Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201

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ABSTRACT

PURPOSE This study evaluated the efficacy and safety of avutometinib (rapidly accelerated fibrosarcoma/mitogen-activated extracellular signal-regulated kinase [MEK] clamp) alone or in combination with defactinib (focal adhesion kinase inhibitor) in patients with recurrent low-grade serous ovarian cancer (LGSOC).

METHODS In this phase II, open-label study, patients with recurrent, measurable LGSOC after ≥1 line of platinum chemotherapy were stratified by tumor Kirsten rat sarcoma virus homolog (*KRAS*) mutation status and randomly assigned to oral avutometinib 4.0 mg two times per week monotherapy or avutometinib 3.2 mg two times per week in combination with oral defactinib 200 mg two times per day. The combination was selected as the go-forward regimen for expansion. The primary end point was objective response rate (ORR) by blinded independent central review.

RESULTS A total of 115 patients received the go-forward combination regimen. Patients had a median of 3 (range, 1-9) prior lines of therapy, including hormonal (86%), bevacizumab (51%), and MEK inhibitor (22%). Confirmed ORR was 31% (95% CI, 23% to 41%) with a median duration of response of 31.1 months (95% CI, 14.8 to 31.1). ORR was 44% in *KRAS*-mutant and 17% in *KRAS* wild-type cohorts. The median progression-free survival was 12.9 months (95% CI, 10.9 to 20.2) overall and 22.0 months (95% CI, 11.1 to 36.6) and 12.8 months (95% CI, 7.4 to 18.4) in *KRAS*-mutant and wild-type cohorts, respectively. The most frequent grade ≥3 treatment-related adverse events (AEs) were elevated creatine phosphokinase (24%), diarrhea (8%), and anemia (5%). Ten percent of patients discontinued because of AEs.

CONCLUSION The efficacy and safety profile of avutometinib in combination with defactinib support this combination as a potential standard of care for recurrent LGSOC. A randomized phase 3 study of avutometinib and defactinib versus investigator's choice of therapy for women with recurrent LGSOC is currently enrolling (RAMP301; ClinicalTrials.gov identifier: NCT06072781).

ACCOMPANYING CONTENT

Appendix

Data Sharing Statement

Protocol

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INTRODUCTION

Low-grade serous ovarian cancer (LGSOC) is a rare, histopathologically, molecularly, and clinically distinct cancer from high-grade serous ovarian cancer (HGSOC), accounting for <10% of new epithelial ovarian cancers.[1-4] Relative to HGSOC, LGSOC generally presents at a younger age and is less sensitive to chemotherapy.[1,3,5,6] LGSOC is often driven by mitogen-activated protein kinase (*MAPK*) mutations, the most common of which are Kirsten rat sarcoma virus homolog (*KRAS*) mutations, which occur in approximately 30% of patients.[7,8] Furthermore, data suggest that patients with LGSOC tumors harboring *KRAS* mutations (*KRAS* mt) have an improved prognosis when compared with those with *KRAS* wild-type (*KRAS* wt) tumors.[8,9]

The initial preferred treatment of LGSOC is primary cytoreductive surgery with the goal of achieving a

CONTEXT

Key Objective

What are the efficacy and safety of avutometinib (a rapidly accelerated fibrosarcoma/mitogen-activated extracellular signal-regulated kinase clamp) with and without defactinib (a focal adhesion kinase inhibitor) in a phase II trial of patients with recurrent low-grade serous ovarian cancer (LGSOC)?

Knowledge Generated

The combination of avutometinib 3.2 mg two times per week + defactinib 200 mg two times per day resulted in clinically meaningful responses, duration of response, and progression-free survival. Adverse events were manageable, mainly with dose holds or reductions, allowing most patients to stay on therapy.

Relevance *(G.F. Fleming)*

This combination regimen was recently granted accelerated approval by the US Food and Drug Administration for patients with recurrent LGSOC with a Kirsten rat sarcoma virus mutation.*

*Relevance section written by *JCO* Associate Editor Gini F. Fleming, MD.

complete gross resection followed by chemotherapy and/or hormonal therapy.[4,10] However, most patients will have disease recurrence.[5,11] Chemotherapy in the recurrent setting has shown overall response rates from 0% to 13%.[9,12] In randomized trials, mitogen-activated extracellular signal-regulated kinase (MEK) inhibitors have shown overall response rates of 26% (trametinib) and 16% (binimetinib); however, approximately one third of patients discontinued because of toxicity.[9,12]

Avutometinib is a first-in-class oral rapidly accelerated fibrosarcoma (RAF)/MEK clamp that potently inhibits MEK while also blocking the compensatory reactivation of MEK by upstream RAF that occurs with MEK inhibition alone.[13-16] However, inhibition of the MAPK pathway by avutometinib leads to a compensatory activation of focal adhesion kinase (FAK), a key adaptive resistance mechanism to MAPK inhibition.[17-20] Addition of a FAK inhibitor to avutometinib in a preclinical model of LGSOC resulted in greater inhibition of tumor growth over avutometinib alone.[21] In a phase I study (FRAME), avutometinib + defactinib (a selective FAK inhibitor) demonstrated promising efficacy and tolerability in this patient population.[22] This phase II trial (ENGOT-ov60/GOG-3052/RAMP 201) was designed to assess the efficacy and safety of avutometinib with and without defactinib in patients with recurrent LGSOC.

