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ANNUAL MEETING
ON WOMEN'S CANCER

San Diego, CA • 2024

Avutometinib + Defactinib in Recurrent Low-Grade Serous Ovarian Cancer (LGSOC): A Subgroup Analysis of ENGOT-ov60/GOG-3052/RAMP 201 Part A

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Scientific Plenary IV: Late Breaking Abstract Session 1
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Financial Disclosures for Prof Susana N. Banerjee, MBBS, MA, FRCP, PhD

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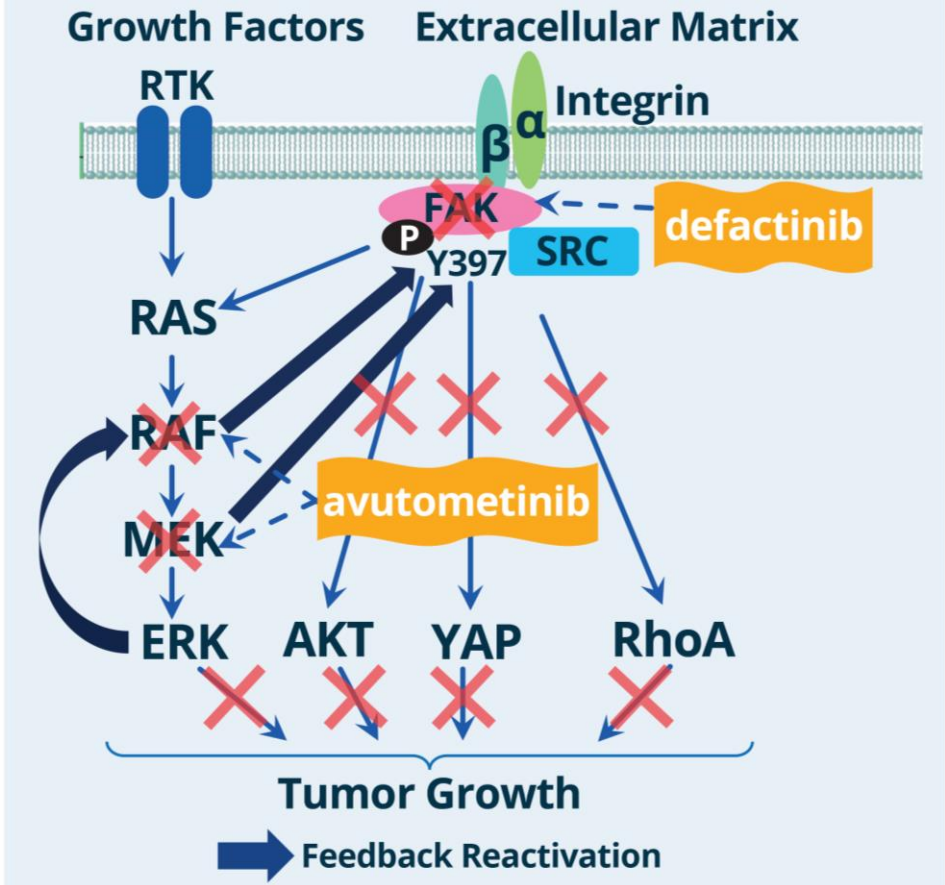
Unlabeled/Investigational Uses

- I will be discussing unlabeled or investigational uses of pharmaceutical products
- Avutometinib and defactinib are investigational agents

New Treatment Options are Needed for Patients with LGSOC

- **LGSOC** is a rare, histopathologically, molecularly, and clinical distinct cancer commonly driven by alterations in the RAS/MAPK pathway, and account for <10% of new epithelial ovarian cancers[1-2]
- Current treatment options for recurrent LGSOC have shown ORRs ranging from 0-26%[3-4]
- **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[5-8]
- **Defactinib** is a selective inhibitor of FAK, a signaling target that has been shown to mediate resistance to multiple anticancer agents[9-11]
- Avutometinib + defactinib demonstrated an ORR of 42% (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)[12-14]
- 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[15-16]

