Abstract 1515

Efficacy and Safety of Avutometinib + Defactinib in Recurrent Low-Grade Serous Ovarian Cancer Following Prior Systemic Therapy:

An Analysis from ENGOT-ov60/GOG-3052/RAMP 201

Plenary 01
November 5, 2023

Rachel N. Grisham, Carol Aghajanian, Els Van Nieuwenhuysen, Manuel Rodrigues, Kari L. Ring, Alessandro D. Santin, Nicoletta Colombo, Emily N. Prendergast, Premal H. Thaker, Katheen N. Moore, Erin A. Salinas, Isabelle Ray-Coquard, Hye Sook Chon, Peter G. Rose, Ana Oaknin, Andrew R. Clamp, Mitul D. Gandhi, Bradley J. Monk, Robert W. Holloway, Toon Van Gorp, Michel Fabbro, Christine Gennigens, Nicholas E. Wojtynek, Stephanie Lustgarten, Susana N. Banerjee

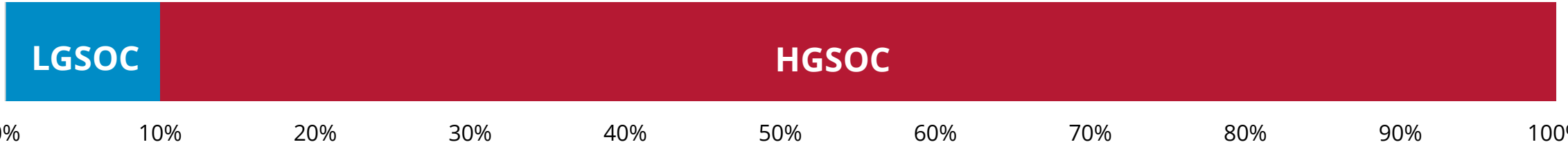
Disclosure

	No, nothing to disclose
X	Yes, please specify:

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*	*Other (please specify)*
AstraZeneca	X	X						
GSK	X	X						
Springworks		X	X					
Corcept		X						
Context			X					
Bayer			X					
Verastem		X	X					
Natera		X						
Novartis			X					
GOG Foundation		X						
Pfizer			X					
Myriad		X						

Molecular and Clinical Features of LGSOC and HGSOC

LGSOC accounts for <10% of new epithelial ovarian cancers[1]



Clinical/Molecular Features	LGSOC	HGSOC
Median age at diagnosis[2,3]	40-50 years	50-60 years
Molecular genetics[4-6]	Mutant: *BRAF*, *RAS* Wild type: *p53*	Mutant: *p53*, *BRCA*, *HRD* Wild type: *BRAF*, *RAS*
GOG158 (stage III, optimal) upfront chemotherapy; BICR (paclitaxel + carboplatin)[3]	n=21 PFS: 45.0 months OS: 126.2 months	n=220 PFS: 19.8 months OS: 53.8 months
Response rate to neoadjuvant chemotherapy[7-9]	4%-23%	80%-90%
Response to chemotherapy in the recurrent setting (weekly paclitaxel, topotecan, or PLD)[10-13]	0%-15%	0%-30%
Rate of hormone receptor positivity[14-16]	ER: 58%-96% PR: 32%-76%	ER: 81%-86% PR: 31%-55%