METHODS

Patients

Patients age ≥18 years with histologically confirmed LGSOC (ovarian, peritoneal) and measurable disease by RECIST v1.1 were enrolled. Eligible patients had radiographic or clinical progression or recurrence of LGSOC after ≥1 prior systemic therapy that included prior platinum. One line of prior MEK or RAF inhibitor therapy was permitted. *KRAS* tumor mutation status using a validated test was required before enrollment. Archival tissue was collected for central confirmation of histology and tumor *KRAS* testing (Protocol).

Study Design and Treatment

This was an adaptive, four-part, phase II, multicenter, parallel cohort, randomized, open-label trial to evaluate the efficacy and safety of avutometinib alone and in combination with defactinib in patients with recurrent LGSOC (Fig 1). In Part A, patients were randomly assigned 1:1 to either avutometinib 4.0 mg orally two times per week for 3 weeks followed by a 1-week rest period (4-week cycle) or to avutometinib 3.2 mg orally two times per week + defactinib 200 mg orally two times per day for 3 weeks followed by a 1-week rest period (4-week cycle). Random assignment was stratified to achieve equal numbers of patients with *KRAS* mt and *KRAS* wt tumors in each regimen. On full enrollment in Part A, Part B was open to expanded enrollment. The combination of avutometinib with defactinib was identified as the go-forward regimen following interim analysis and expanded in Part C.

In Part D, a low starting dose of avutometinib (1.6 mg two times per week) was evaluated in combination with defactinib (200 mg two times per day) for 3 weeks followed by a 1-week rest period (4-week cycle).

Patients received prophylactic medication for rash during the first two cycles (hydrocortisone cream, moisturizer, sunscreen, and systemic antibiotic).

This clinical trial was conducted in the United States, the United Kingdom, France, Spain, Italy, Belgium, and Canada. The study was approved by the institutional review board at each participating site and was conducted in accordance with

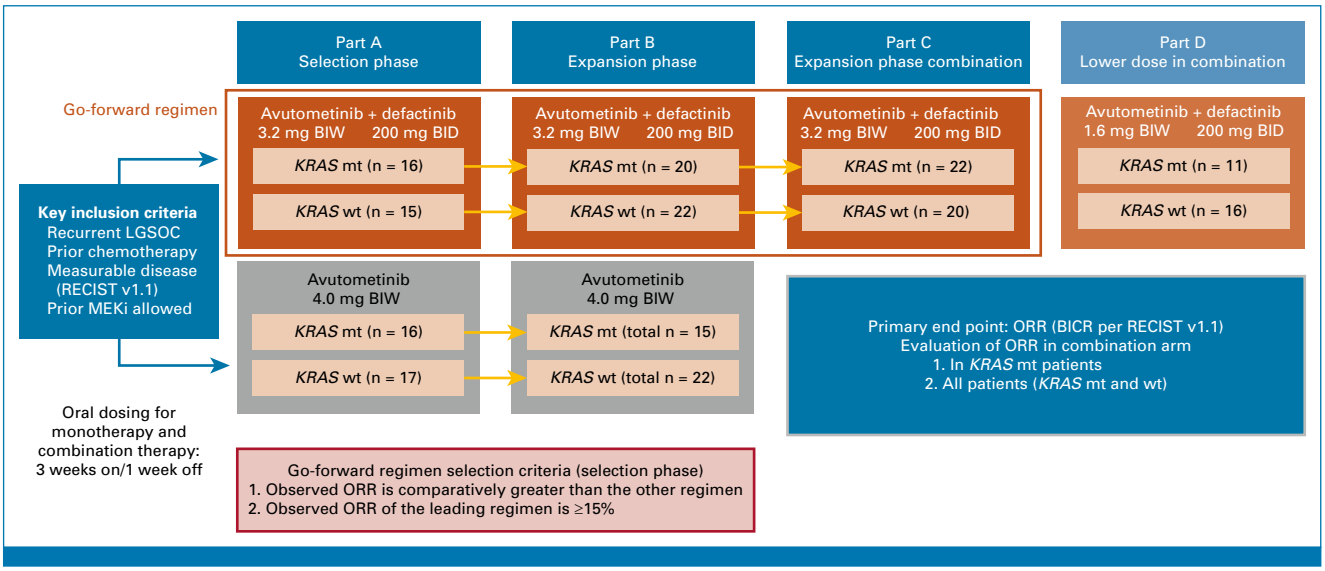

FIG 1. Study design. n values represent patients treated in the study. BICR, blinded independent central review; BID, two times per day; BIW, two times per week; LGSOC, low-grade serous ovarian cancer; *KRAS*, Kirsten rat sarcoma virus; MEKi, mitogen-activated extracellular signal-regulated kinase inhibitor; mt, mutant; ORR, objective response rate; wt, wild-type.

the International Council for Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki, and local regulations regarding the conduct of clinical research. All patients provided written informed consent.

End Points

The primary end point was objective response rate (ORR) according to RECIST v1.1 as assessed by blinded independent central review (BICR). Secondary end points included duration of response (DOR), ORR as assessed by the investigator, progression-free survival (PFS), overall survival, safety, and pharmacokinetics.

Assessments

Tumor response was measured by RECIST v1.1. Patients were assessed for response by computed tomography or magnetic resonance imaging. *KRAS* mutation status was confirmed centrally using the tissue-based Tempus xT v4.0 LDT NGS-based assay.

Statistical Analysis

Efficacy and safety analyses were conducted for all patients who received ≥1 dose of either study-assigned treatment (intention-to-treat population). The efficacy population included patients with ≥1 measurable lesion at baseline. Statistical analyses were conducted using SAS software.

