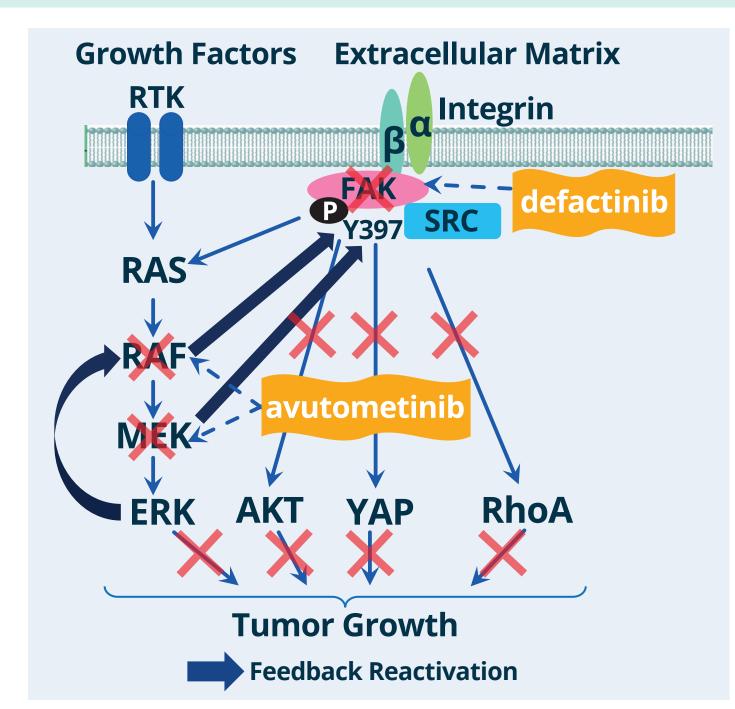
Susana N. Banerjee¹, Kari L. Ring², Els Van Niewenhuysen³, Michel Fabbro⁴, Carol Aghajanian⁵, Ana Oaknin⁶, Nicoletta Colombo⁷, Alessandro D. Santin⁸, Andrew R. Clamp⁹, Kathleen N. Moore¹⁰, Peter G. Rose¹¹, David M. O'Malley¹², Hye Sook Chon¹³, Erin A. Salinas¹⁴, Emily N. Prendergast¹⁵, Stephanie Lustgarten¹⁶, Manuel Rodrigues¹⁷, Christine Gennigens¹⁸, Bradley J. Monk¹⁹, Rachel N. Grisham⁵

¹The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, National Cancer Research Institute (NCRI), London, UK; ²Department of Obstetrics and Gynecology, University of Virginia, Charlottesville, VA, USA; ³University Hospitals Leuven, Belgium; ⁴ICM Val d'Aurelle Parc Euromedecine, Oncology, University of Virginia, Charlottesville, VA, USA; ³University of Virginia, Charlottesville, VA, USA; ³Univ ⁵Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City, NY, USA; ⁶Gynaecologic Cancer Programme; Vall d'Hebron Barcelona Hospital University of Milan-Bicocca, Italy and Gynecology (VHIO), Hospital University of Milan-Bicocca, Italy and Gynecology Program, European Institute of Oncology IRCCS Milan, Italy; ⁸Department of Obstetrics, Gynecology, and Reproductive Sciences, Division of Gynecology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medical Oncology, Yale School of Medicine, New Haven, CT, USA; ⁹Medicine, New Haven, CT, 11 Cleveland Clinic Foundation, Cleveland, OH, USA; 12 The Ohio State University, James Comprehensive Cancer Center, Columbus, OH, USA; 14 Compass Oncology, H. Lee Moffitt Cancer Center, Columbus, OH, USA; 15 Gynecology, Minnesota Oncology, Minne ¹⁶Verastem Inc., Needham, MA, USA; ¹⁷Department of Medical Oncology, INSERM U830, Institut Curie, Paris, France; ¹⁸Department of Medical Oncology, Centre Hospitalier University of Arizona, Creighton University, Phoenix, AZ, USA