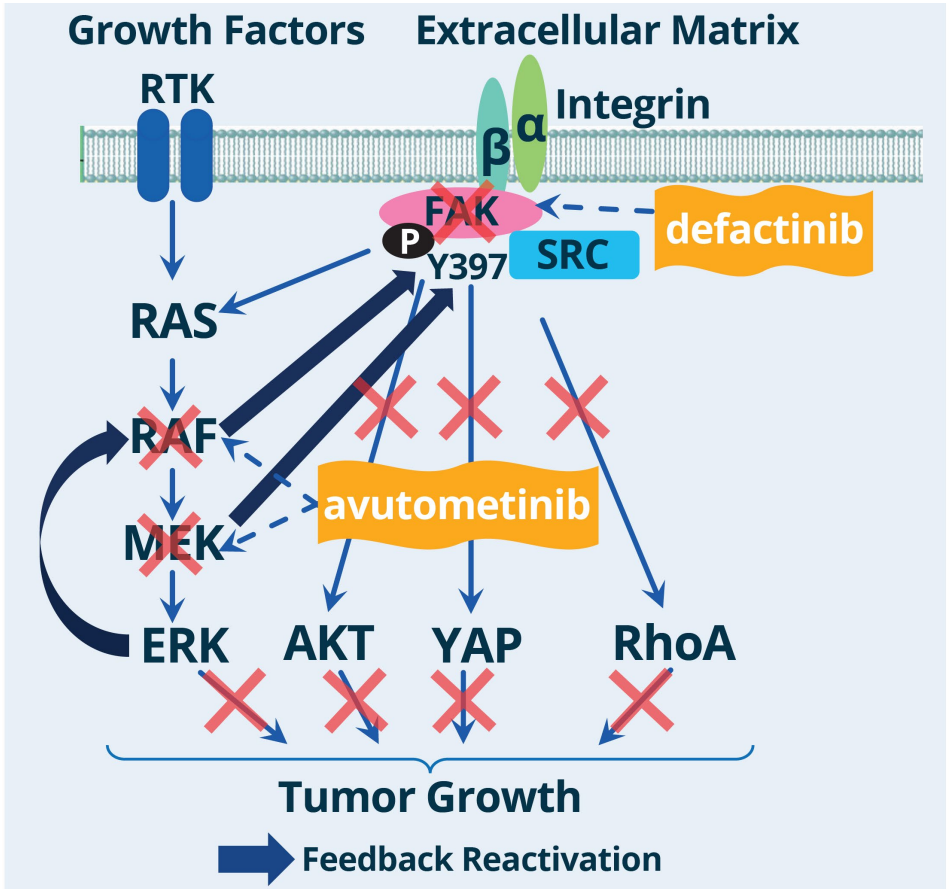
BICR, blinded independent central review; *BRAF,* B-Raf proto-oncogene; *BRCA,* breast cancer gene; ER, estrogen receptor; HGSOC, high-grade serous ovarian cancer; *HRD*, homologous recombination deficiency; LGSOC, low-grade serous ovarian cancer; OS, overall survival; *p53,* tumor protein p53 gene; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, progesterone receptor; *RAS,* rat sarcoma gene.

1. Grisham RN, et al, *Int J Gyn Can*. 2023;33(9):1331-1344; 2. Grisham RN. *Oncology.* 2016;30(7):650-652; 3. Bodurka DC, et al. *Cancer.* 2012;118(12):3087-3094; 4. Bookman MA, et al. *J Natl Cancer Inst.* 2014;106(4):1-8; 5. Mullany LK, et al. *Endocrinology*. 2012;153(4):1638-1648; 6. Vang R, et al. *Adv Anat Path.* 2009;16(5):267-282; 7. du Bois A, et al. *J Clin Oncol.* 2019;37(27):2398-2405; 8. Schmeler KM, et al. *Gynecol Oncol.* 2008;108(3):510-514; 9. Grabowski JP, et al. *Gynecol Oncol.* 2016;140(3):457-462; 10. Poveda AM, et al. *J Clin Oncol.* 2015;33(32):3836-3838; 11. Monk BJ, et al. *J Clin Oncol.* 2020;38(32):3753-3762; 12. Gershenson DM, et al. *Gynecol Oncol.* 2009;114(1):48-52; 13. Pujade-Lauraine E, et al. *J Clin Oncol.* 2014;32(13):1302-1308; 14. Chen S, et al. *Sci Rep.* 2017;7(1):16922; 15. Sieh et al, *Lancet Oncol*, 2013;14(9):853-862; 16. Gadducci A, Cosio S. *Cancers*. 2020;12(5):1336.