For determination of the go-forward regimen, assuming an absolute difference in ORRs of ≥15%, 32 patients per group provided an 88% probability of choosing the correct regimen. Evaluation of the go-forward algorithm was based on a comparison of ORRs between the avutometinib and avutometinib + defactinib groups, and the totality of efficacy and safety data was evaluated before proceeding to expansion in Part C.

The primary efficacy and safety analysis of confirmed ORR was conducted for Parts A, B, and C combined in patients treated with the go-forward regimen of avutometinib and defactinib. ORR was assessed by an exact binomial test with a nominal 2.5% two-sided significance level using a null hypothesis ORR of 15% and alternative hypothesis of 40%, with 88% power to detect the difference between hypotheses when the sample size is 36 patients. Confirmed ORR was evaluated simultaneously in all patients and in patients with *KRAS* mutations as determined by local testing. DOR and PFS were estimated using the Kaplan-Meier method. The two-sided 95% CI for median DOR and median PFS were determined using the Brookmeyer-Crowley method.

Disease progression in the low-dose group (Part D) was compared with that of the go-forward regimen (Parts A, B, and C). If the rate of disease progression by 4 months was >50% higher than that observed with avutometinib 3.2 mg two times per week + defactinib, the starting dose combination of avutometinib 1.6 mg two times per week + defactinib was determined to be suboptimal.

Severity of adverse events (AEs) was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, Version 5.0 or higher.

RESULTS

Determination of KRAS Status

The results are summarized for the monotherapy and combination therapy groups overall and by *KRAS* mutation

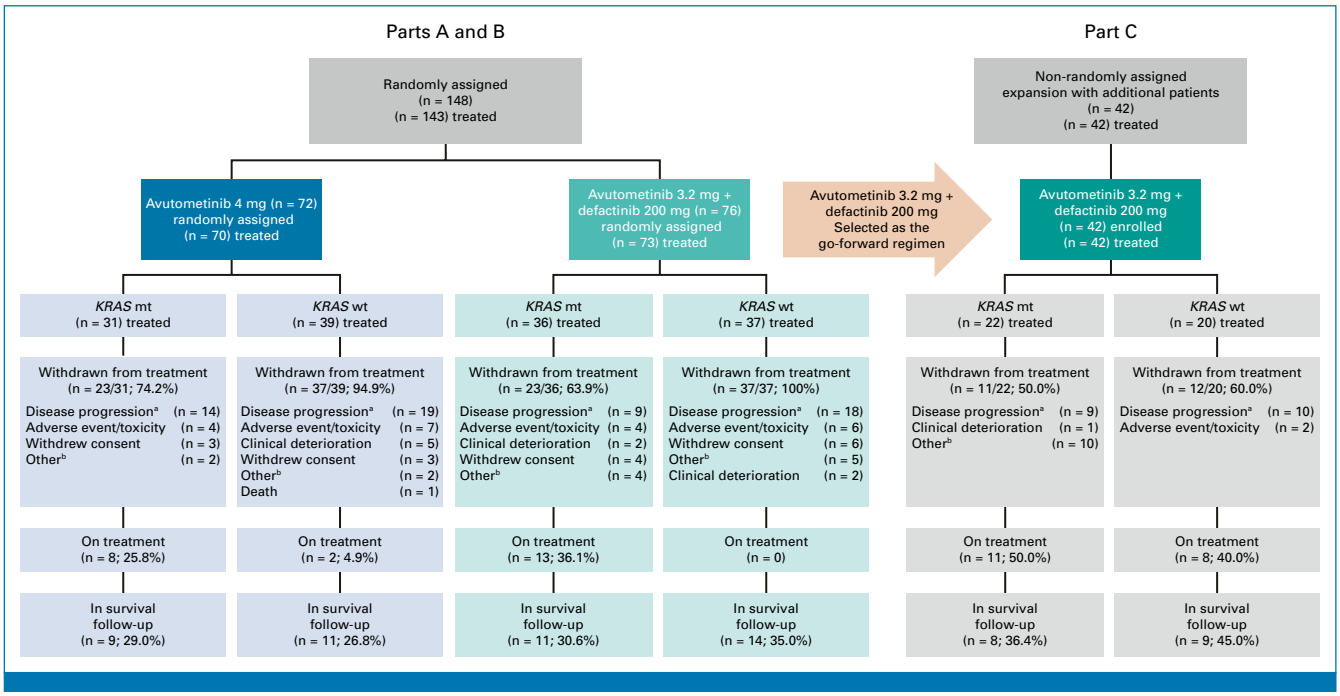

FIG 2. Patient disposition is depicted by a CONSORT diagram for Parts A, B, C, and is summarized by *KRAS* mutation status and treatment group. [a]Disease progression measured by RECIST v1.1. [b]Other reasons include clinical progression, patient noncompliance, physician decision, debulking surgery, patient withdrawal, and disease progression. *KRAS*, Kirsten rat sarcoma virus; mt, mutant; wt, wild-type.

status as determined by local testing. The concordance rate between local and central tumor tissue-based testing was 96% (78/81); Appendix Table A1, online only.

Determination of Go-Forward Regimen

At the time of a prespecified analysis to determine the go-forward regimen in Part A (data cutoff August 12, 2022), 33 patients receiving avutometinib 4.0 mg two times per week monotherapy and 31 receiving the combination of avutometinib 3.2 mg two times per week +200 mg defactinib two times per day were evaluable for efficacy. ORR by BICR was higher in the combination group compared with the monotherapy group (28% *v* 7%), with similar toxicity profiles. At the time of the current data cutoff (June 30, 2024), the updated ORR in Part A was 39% versus 9%, respectively.