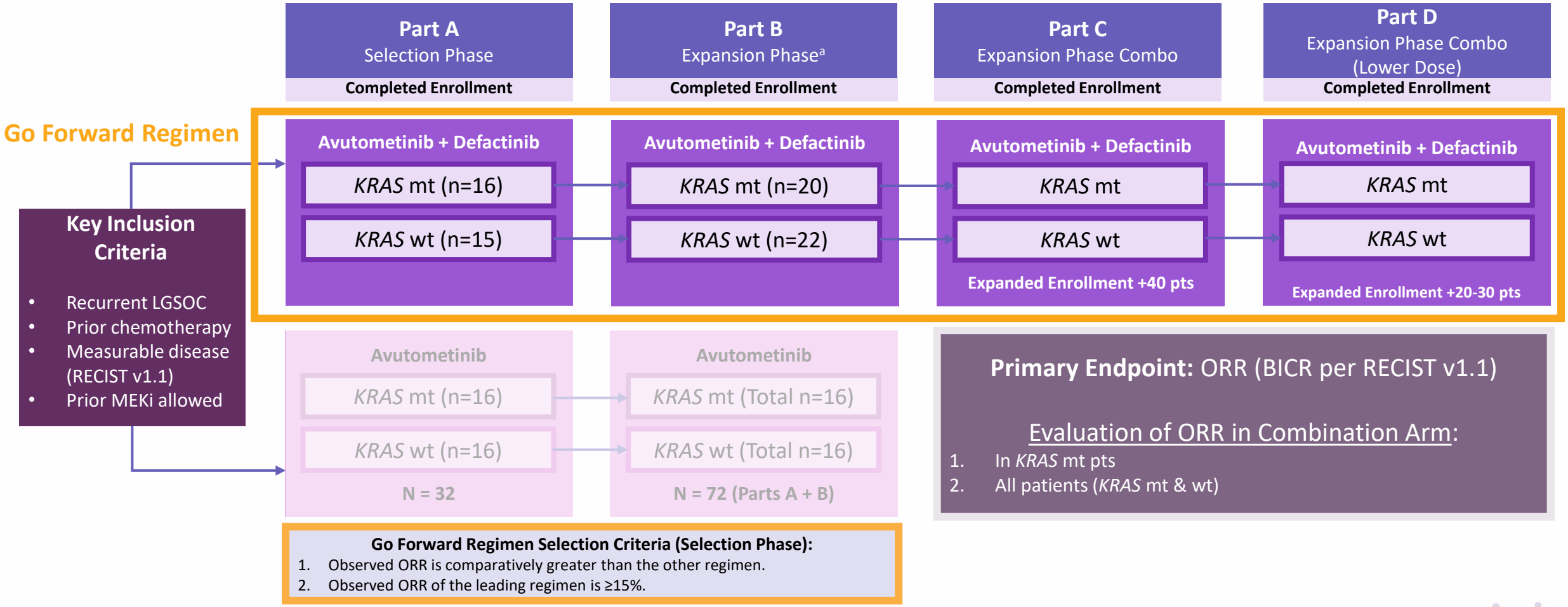
Avutometinib + Defactinib Mechanism of Action



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. Grisham RN, et al *Int J Gynecol Cancer* 2023;4(33):1331-1344; **2**. Matsuo K, et al. *J Gynecol Oncol.* 2018;29(a):e15; **3**. Monk BJ, et al *J Clin Oncol* 2020;38(32):3753-3762; **4**. Gershenson DM, et al *Lancet* 2022;399(10324):541-553; **5**. Martinez-Garcia C, et al. *Clin Cancer Res.* 2012;18:4806-4819; **6**. Ishii N, et al. *Cancer Res.* 2013;73:4050-4060; **7**. Lito P, et al. *Cancer Cell.* 2014;25:697-710; **8**. Gonzalez-Del Pino GL, et al. *PNAS.* 2021;118:e2107207118; **9**. Dawson JC, et al. *Nat Rev Cancer.* 2021;21:313-324; **10**. Shinde R, et al. *Cancer Res.* 2020;80(suppl 16):CT143; **11**. Kang Y, et al. *J Natl Cancer Inst.* 2013;105(19):1485-1495; **12**. Banerjee S, et al. *Ann Oncol.* 2021;32(suppl_5):S725-S772; **13**. Banerji Udai. Targeting RAS 2023 SYMPOSIUM. Proteomic profiling of KRAS signaling; Context, CAFs and Combinations; **14**. Denis L. 5th RAS- Targeted Drug Development Summit. Introducing Rational Combinations of RAF/MEK Clamp Avutometinib: Breakthrough Designation & Beyond; **15**. Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515; **16**. 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: Registration-Directed Phase 2 Trial of Avutometinib ± Defactinib in Patients With Recurrent LGSOC



BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; KRAS, kristen rat sarcoma virus; LGSOC, low grade serous ovarian cancer; MEKi, MEK inhibitor; mt, mutant; pts, patients; ORR, objective response rate; RECIST v1.1, response evaluation criteria in solid tumours version 1.1; wt, wild type.