New Treatment Options Are Needed for Patients With 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[1-4]
- **Defactinib** is a selective inhibitor of FAK, a signaling target that has been shown to mediate resistance to multiple anticancer agents[5-7]
- Avutometinib + defactinib demonstrated an ORR of 42% (n/N=11/26), a mDOR of 26.9 months (95% CI, 8.5-47.3), and a mPFS of 20.0 months (95% CI, 11.1-31.2) in recurrent LGSOC in the FRAME study (NCT03875820)[8-10]
- Results of the FRAME study led to **FDA Breakthrough Therapy Designation** and rationale for the phase 2 ENGOT-ov60/GOG-3052/RAMP 201 (NCT04625270) study[11-12]

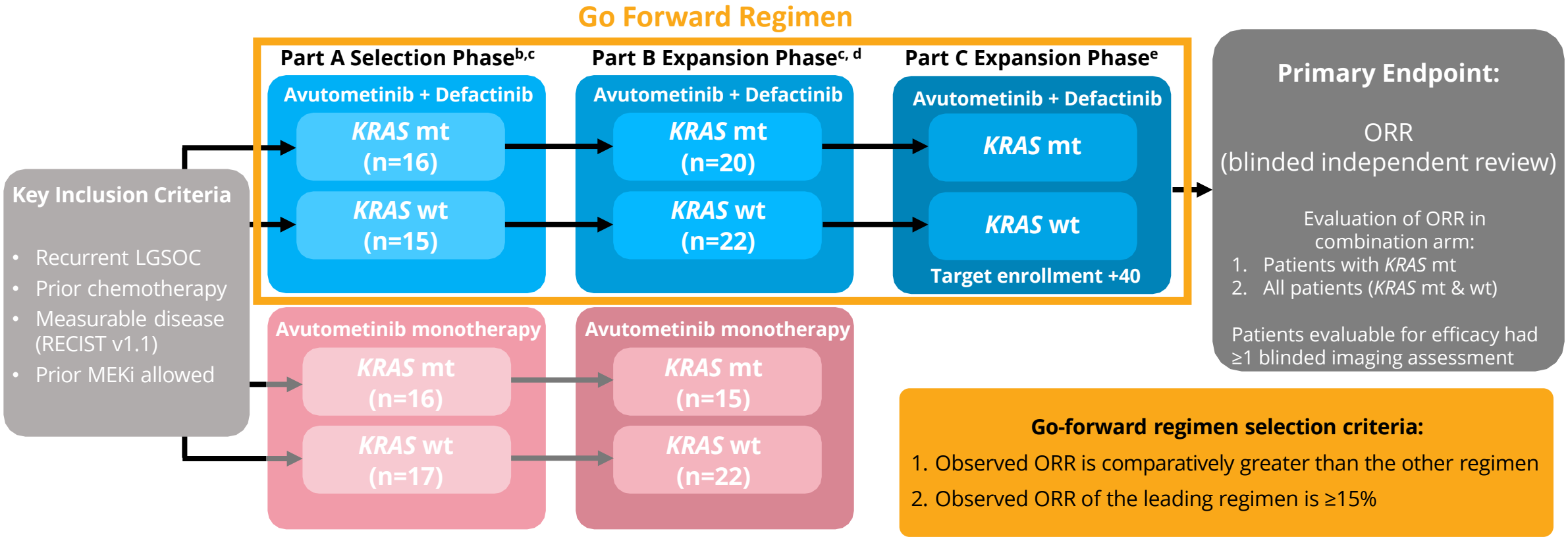
Avutometinib + Defactinib Mechanism of Action



FDA, US Food and Drug Administration; LGSOC, low-grade serous ovarian cancer; mDOR, median duration of response; mPFS, median progression-free survival; ORR, objective response rate.