BACKGROUND

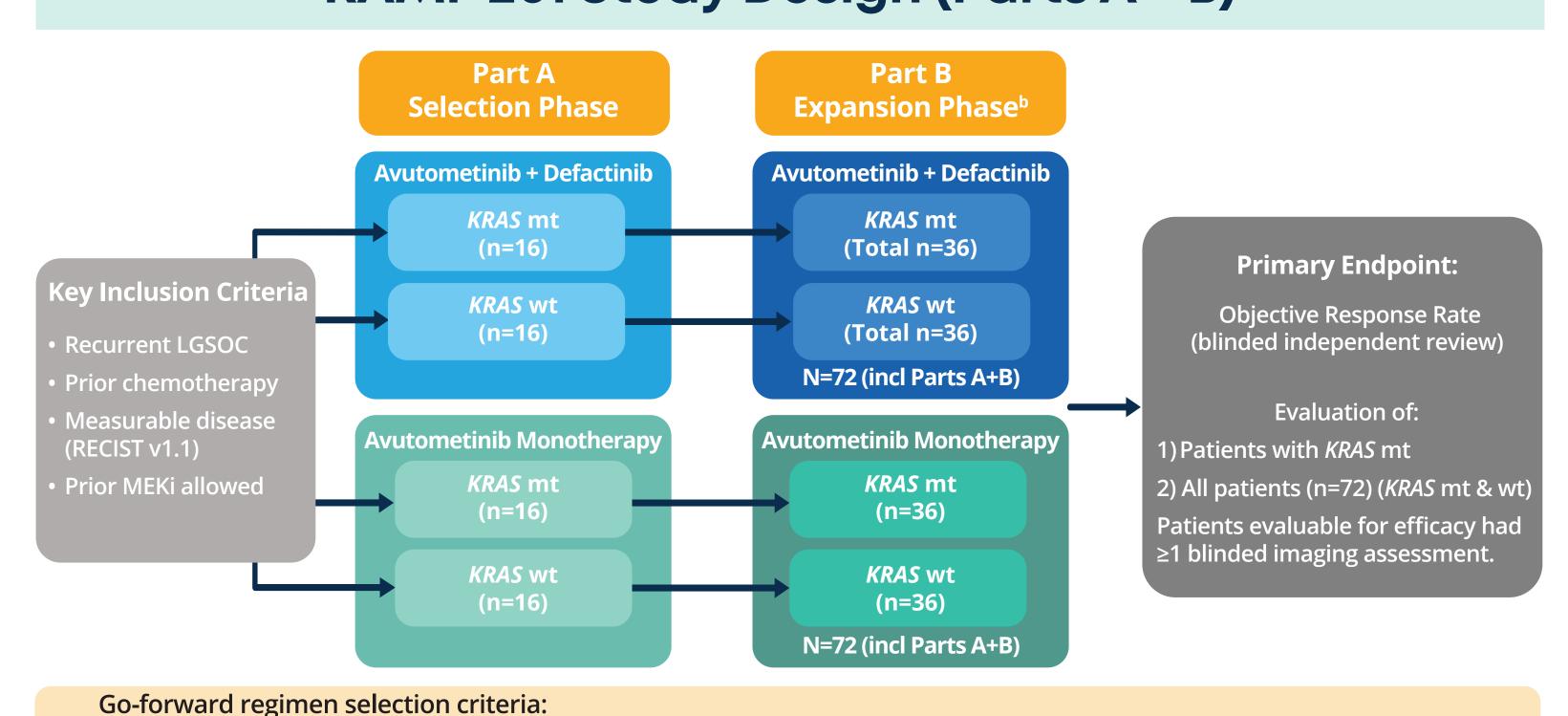
- LGSOC is a RAS/MAPK pathway-driven cancer that constitutes ≤10% of ovarian cancer.^{1,2}
- Current treatment options in recurrent LGSOC have shown responses ranging between 0-26%.3
- There are no FDA or EMA-approved treatments specifically for LGSOC.
- Avutometinib is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity while also blocking the compensatory reactivation of MEK by upstream
- 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
- 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).