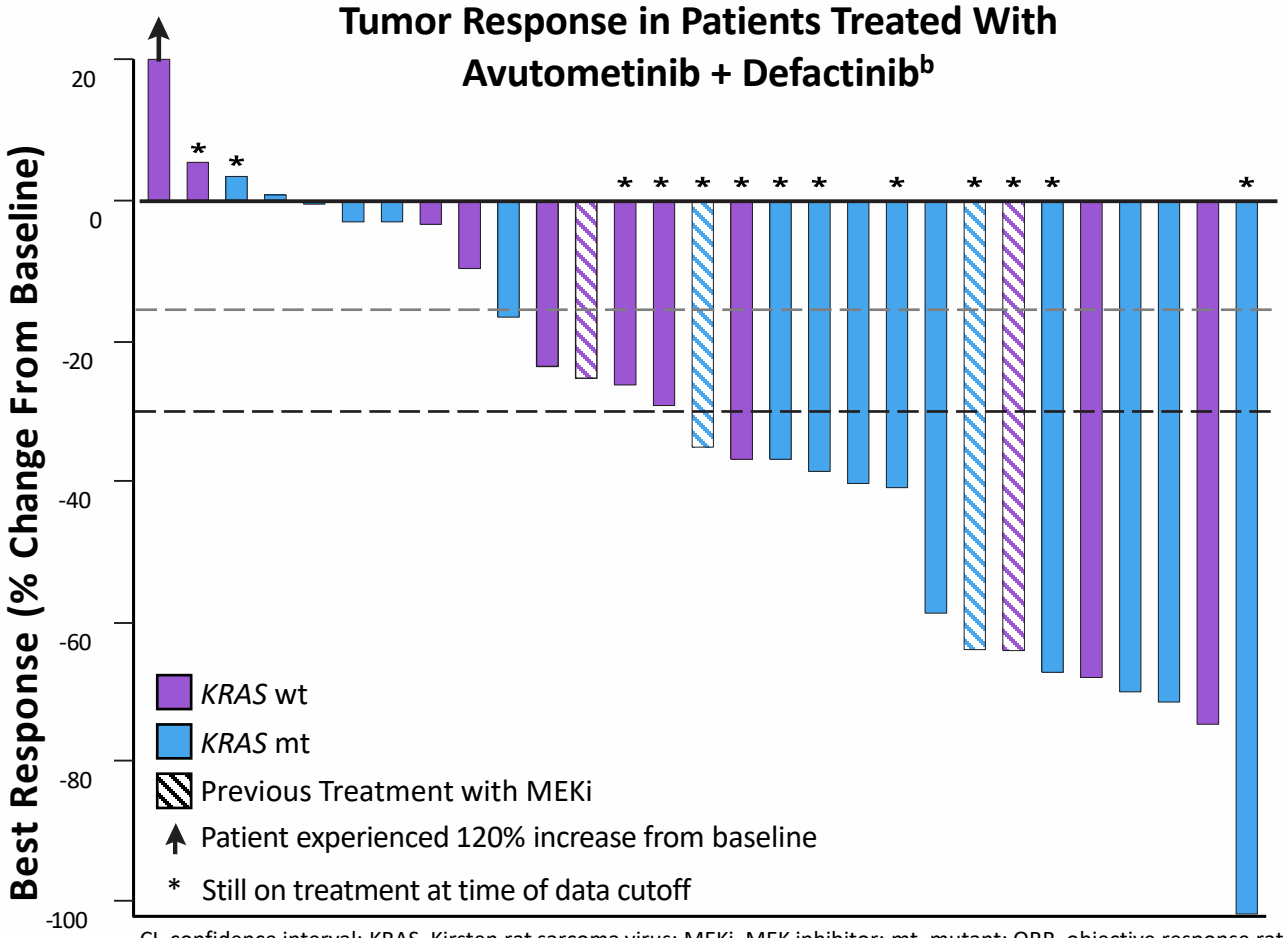
ClinicalTrials.gov identifier: NCT04625270. [a]Final sample size to be adjusted based on adaptive design. Patients evaluable for efficacy had ≥1 blinded imaging assessment. Avutometinib Monotherapy Dosing: Avutometinib 4.0 mg PO BIW 3/4 wks. Avutometinib + Defactinib Dosing: Avutometinib 3.2 mg PO BIW 3/4 wks + Defactinib 200 mg PO BID: 3/4 wks. Avutometinib + Defactinib Part D Dosing: Avutometinib 1.6 mg PO BIW 3/4 wks + Defactinib 200 mg PO BID 3/4 wks.