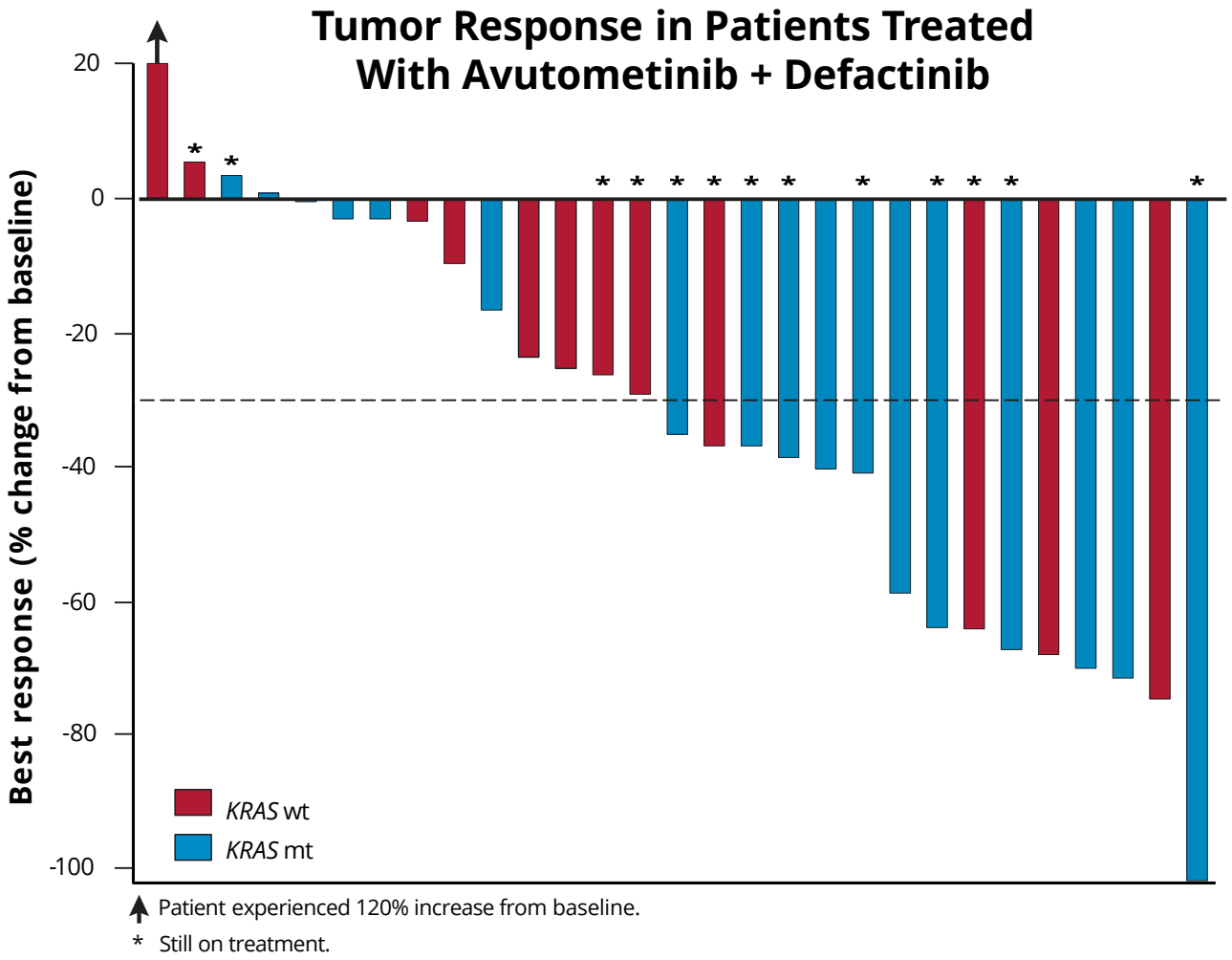
1. Martinez-Garcia C, et al. *Clin Cancer Res.* 2012;18:4806-4819; 2. Ishii N, et al. *Cancer Res.* 2013;73:4050-4060; 3. Lito P, et al. *Cancer Cell.* 2014;25:697-710; 4. Gonzalez-Del Pino GL, et al. *PNAS.* 2021;118:e2107207118; 5. Dawson JC, et al. *Nat Rev Cancer.* 2021;21:313-324; 6. Shinde R, et al. *Cancer Res.* 2020;80(suppl 16):CT143; 7. Kang Y, et al. *J Natl Cancer Inst.* 2013;105(19):1485-1495; 8. Banerjee S, et al. *Ann Oncol.* 2021;32(suppl_5):S725-S772; 9. Banerji Udai. Targeting RAS 2023 SYMPOSIUM. Proteomic profiling of KRAS signaling; Context, CAFs and Combinations; 10. Denis Louis. 5th RAS- Targeted Drug Development Summit. Introducing Rational Combinations of RAF/MEK Clamp Avutometinib: Breakthrough Designation & Beyond; 11. Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515; 12. Verastem Oncology Receives Breakthrough Therapy Designation for VS-6766 with Defactinib in Recurrent Low-Grade Serous Ovarian Cancer. Press Release. Verastem Oncology. May 24, 2021. Accessed September 28, 2023. https://investor.verastem.com/node/12421/pdf.