Avutometinib + Defactinib Mechanism of Action



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.

RAMP 201 Study Design (Parts A + B)a



1) Observed ORR is comparatively greater than the other regimen; 2) Observed ORR of the leading regimen is ≥15%.

^aPart C (combination arm expansion) is ongoing to futher characterize safety and efficacy. ^bFinal sample size 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.

Patient Demographics and Baseline Characteristics

Baseline Characteristics of RAMP 201 Part A

	A	vutometini	b	Avutometinib + Defactinib			
	<i>KRAS</i> mt (n=16)	<i>KRAS</i> wt (n=17)	Total (n=33)	<i>KRAS</i> mt (n=16)	<i>KRAS</i> 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	13 (81)	16 (94)	29 (88)	12 (75)	15 (100)	27 (87)	
Black	1 (6)	0	1 (3)	2 (13)	0	2 (7)	
Asian	1 (6)	0	1 (3)	2 (13)	0	2 (7)	
Not reported/Other	1 (6)	1 (6)	2 (6)	0	0	0	

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

RAMP 201 Part A Patient Disposition^a

	Avı	utometinib		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	

^aMinimum follow-up: 12 months. AE, adverse event.

Data cutoff: April 6, 2023

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 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.

RAMP 201 Part A Efficacy Results per BICR (Efficacy Evaluable Patient Population^a)

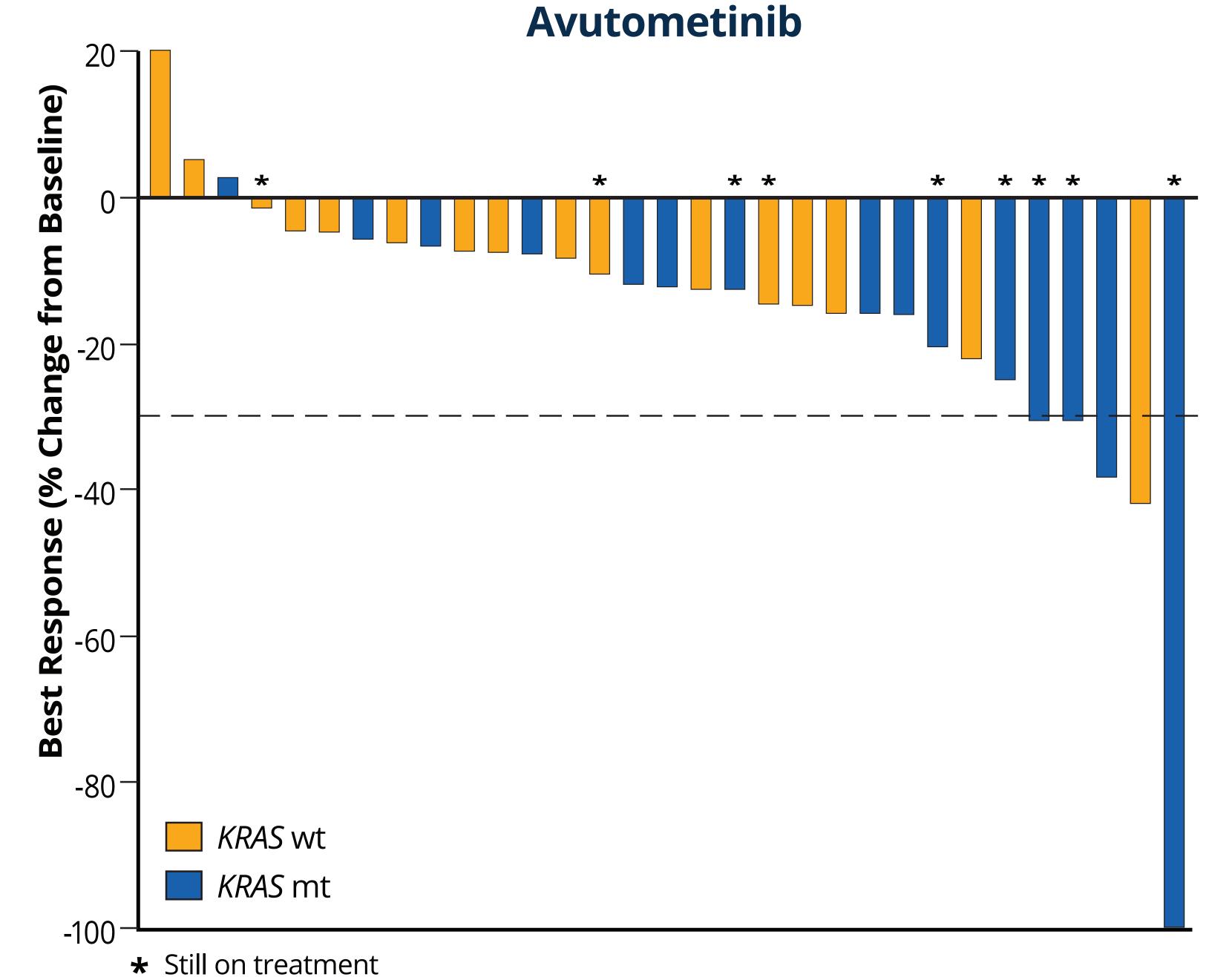
	A	Avutometinib			Avutometinib + Defactinib			
	<i>KRAS</i> mt (n=15)	<i>KRAS</i> wt (n=16)	Total (n=31)	<i>KRAS</i> mt (n=15)	<i>KRAS</i> wt (n=14)	Total (n=29)		
Confirmed ORR, n (%)	2 (13)	1 (6)	3 (10)	9 (60)	4 (29)	13 (45)		
CR, n (%)	1 (7)	0	1 (3)	0	0	0		
PR, n (%)	1 (7)	1 (6)	2 (7)	9 ^b (60)	4 (29)	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)		