Methods

- Planned subgroup analysis of patients from the combination arm of ENGOT-ov60/GOG-3052/RAMP 201 from the **April 6, 2023 data cutoff** was performed to assess efficacy[a] and safety[b] of avutometinib + defactinib in the context of:
    1. **Lines of prior systemic therapy (LoT):** 1-3 prior LoT vs. ≥4 prior LoT
    2. **Best response to most recent prior treatment in the metastatic/recurrent setting:** PR/CR, no PR/CR (investigator assessed)
- Analysis of patients who experienced SD and patients who previously received a MEKi were further characterized

BICR, blinded independent central review; LoT, lines of therapy; MEKi, MEK inhibitor; mo, months; ORR, objective response rate; PR, partial response; SD, stable disease; TRAE, treatment emergent adverse events.
[a]Confirmed ORR by BICR per RECIST v1.1 of efficacy evaluable patients from Part A (12 mo minimum follow up; N=29). [b]TEAEs from all treated patients, N=81.

Tumor Regression Was Observed in Most Patients Treated With Avutometinib + Defactinib in RAMP 201 Part A (April 6, 2023 Data Cutoff)[a]



- **Confirmed ORR of 45%** (13/29; 95% CI, 26%-46%)[1]
  - *KRAS* mt ORR 60% (9/15)
  - *KRAS* wt ORR 29% (4/14)
- Similar ORRs and safety profile observed in patients treated with 1-3 (5/11, 45.5%) and ≥4 (8/18, 44.4%) prior LoT[2]
- **Tumor regression in 86% of patients** treated with avutometinib + defactinib[1]
- **Confirmed responses in 3/4 patients previously treated with MEKi[1]**
- Of the 13 patients with SD, 10 achieved tumor shrinkage, 6 with ≥15% tumor regression[c]
  - Median time from last LoT = 1.84 mo
  - Last LoT for 13 patients with SD included chemotherapy (n=2), bevacizumab ± chemotherapy (n=2), hormonal therapy (n=7), MEKi (n=1), and everolimus (n=1)

CI, confidence interval; KRAS, Kirsten rat sarcoma virus; MEKi, MEK inhibitor; mt, mutant; ORR, objective response rate; PR, partial response wt, wildtype.
[a]Minimum follow-up for Part A is 12 months; [b]2 unconfirmed PRs are included in the waterfall plot, with best responses of -39.6% and -36.2% at the time of data cutoff; [c]2/3 SD pts that did not experience tumor regression remained on study at data cutoff.

1. Banerjee SN, et al. *J Clin Oncol.* 2023;41(16 suppl):5515 and Banerjee SN, et al. ASCO 2023. Poster 5515; **2**. Grisham RN, et al. *Int J Gyn Cancer* 2023;33:A3-A4 and Grisham RN, et al. IGCS 2023. Abstract 1515.