ENGOT-ov60/GOG-3052/RAMP 201[a]: Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients With Recurrent LGSOC



BID, twice daily; LGSOC, low-grade serous ovarian cancer; MEKi, MEK inhibitor; mt, mutant; ORR, objective response rate; PO, oral; RECIST, Response Evaluation Criteria in Solid Tumors; wt, wild type.
[a]Trial is registered as NCT04625270. [b]Minimum follow-up for Part A is 12 months. [c]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. [d]Final sample size to be adjusted based on adaptive design. [e]Part C (combination arm expansion) is ongoing to further characterize safety and efficacy.
Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515 and Banerjee SN, et al. ASCO 2023. Poster 5515.

Tumor Regression Was Observed in Most Patients Treated With Avutometinib + Defactinib in RAMP 201 Part A[a]



- **Confirmed ORR of 45%** (n/N=13/29; 95% CI, 26%-46%)
  - *KRAS* mt ORR 60% (n/N=9/15)
  - *KRAS* wt ORR 29% (n/N=4/14)
- **Tumor reduction in 86% of patients** treated with avutometinib + defactinib

CI, confidence interval; mt, mutant; ORR, objective response rate; wt, wildtype.
[a]Data presented are at April 6, 2023 data cutoff. Minimum follow-up for Part A is 12 months
Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515 and Banerjee SN, et al. ASCO 2023. Poster 5515.

Methods: A Planned Subgroup Analysis of Patients Treated With Avutometinib + Defactinib Based on Prior Lines of Therapy (LoT)

- Includes patients from the combination arm from the April 6, 2023, data cutoff
- Confirmed ORR (per RECIST v1.1) was assessed by blinded independent central review of 29 efficacy evaluable[a] patients from Part A
- Incidence of TEAEs was evaluated in 81 patients treated with avutometinib + defactinib
- Efficacy and safety in patients with 1-3 prior LoT vs ≥4 prior LoT were analyzed