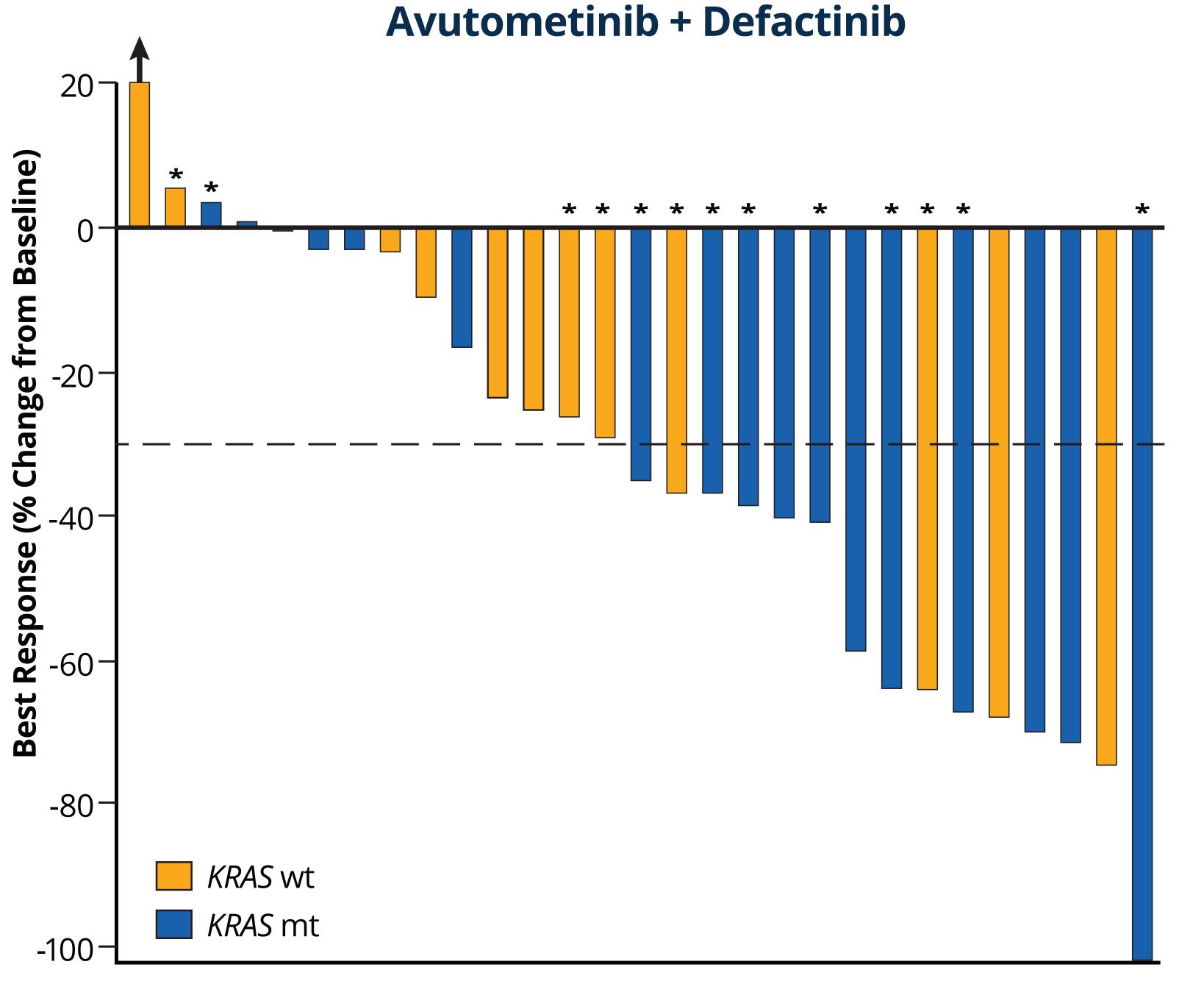
^aEvaluable for efficacy: At least one blinded imaging assessment in 31 of 33 and 29 of 31 patients enrolled in monotherapy and combination arms, respectively. bOne patient deepened to CR at last assessment; CR not yet confirmed. ^cDisease control rate (SD + PR + CR) at 8 weeks.