Confirmed Responses in Patients Previously Treated with MEKi

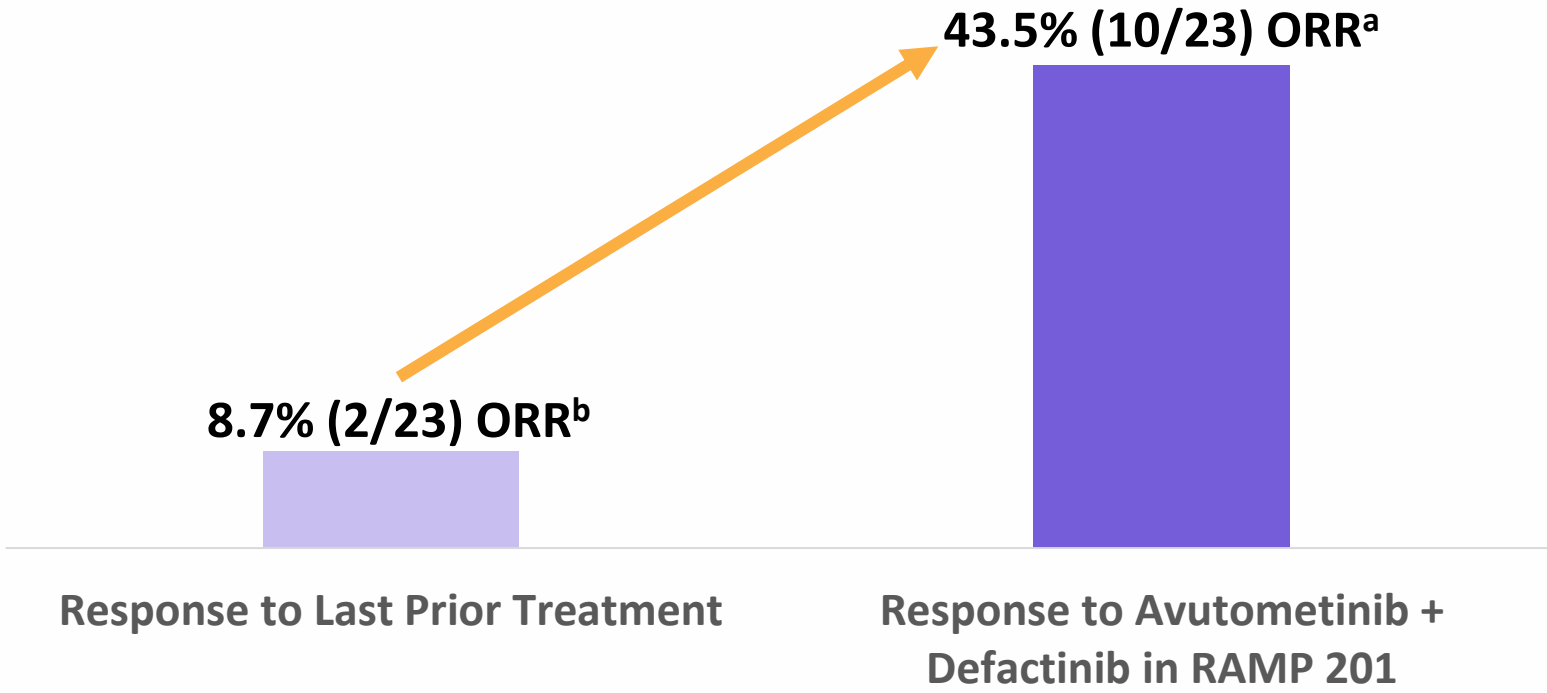
Profiles of RAMP 201 Part A patients (avutometinib + defactinib arm) treated with previous MEKi

	Patient 1	Patient 2	Patient 3	Patient 4
KRAS Status	Wildtype	Mutant	Wildtype	Mutant
Prior LoT	5	4	7	5
Prior MEKi	**Trametinib**	**Trametinib (with dabrafenib)**	**Trametinib**	**Binimetinib**
MEKi as Last LoT?	Yes	Yes	No	No
Best Response to Prior MEKi[a]	PD	Unknown	Unknown	SD
Duration of Prior MEKi Treatment	5.3 mo	21.0 mo	~4.0 mo[c]	71.5 mo
Reason for Prior MEKi Discontinuation	Relapse/PD	Relapse/PD	Unknown	Relapse/PD
RAMP 201 Best Confirmed Response (% regression target lesions)[b]	**SD (-24.9%)**	**PR (-34.5%)**	**PR (-62.8%)**	**PR (-62.8%)**

KRAS, Kirsten rat sarcoma virus; LoT, lines of therapy; MEKi, MEK inhibitor; mo, months; PD, progressive disease; PR, partial response; SD, stable disease.
April 6, 2023 data cutoff. Minimum follow-up for Part A is 12 months.
[a]Investigator assessed response.
[b]Response by blinded independent central review per RECIST v1.1.
[c]Start date July 2020, end date unknown, next regimen started October 2020.