Patient Disposition and Baseline Characteristics

Avutometinib Monotherapy (Parts A and B) and Avutometinib + Defactinib (Parts A, B, and C)

At the time of data cutoff for the primary analysis (June 30, 2024), 115 patients received avutometinib + defactinib treatment (58 *KRAS* mt, 57 *KRAS* wt); 70 received avutometinib monotherapy (31 *KRAS* mt, 39 *KRAS* wt; Fig 2). A total of 109 and 69 patients in the combination and monotherapy groups, respectively, had measurable disease at baseline by BICR and were included in the efficacy-evaluable population. The median duration of follow-up was 13.6 months (range, 1.4-39.5 months) in the combination treatment group and 18.5 months (range, 1.0-36.9 months) in the monotherapy group.

Demographic and baseline characteristics were generally similar between patients receiving avutometinib + defactinib combination therapy and avutometinib monotherapy (Table 1).

Lower Starting Dose of Avutometinib + Defactinib (Part D)

Of the 27 patients enrolled in Part D and treated with avutometinib 1.6 mg two times per week + defactinib 200 mg two times per day, 23 were evaluable for efficacy (Appendix 1).

Efficacy

Avutometinib Monotherapy (Parts A and B) Versus Avutometinib + Defactinib (Parts A, B, and C)

The ORR by BICR (primary end point) was 31% in the combination treatment group (44% in *KRAS* mt, 17% in *KRAS* wt; Table 2) and 17% in the avutometinib monotherapy group (23% in *KRAS* mt, 13% in *KRAS* wt; Table 2). ORR values by investigator assessment are in Appendix Table A2. DOR and PFS by BICR in the monotherapy group are in Appendix Table A3.

TABLE 1. Baseline Characteristics in the Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day) Group and the Avutometinib (4.0 mg two times per week) Group

	Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day)			Avutometinib (4.0 mg two times per week)		
Characteristic	All Patients, n = 115	*KRAS* mt, n = 58	*KRAS* wt, n = 57	All Patients, n = 70	*KRAS* mt, n = 31	*KRAS* wt, n = 39
Age (years), median (min, max)	54 (21, 87)	60 (29, 87)	45 (21, 80)	54 (21, 77)	57 (27, 74)	48 (21, 77)
Race,[a] No. (%)						
White	88 (77)	43 (74)	45 (80)	59 (84)	24 (77)	35 (90)
Asian	4 (3)	2 (3)	2 (4)	1 (3)	1 (3)	0
Black or African American	5 (4)	3 (5)	2 (4)	1 (3)	1 (3)	0
Other	5 (4)	0	5 (9)	2 (3)	2 (6)	0
Not reported	13 (11)	10 (17)	3 (5)	6 (9)	3 (10)	3 (8)
Unknown	0	0	0	1 (1)	0	1 (3)
ECOG PS, No. (%)						
0	78 (68)	42 (72)	36 (63)	50 (71)	19 (61)	31 (80)
1	37 (32)	16 (28)	21 (37)	20 (29)	12 (39)	9 (20)
Prior systemic regimens, No., median (min, max)	3 (1, 9)	3 (1, 9)	3 (1, 9)	3 (1, 10)	3 (1, 10)	3 (1, 9)
Prior platinum-based chemotherapy, No. (%)	114 (99)	58 (100)	56 (98)	69 (99)	30 (97)	39 (100)
Prior hormonal therapy, No. (%)	99 (86)	49 (85)	50 (88)	58 (83)	25 (81)	33 (85)
Prior bevacizumab, No. (%)	59 (51)	23 (40)	36 (63)	34 (49)	17 (55)	17 (44)
Prior MEK inhibitor therapy, No. (%)	25 (22)	12 (21)	13 (23)	18 (26)	8 (26)	10 (26)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; *KRAS*, Kirsten rat sarcoma virus homolog; MEK, mitogen-activated extracellular signal-regulated kinase; mt, mutant; wt, wild type.
[a]Self-reported.

TABLE 2. ORR (RECIST v1.1) by BICR in the Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day) Group and the Avutometinib (4.0 mg two times per week) Monotherapy Group

	Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day)			Avutometinib (4.0 mg two times per week)		
Clinical Outcome	All Patients, n = 109	*KRAS* mt, n = 57	*KRAS* wt, n = 52	All Patients, n = 69	*KRAS* mt, n = 30	*KRAS* wt, n = 39
Confirmed[a] ORR, No. (%)	34 (31)	25 (44)	9 (17)	12 (17)	7 (23)	5 (13)
Complete response	2 (2)	2 (4)	0	1 (1)	1 (3)	0
Partial response	32 (29)	23 (40)	9 (17)	11 (16)	6 (20)	5 (13)
Stable disease,[b] No. (%)	62 (57)	28 (49)	34 (65)	43 (62)	17 (57)	26 (67)
Progressive disease, No. (%)	9 (8)	2 (4)	7 (14)	7 (10)	3 (10)	4 (10)
Not evaluable, No. (%)	4 (4)	2 (4)	2 (4)	7 (10)	3 (10)	4 (10)

Abbreviations: BICR, blinded independent central review; *KRAS*, Kirsten rat sarcoma virus homolog; mt, mutant; ORR, objective response rate; wt, wild type.
[a]By BICR.
[b]Includes unconfirmed partial response; stable disease (or unconfirmed partial response) must occur ≥53 days after first dose date.

Avutometinib + Defactinib (Parts A, B, and C)

In the combination treatment group, the median time to confirmed response was 3.7 months (range, 1.7-19.2), and the median DOR (Kaplan-Meier estimate) was 31.1 months (95% CI, 14.8 to 31.1; Fig 3A). Among patients with confirmed objective responses, 81% (95% CI, 62% to 91%) and 72% (95% CI, 54% to 89%) of responses were maintained at 6 months and 12 months, respectively. Kaplan-Meier estimates by *KRAS* mutation status are shown in Figure 3A.