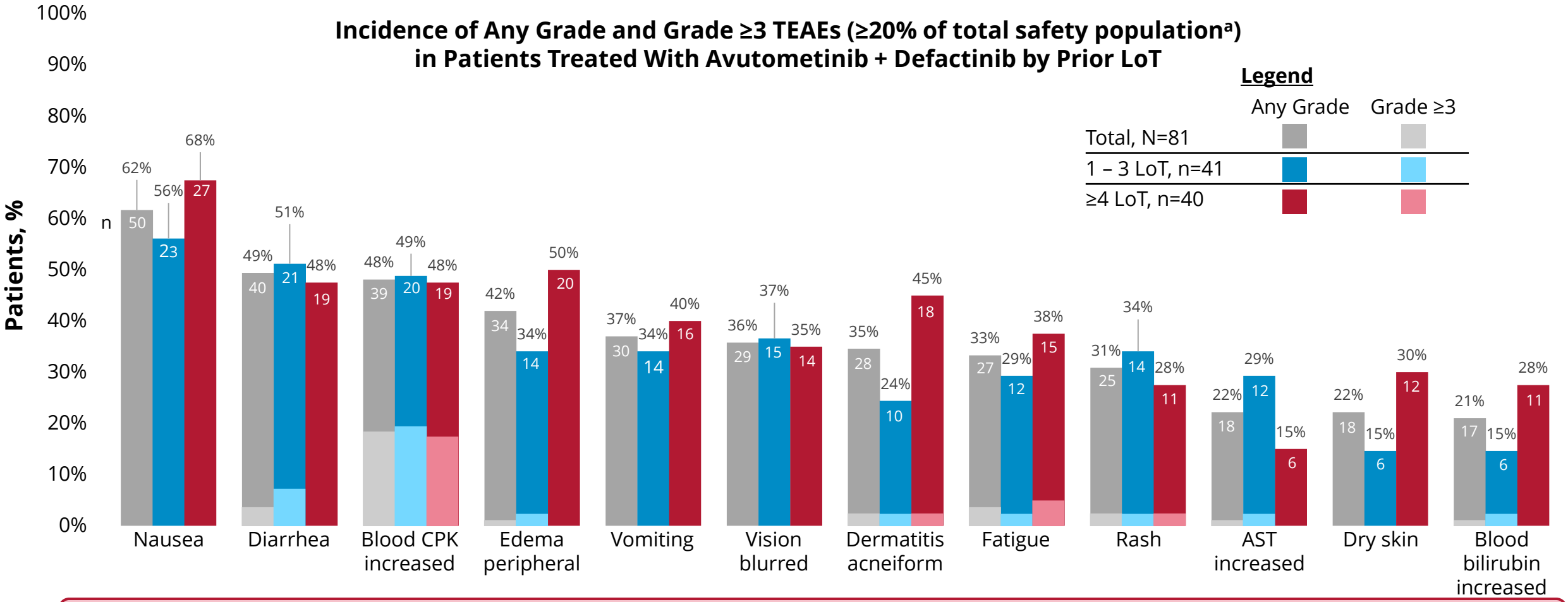
BICR, blinded independent central review; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; TEAE, treatment-emergent adverse event.
[a]Evaluable for efficacy: At least one blinded imaging assessment in 29/31 patients enrolled in avutometinib + defactinib arm of RAMP 201 Part A.

Similar Response Rates to Avutometinib + Defactinib in Patients Treated With 1-3 Prior LoT Versus ≥4 Prior LoT

ORR per BICR by Number of Prior LoT in Patients Treated With Avutometinib + Defactinib[a]	1-3 LoT (n=11)	≥4 LoT (n=18)	Total (n=29)
Confirmed ORR, n (%, 95% CI)	**5 (45.5, 17-77)**	**8 (44.4, 22-69)**	**13 (44.8)**
CR, n (%)	0 (0)	0 (0)	0 (0)
PR, n (%)	**5 (45.5)**	**8 (44.4)**	**13 (44.8)**
SD,[b] n (%)	5 (45.5)	8 (44.4)	13 (44.8)
PD, n (%)	1 (9.1)	2 (11.1)	3 (10.34)
DCR,[c] n (%)	10 (90.9)	16 (88.9)	26 (89.7)

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; LoT, lines of therapy; ORR, objective response rate; PR, partial response; PD, progressive disease; SD, stable disease.
[a]Evaluable for efficacy: At least 1 blinded imaging assessment in 29 of 31 patients enrolled in avutometinib + defactinib arm of RAMP 201 Part A.
[b]Includes patients with unconfirmed PR who have a chance to be confirmed at their next assessment.
[c]Disease control rate (SD + PR + CR) at 8 weeks.

Incidence of TEAEs in Patients Treated With Avutometinib + Defactinib Was Consistent in Patients With 1-3 Prior LoT or ≥4 Prior LoT



10/81 (12.3%) of patients **discontinued avutometinib + defactinib** as a result of ≥1 TEAE;
4 of 10 patients discontinued due to elevated blood CPK as required per protocol at the time of TEAE[1]

AST, aspartate aminotransferase; CPK, creatine phosphokinase; LoT, lines of treatment; TEAE, treatment-emergent adverse event.
[a]Incidence of TEAEs was evaluated in 81 patients treated with avutometinib + defactinib.