Avutometinib + defactinib provides efficacy in patients who had poor responses to last LoT in the metastatic or recurrent setting[1]

- **10 of 23 (43.5% ORR)[a]** recurrent/metastatic LGSOC patients had a response (CR/PR) to treatment with **avutometinib + defactinib** in RAMP 201, after having last LoT including chemotherapy (n=2), bevacizumab ± chemotherapy (n=2), hormonal therapy (n=4), MEKi (n=1), and pembrolizumab (n=1), and median time from last LoT being 2.7 months.
- Only **2/23 (8.7% ORR)[b]** of these same patients achieved a response(CR/PR) on their **most recent prior treatment in the metastatic/recurrent setting.**



CR, complete response; LGSOC, low grade serous ovarian cancer; ORR, objective response rate; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.
April 6, 2023 data cutoff. Minimum follow-up for Part A is 12 months.
[a]Response by blinded independent central review per RECIST v1.1.
[b]Investigator reported response.
1. Grisham RN, et al. *Int J Gyn Cancer* 2023;33:A3-A4.

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

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, 26-64)**
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.

April 6, 2023 data cutoff

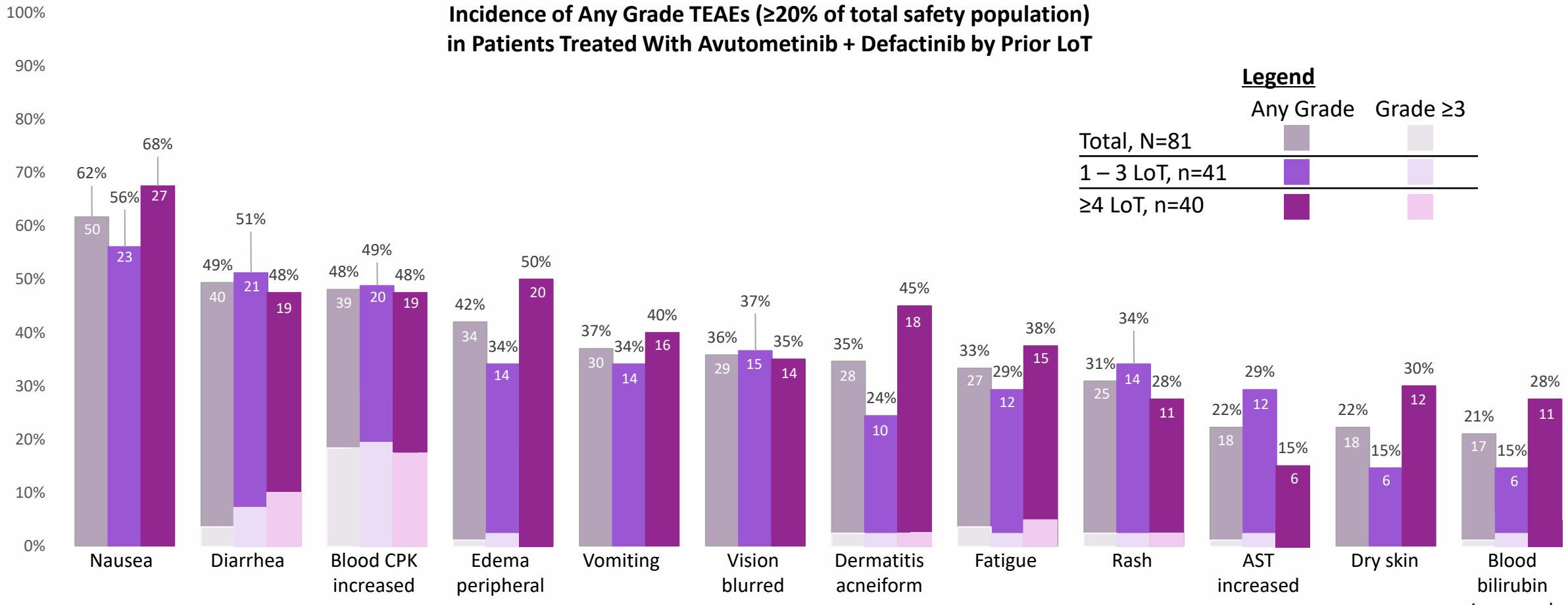
[a]Evaluable for efficacy: At least 1 blinded imaging assessment in 29/31 patients enrolled in avutometinib + defactinib arm of RAMP 201 Part A.