A planned subgroup analysis of confirmed ORR was conducted on the basis of prior therapies: prior MEK inhibitor (24%; 95% CI, 9% to 45%), no prior MEK inhibitor (33%; 95% CI, 23%, to 44%), prior bevacizumab (20%; 95% CI, 10% to 33%), no prior bevacizumab (43%; 95% CI, 29% to 57%), >3 prior regimens (24%; 95% CI, 13% to 39%), and 1-3 prior lines of therapy (37%; 95% CI, 25% to 50%; Appendix Fig A1). The study was not powered to assess differences in efficacy between these subgroups.

Fifty-seven percent of patients had stable disease as their best response, for a disease control rate (DCR) of 88%. DCR was maintained for ≥6 months in 61% of patients, with 70% in *KRAS* mt and 50% in *KRAS* wt. The majority of patients (82%) had some reduction in target lesions, regardless of *KRAS* mutation status (Fig 3C).

The median PFS was 12.9 months (95% CI, 10.9 to 20.2). In the *KRAS* mt and wt groups, the median PFS was 22.0 months (95% CI, 11.1 to 36.6) and 12.8 months (95% CI, 7.4 to 18.4), respectively (Fig 3B). For all patients, the 6-month PFS rate was 79% (95% CI, 70% to 86%), and the 12-month PFS rate was 58% (95% CI, 47% to 68%).

Lower Starting Dose of Avutometinib + Defactinib (Part D)

The rate of disease progression within 4 months was 83% greater with avutometinib 1.6 mg two times per week + defactinib 200 mg two times per day compared with avutometinib 3.2 mg two times per week + defactinib 200 mg two times per day (22% *v* 12%). The lower starting dose was determined to be suboptimal per protocol definition.

Safety

Avutometinib Monotherapy (Parts A and B)

AEs in the monotherapy group are in Table 3. AEs (regardless of causality) led to treatment discontinuation in 16% of patients. Treatment-related serious AEs (SAEs) occurred in 7% of patients, the most common of which was diarrhea in two patients.

Avutometinib + Defactinib (Parts A, B, and C)

In the combination treatment group, the most frequent treatment-related nonlaboratory AEs (all grades) were nausea (67%), diarrhea (58%), peripheral edema (53%), rash (50%), fatigue (44%), and vomiting (43%). Most events were grade 1 or 2 (Table 3). The most frequent grade 3 or 4 treatment-related nonlaboratory AEs were diarrhea (8%), anemia (5%), and dermatitis acneiform (4%). Increased creatine phosphokinase (CPK) related to treatment occurred in 60% of patients, with 19% grade 3 and 5% grade 4. These laboratory events were manageable and resolved mainly with dose holds per protocol.

AEs (regardless of causality) led to treatment discontinuation in 10% of patients; the most common was elevated CPK (4% of patients). Patients with repeat grade 3 or grade 4 CPK elevation were required to discontinue treatment in initial protocol versions; however, the protocol was amended to allow initial management with drug interruption and, subsequently, no patient discontinued for elevated CPK.

Treatment-related skin reactions reported in >20% of patients included rash (50%), dermatitis acneiform (34%), and