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

RESULTS





↑ Patient experienced 120% increase from baseline

★ Still on treatment

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)

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

TRAE	Avuton (n=		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)	
Edema 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	
Anemia, 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 (Part C) of the ENGOT-ov60/GOG-3052/RAMP 201 study continues in all patients with recurrent LGSOC, irrespective of KRAS mt status.

REFERENCES

1. Slomovitz BM, et al. *J Gynecol Oncol.* 2020;156:715-720. **2.** Matsuo K, et al. *J Gynecol Oncol.* 2018;29:e69. **3.** Cobb L, et al. *Int J Gynecol Cancer*. 2023;33(3):377-384. **4.** Martinez-Garcia C, et al. *Clin Cancer Res.* 2012;18:4806-4819. **5.** Ishii N, et al. *Cancer Res.* 2013;73:4050-4060. **6.** Lito P, et al. *Cancer Cell.* 2014;25:697-710.

7. Gonzalez-Del Pino GL, et al. PNAS. 2021;118:e2107207118. 8. Dawson JC, et al. Nat Rev Cancer. 2021;21:313-324. **9.** Shinde R, et al. *Cancer Res.* 2020;80(Suppl 16):CT143. **10.** Chen G, et al. *Mol Cancer Ther.* 2018;17:806-813. **11.** Kang Y, et al. *J Natl Cancer Inst.* 2013;105(19):1485-95. **12.** Banerjee S, et al. *Ann Oncol.* 2021;32(suppl_5):S725-S772.

ACKNOWLEDGEMENTS: We thank the patients and their families, the trial teams at the participating centers, and ENGOT and GOG for supporting this study.