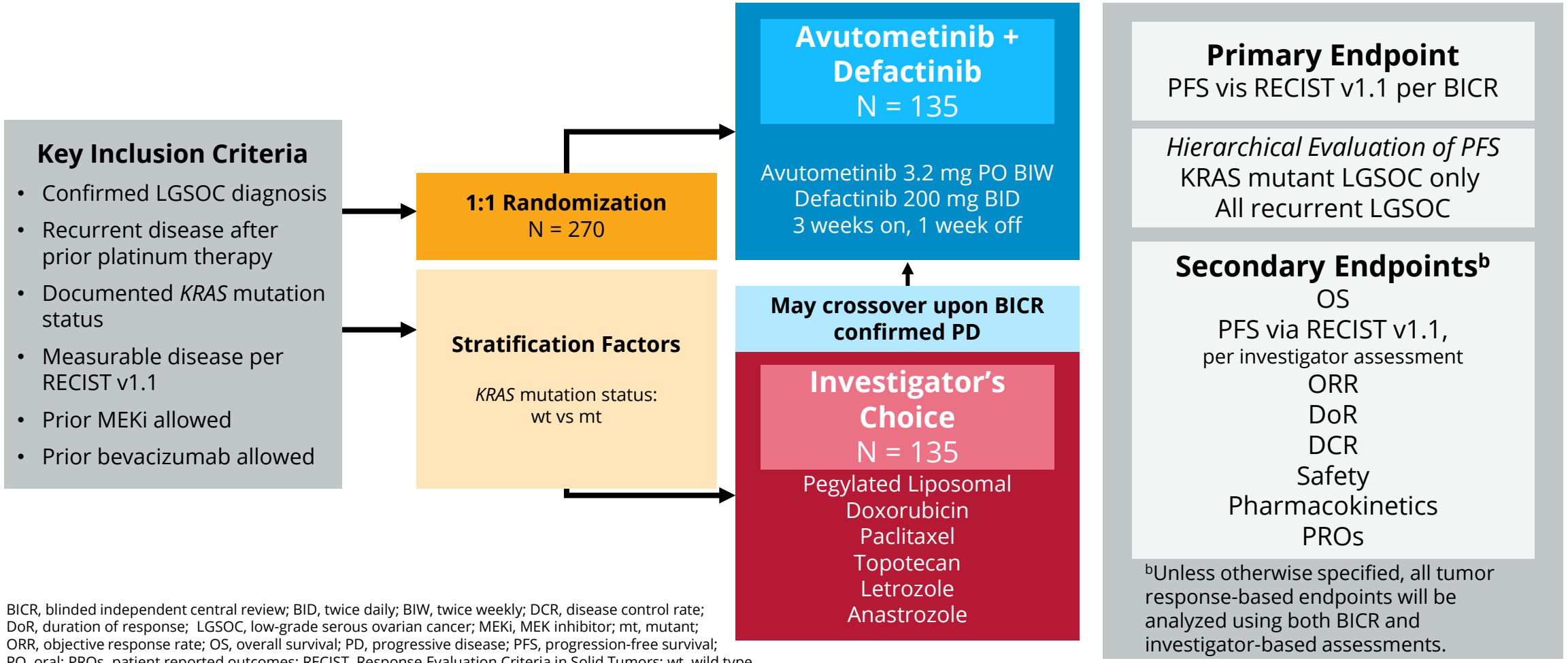
1. Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515 and Banerjee SN, et al. ASCO 2023. Poster 5515.

Conclusions

- Avutometinib + defactinib maintains exceptionally high tumor response rates in heavily pretreated patients with recurrent LGSOC
- Incidence of TEAEs with combination of avutometinib + defactinib is similar in patients who have experienced 1-3 or ≥4 prior lines of therapy
- Given the consistency of avutometinib and defactinib efficacy and safety in heavily pretreated LGSOC patient populations, further investigations evaluating avutometinib + defactinib are ongoing in RAMP 301

LGSOC, low-grade serous ovarian cancer; TEAE, treatment-emergent adverse event.