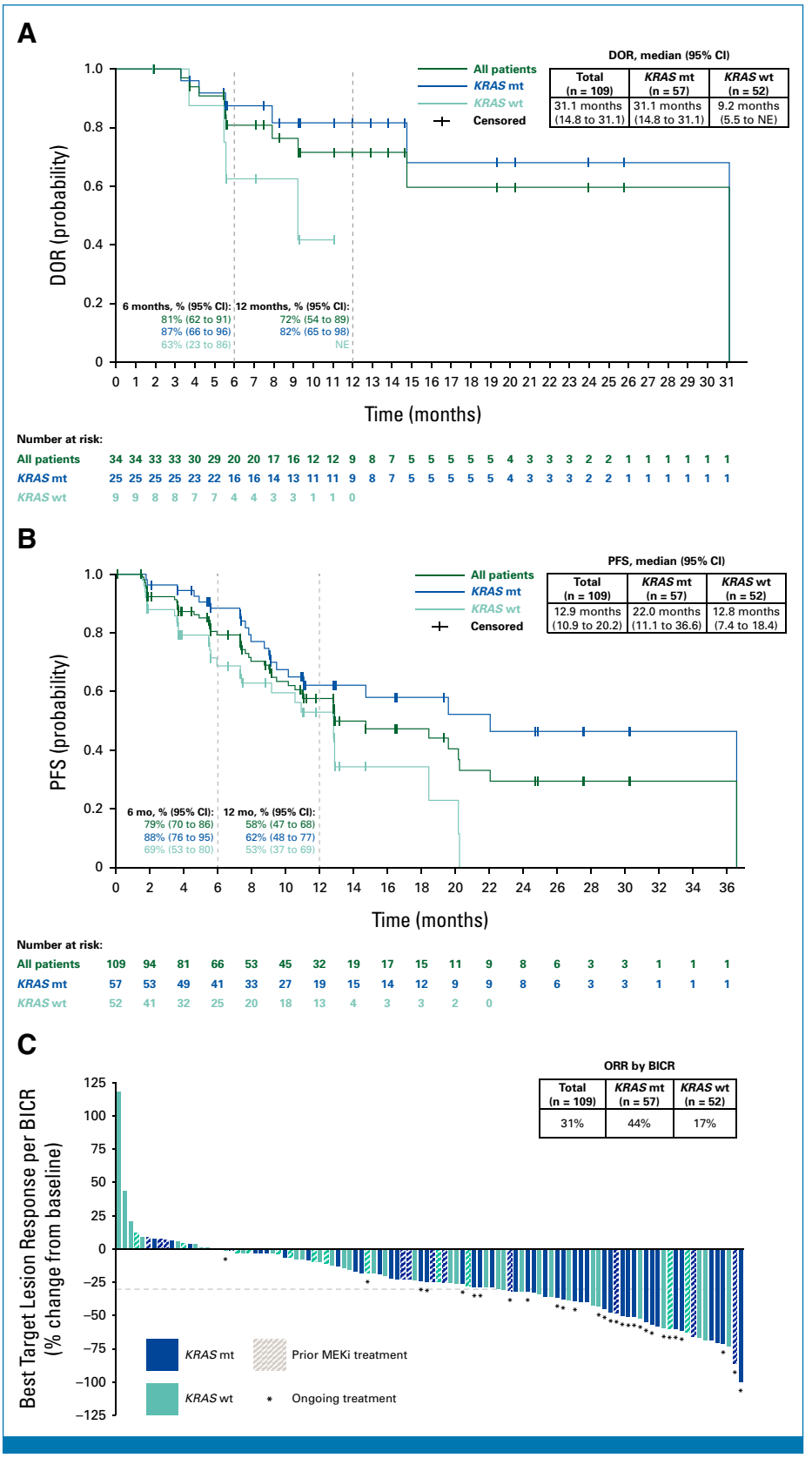

FIG 3. (A) DOR as assessed by the BIRC was calculated for patients with a complete response or partial response from the time of first response to progressive disease using Kaplan-Meier methods and (B) PFS as assessed by the BIRC is summarized by *KRAS* mutation status, phase, and treatment group for the efficacy-evaluable population. (C) Best response (percent change from baseline) of the sum of target lesions as assessed by the BIRC for the (continued on following page)

FIG 3. (Continued). efficacy evaluable population for the avutometinib 3.2 mg BIW + defactinib 200 mg BID combination therapy group. BID, two times per day; BIRC, blinded independent central review; BIW, two times per week; DOR, duration of response; *KRAS*, Kirsten rat sarcoma virus homolog; MEKi, mitogen-activated extracellular signal-regulated kinase inhibitor; mt, mutant; NE, not evaluable or unknown; PFS, progression-free survival; wt, wild type.

dry skin (26%); most were grade 1 or 2. The median onset of the first treatment-related skin reaction was 15 days, with a median duration of 35 days. A total of 6% of patients had a treatment-related skin reaction that resulted in a dose interruption or dose reduction. One patient discontinued because of dermatitis acneiform; no grade 4 or serious skin reactions were observed.

Blurred vision was the most common treatment-related ocular event (41% of patients), with the majority of events occurring within the first week (median onset 2 days). All events of blurred vision were grade 1 or 2, often resolved without treatment interruption, and did not lead to treatment discontinuation. Two patients had a treatment-related ocular event of ≥grade 3 (chorioretinopathy and retinal detachment); both resolved with dose modifications. Cardiovascular events were infrequent (2 patients with ≥grade 3 treatment-related events). One patient experienced decreased ventricular ejection fraction that resolved.

The proportion of patients with blood bilirubin increased and hyperbilirubinemia resulting in reduction or hold of study drug was 22%. None required study treatment discontinuation. Few patients with increased ALT or AST required treatment interruption (four and three patients, respectively), or dose reduction (one patient each). One and 0 patients, respectively, discontinued for increased ALT or AST.

Dose holds were the most common intervention to mitigate AEs. Treatment-related AEs led to dose holds of avutometinib and defactinib in 56% of patients and to dose reductions in 10% of patients. Patients maintained a high relative dose intensity (mean actual/planned cumulative dose) for both avutometinib (0.84) and defactinib (0.77).

Treatment-related SAEs occurred in 7% of patients, the most common was abdominal pain in two patients. There were five deaths in the combination group (on treatment or within 30 days of discontinuation): one each with GI hemorrhage, intestinal obstruction, and large intestine perforation and 2 with disease progression; none were considered by the investigator to be related to study treatment.

DISCUSSION

These findings represent a promising advance in the management of patients with recurrent LGSOC, who currently have few effective treatment options. Conventional treatment approaches have been adopted from HGSOC with limited success, both in terms of efficacy and safety.[9,12] The combination of avutometinib 3.2 mg twice weekly with defactinib 200 mg twice daily resulted in clinically meaningful and durable responses. Overall, 31% of patients achieved an objective response by BICR with a median DOR of 31 months.

Although avutometinib monotherapy (4.0 mg twice weekly) demonstrated clinical activity, the combination regimen demonstrated more robust efficacy without the addition of significant toxicities, supporting the combination as the go-forward regimen. The higher ORR observed with the combination versus avutometinib monotherapy is consistent with the known mechanism of action of each drug. Avutometinib inhibits MEK activities and induces dominant negative RAF/MEK complexes (RAF/MEK clamp), thereby blocking compensatory reactivation of MEK. The addition of defactinib may deepen and prolong responses by addressing adaptive resistance by FAK than occurs with MAPK inhibition alone.