[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.

1. Grisham RN, et al. *Int J Gyn Cancer* 2023;33:A3-A4 and Grisham RN, et al. IGCS 2023. Abstract 1515.

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



AST, aspartate aminotransferase; CPK, creatine phosphokinase; LoT, lines of therapy

April 6, 2023 data cutoff.

1. Grisham RN, et al. *Int J Gyn Cancer* 2023;33:A3-A4 and Grisham RN, et al. IGCS 2023. Abstract 1515.

Conclusions

- In RAMP 201 Part A, avutometinib + defactinib achieved high response rates in heavily pretreated recurrent LGSOC, regardless of previous line of therapy.
- Notably, tumor regression was observed in the majority of patients, including those with stable disease or progressive disease with last line of therapy including previous MEKi.
- Incidence of Grade ≥3 TEAEs in patients treated with avutometinib + defactinib was consistent in patients with 1-3 prior LoT or ≥4 prior LoT.
- **GOG-3097/ENGOT-ov81/NCRI/RAMP 301**, an international Phase 3 confirmatory trial, evaluating avutometinib + defactinib vs. SoC chemotherapy or hormonal therapy in recurrent LGSOC, **has been initiated and is enrolling**.

GOG-3097/ENGOT-ov81/NCRI/RAMP 301: A Phase 3, Randomized, Open-Label Study of Combination Therapy with Avutometinib plus Defactinib Versus Investigator's Choice of Treatment in Patients with Recurrent Low-Grade Serous Ovarian Cancer [Grisham RN et al, SGO 2024. Poster 2120]

International Coordinating Investigator: Rachel N. Grisham, MD
ENGOT Lead: Susana N. Banerjee, MBBS, MA, FRCP, PhD

Key Inclusion Criteria

- Confirmed LGSOC diagnosis
- Recurrent disease after prior platinum therapy
- Documented *KRAS* mutation status
- Measurable disease per RECIST v1.1
- Prior MEKi allowed[a]
- Prior Bev allowed

1:1 Randomization
N ~ 270

Stratification Factors
- *KRAS* mutation status: wt vs mt
- Geography: North America/Europe vs rest of the world
- Number of therapies: 1-3 vs ≥4

Avutometinib + Defactinib
n ~ 135

Avutometinib 3.2 mg PO BIW
Defactinib 200 mg BID
3 weeks on, 1 week off

May crossover upon BICR-confirmed PD

Investigator's Choice of Therapy
n ~ 135

Pegylated liposomal doxorubicin
Paclitaxel
Topotecan
Letrozole
Anastrozole

Participating Countries: United States (GOG Foundation), United Kingdom (NCRI), Spain (GEICO), Belgium (BGOG), France (GINECO), Italy (MaNGO, MITO), Canada (GOG Foundation), Germany (AGO), Denmark (NSGO), South Korea (KGOG), Australia (ANZGOG)

Primary Endpoint: PFS
per BICR by RECIST v1.1

Secondary Endpoints[b]
- OS
- PFS via RECIST v1.1 by investigator assessment
- ORR
- DOR
- DCR
- Safety
- Pharmacokinetics
- PROs

Primary Analysis: Hierarchical Evaluation
1. *KRAS* mutant LGSOC only
2. All recurrent LGSOC

Bev, bevacizumab; BICR, blinded independent central review; BID, twice daily; BIW, twice weekly; DCR, disease control rate; DOR, duration of response; *KRAS,* Kirsten rat sarcoma virus; LGSOC, low-grade serous ovarian cancer; MEKi, MEK inhibitor; mg, milligram; mt, mutant; PFS, progression free survival; ORR, objective response rate; OS, overall survival; PO, orally; PROs, patient reported outcomes; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; vs, versus; wt, wildtype.

ClinicalTrials.gov identifier: NCT0607281. [a]One prior line of treatment with a MEK and/or RAF inhibitor is permitted only if there was prior clinical benefit (objective response or SD ≥6 months) and not received within 6 months of signing informed consent. [b]Unless otherwise specified, all tumor response-based endpoints will be analyzed using both BICR and investigator-based assessments.

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

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The Christie NHS Foundation Trust (Andrew Clamp)
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Western General Hospital (Charlie Gourley)

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