GOG-3097/ENGOT-ov81/NCRI/RAMP 301[a]: A Phase 3, Randomized Controlled Trial Evaluating Avutometinib + Defactinib Compared With Investigator's Choice in Patients With Recurrent LGSOC



BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; DCR, disease control rate; DoR, duration of response; LGSOC, low-grade serous ovarian cancer; MEKi, MEK inhibitor; mt, mutant; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, oral; PROs, patient reported outcomes; RECIST, Response Evaluation Criteria in Solid Tumors; wt, wild type.
[a]Trial is registered as NCT06072781.

Acknowledgments

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

United Kingdom (NCRI)
Royal Marsden NHS Foundation Trust (Susana Banerjee)
Beatson West of Scotland Cancer Centre (Rosalind Glasspool)
The Christie NHS Foundation Trust (Andrew Clamp)
UCLH Cancer Clinical Trials Unit (Rowan Miller)
Western General Hospital (Charlie Gourley)

Belgium (BGOG)
CHU de Liège (Christine Gennigens)
UZ Gent Medische Oncologie (Hannelorre Denys)
UZ Leuven (Els Van Nieuwenhuysen and Toon Van Gorp)

France (GINECO)
Centre Leon Berard (Isabelle Ray-Coquard)
Hospital Jean Minjoz (Elsa Kalbacher)
ICM Vall d'Aurelle (Michel Fabbro)
Institut Curie (Manuel Rodrigues)

Italy (MaNGO)
Instituto Europeo di Oncologia IRCCS (Nicoletta Colombo)
UOC Oncologia 2, Istituto Oncologico Veneto IRCCS (Valentina Guarneri)

Spain (GEICO)
Hospital Clínico Universitario de Valencia (Jose Alejandro Perez Fidalgo)
Hospital Universitario Ramon y Cajal (Alfonso Cortes-Salgado)
Hospital Universitario Reina Sofia (Maria Jesus Rubio)
Hospital Universitario Vall D'Hebron (Ana Oaknin)

Canada (ENGOT)
Centre de recherche di Centre Hospitalier de i'Universite de Montreal (Diane Provencher)
Princess Margaret Cancer Centre (Amit Oza)

United States (GOG)
Memorial Sloan Kettering Cancer Center (Rachel Grisham)
Advent Health (Robert Holloway)
Arizona Oncology Associates (Bradley J. Monk)
Cleveland Clinic Women's Health Institute (Peter Rose)
Comprehensive Cancer Centers of Nevada (Anu Thummala)
H. Lee Moffitt Cancer Center and Research Institute (Hye Sook Chon)
Maryland Oncology and Hematology (Carol Tweed)
Minnesota Oncology Hematology (Lauren Bollinger)
Northwest Cancer Specialists (Erin Salinas)
Sansum Clinic (Gregg Newman)

United States (GOG, continued)
Sarah Cannon Research Institute (Erika Hamilton)
The Ohio State University Wexner Medical Center & James Cancer Hospital (David O'Malley)
Texas Oncology Austin (Lynne Knowles)
Texas Oncology Dallas (Kristi McIntyre)
Texas Oncology Longview (Anna M. Priebe)
Texas Oncology McAllen (Suresh Ratnam)
Texas Oncology San Antonio (Antonio Santillian-Gomez)
Texas Oncology The Woodlands (Christine Lee)
University of Chicago (John Maroney)
University of New Mexico Comprehensive Cancer Center (Carolyn Muller)
University of Oklahoma Medical Center (Kathleen Moore)
University of Virginia (Kari Ring)
UT Southwestern Medical Center (David S. Miller)
Washington University School of Medicine (Premal Thaker)
Willamette Valley Cancer Institute and Research Center (Charles Anderson)
Yale School of Medicine (Alessandro Santin)
Virginia Cancer Specialists (Mitul Gandhi)

ENGOT-ov60/GOG-3052/RAMP 201 was sponsored by Verastem Oncology.
Medical writing assistance was provided by Sarah A. Hutchinson, PhD, CMPP, from ProEd Communications, and funded by Verastem Oncology.