In patients receiving the go-forward combination regimen, ORR was higher in patients with the *KRAS* mutation (44%) than in patients without the *KRAS* mutation (17%). A similar trend was observed in PFS, with a median of 22.0 months in *KRAS* mt and 12.8 months in *KRAS* wt patients. The differences in efficacy by *KRAS* mutation status may be driven by differences in prognosis, supported by other LGSOC studies showing worse outcomes and more rapid disease progression in *KRAS* wt patients.[8,9,12,23] Similarly, *KRAS* wt patients in this study had a younger median age than *KRAS* mt patients (45 *v* 60 years), consistent with previous studies showing that patients with *KRAS* mt LGSOC are more likely to be diagnosed at a more advanced age and have improved response rates to chemotherapy and improved overall survival. However, despite differences in prognosis, most (82%) patients achieved some reduction in target lesions, including both *KRAS* mt and wt patients as well as those who had received prior MEK inhibitor therapy.

AEs were manageable with dose holds or reductions, allowing most patients to have prolonged exposure and remain on treatment until disease progression. This was demonstrated by the high relative dose intensity (mean, 0.8) and 10% discontinuation rate because of AEs. By contrast, prior phase II/III studies with MEK-only inhibitors (trametinib and binimetinib) have reported discontinuation rates for AEs of >30%.[9,12] In addition to the use of dose

TABLE 3. Most Frequently Reported Treatment-Related AEs (>20% of Patients) for Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day) and Avutometinib (4.0 mg two times per week)

	Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day), n = 115		Avutometinib (4.0 mg two times per week), n = 70	
Preferred Term	All Grades, No. (%)	Grade ≥3,[a] No. (%)	All Grades, No. (%)	Grade ≥3,[a] No. (%)
Nonlaboratory AEs				
Nausea	77 (67)	3 (3)	29 (41)	2 (2)
Diarrhea	67 (58)	9 (8)	46 (66)	7 (10)
Edema peripheral	61 (53)	1 (1)	30 (43)	0
Rash[b]	58 (50)	3 (3)	41 (59)	7 (10)
Fatigue	50 (44)	3 (3)	26 (37)	1 (1)
Vomiting	49 (43)	3 (3)	19 (27)	2 (3)
Vision blurred	47 (41)	0	28 (40)	1 (1)
Dermatitis acneiform	39 (34)	5 (4)	28 (40)	7 (10)
Dry skin	30 (26)	0	25 (36)	0
Anemia	26 (23)	6 (5)	17 (24)	7 (10)
Stomatitis	18 (16)	3 (3)	17 (24)	1 (1)
Laboratory-related AEs				
Increased blood CPK	69 (60)	28 (24)	40 (57)	17 (24)
Increased blood bilirubin/hyperbilirubinemia	38 (33)	5 (4)	1 (1)	0
AST increased	36 (31)	2 (2)	11 (16)	1 (1)
ALT increased	25 (22)	2 (2)	7 (10)	1 (1)

NOTE. Most common AEs (preferred term) considered by the investigator to be related to study drug (either avutometinib or defactinib).
Abbreviations: AE, adverse event; CPK, creatine phosphokinase.
[a]Grade 4 treatment-related AEs were reported in 7 (6%) patients in the combination treatment group (six [5%] patients with CPK increased, and one [1%] patient with magnesium decreased); and two (3%) patients in the monotherapy group (one [1%] patient with large intestinal obstruction, and one [1%] patient with CPK increased).
[b]Treatment-related AEs for rash include the preferred terms: butterfly rash, rash, rash erythematous, rash macular, rash maculopapular, rash papular, and rash pruritic.

modifications (mainly dose holds) to manage toxicities with avutometinib + defactinib, the dosing schedule of 3 weeks on and 1 week off may mitigate the accumulation of toxicities and contribute to a low discontinuation rate.

Elevated blood CPK, a recognized mechanism-based effect of drugs that inhibit the MAPK pathway,[12,24] was the most common laboratory abnormality; however, these events were mainly asymptomatic and effectively managed with dose holds. The majority of skin reactions occurred within the first 2 months of the study and were grade 1 or 2. To mitigate dermatologic toxicities, prophylactic medications were mandatory during the first 2 cycles and optional from Cycle 3 onward. Ocular events are a recognized class-effect toxicity of MEK inhibitors.[25,26] Abnormal ophthalmologic examination findings were recorded as AEs even if they were asymptomatic. Overall, ocular events had an early onset, were generally nonserious and mild in severity, and were self-limiting without treatment or discontinuation of study drugs.

Unlike previous studies in LGSOC,[9,12] patients were stratified by the presence or absence of *KRAS* mutation. More than 20% of patients enrolled had received prior MEK inhibitor therapy, and more than 50% received prior bevacizumab. The impact of prior therapies on patient outcomes warrants further investigation. The main limitation of this study is the lack of a comparator arm with current standard of care, which is currently being explored in a phase 3 trial with PFS as the primary end point (GOG-3097/ENGOT-ov81/GTG-UK/RAMP 301; ClinicalTrials.gov identifier: NCT06072781).[27]

In this population of women with recurrent LGSOC and few available treatment options, the combination of avutometinib 3.2 mg twice weekly + defactinib 200 mg twice daily resulted in clinically meaningful response rates, DOR, and PFS. AEs were manageable, allowing most patients to stay on therapy. These data support the combination of avutometinib and defactinib as a potential new standard of care for women with recurrent LGSOC.

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Efficacy and Safety of Avutometinib ± Defactinib in Recurrent Low-Grade Serous Ovarian Cancer: Primary Analysis of ENGOT-OV60/GOG-3052/RAMP 201

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APPENDIX 1. SUPPLEMENTAL RESULTS FOR PART D: AVUTOMETINIB 1.6 MG TWICE WEEKLY + DEFACTINIB 200 MG TWICE DAILY

Lower Starting Dose of Avutometinib + Defactinib (Part D)

Of the 27 patients enrolled in Part D and treated with avutometinib 1.6 mg twice weekly + defactinib 200 mg twice daily, 23 were evaluable for efficacy (nine *KRAS* mt and 14 *KRAS* wt). The percentage with specific prior therapies was similar to patients enrolled in Parts A, B, and C (41% received prior bevacizumab, and 37% received prior mitogen-activated extracellular signal-regulated kinase inhibitor treatment).

The rate of disease progression within 4 months was 83% greater with avutometinib 1.6 mg twice weekly + defactinib 200 mg twice daily compared with avutometinib 3.2 mg twice weekly + defactinib 200 mg twice daily (22% *v* 12%). On the basis of these data, the lower starting dose was determined to be suboptimal.

The most common treatment-related AEs in Part D were nausea (56%), fatigue (44%), and increased CPK (33%). Five patients had grade ≥3 treatment-related AEs, most commonly increased CPK in two patients. AEs leading to discontinuation occurred in 15% of patients.

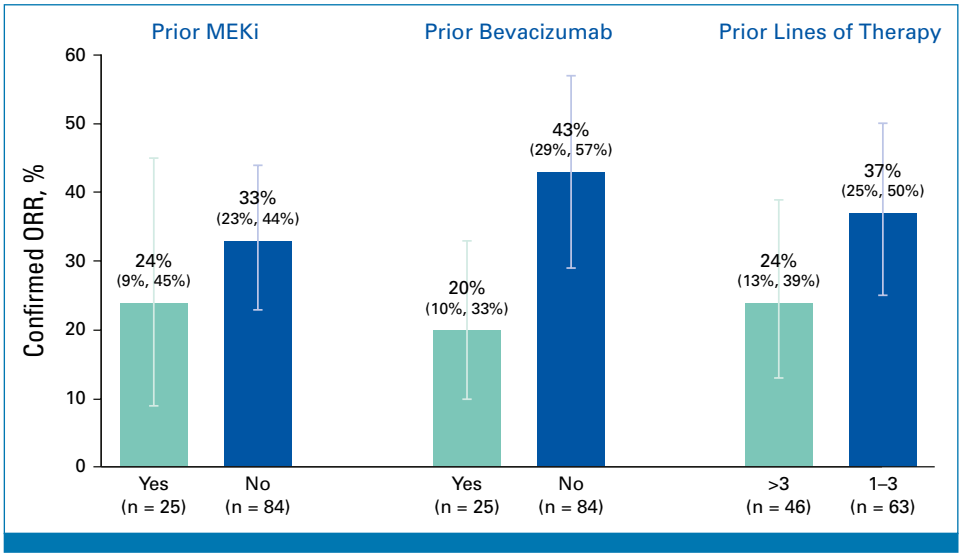

FIG A1. Confirmed ORR in subgroups by prior therapies: Parts A, B, and C. Error bars represent 95% CI. MEKi, mitogen-activated extracellular signal-regulated kinase inhibitor; ORR, objective response rate.

TABLE A1. Summary of RAMP-201 Patients Treated With 3.2 mg Avutometinib Twice Weekly in Combination With 200 mg Defactinib Twice Daily for Whom *KRAS* Mutation Status Differed Between Local and Central Tumor Tissue-Based Testing

Local Test			Central Test			
KRAS Mutation Status	*KRAS* VAF	Assay	*KRAS* Mutation Status	*KRAS* VAF	Tempus Result	Comparison
WT	NA	CARIS	G13C	4.5%	*KRAS* detected but a very low VAF (4.5%)	4.5% VAF is at or below the limit of detection of most assays
G12D	15%	Roche Diagnostics (KAPA HyperPlus Library)	WT	NA	No mutations detected	*KRAS* G12D detected by local test, but not Tempus test
G12V	36%	Roche Diagnostics (KAPA HyperPlus Library)	WT	NA	*KRAS* G12V (VAF 5.5%) filtered because of high TMB but MSI not called	*KRAS* G12V detected by both local and Tempus tests
G12V	ND	Foundation One CDx	G12D	15%	*KRAS* filtered because of germline contamination (G12D with VAF 15% in tumor and VAF 3.6% in normal tissue)	*KRAS* mutation detected by both local and Tempus tests; however, different variants

Abbreviations: *KRAS*, Kirsten rat sarcoma virus; MSI, microsatellite instability; NA, not applicable; ND, not determined; TMB, mutational burden; VAF, variant allele frequency; WT, wild-type.

TABLE A2. Summary of Concordance (RECIST v1.1) Between BICR Committee and Investigator Efficacy Evaluations in the Avutometinib (3.2 mg two times per week) + Defactinib (200 mg two times per day) Group

	Best Overall Response by Investigator (n = 115)				
Best Overall Response by BICR	Complete Response (confirmed)	Partial Response (confirmed)	Stable Disease	Progressive Disease	NE
Complete response (confirmed[a]), No. (%)	1 (1)	1 (1)	0	0	0
Partial response (confirmed[a]), No. (%)	1 (1)	17 (15)	14 (12)	0	0
Stable disease[b], No. (%)	0	11 (10)	47 (41)	4 (4)	0
Progressive disease, No. (%)	0	1 (1)	6 (5)	2 (2)	0
NE, No. (%)	0	0	0	1 (1)	3 (3)

Abbreviations: BICR, blinded independent central review; NE, not evaluable or unknown.
[a]By BICR.
[b]Includes unconfirmed partial response; stable disease (or unconfirmed partial response) must occur ≥53 days after first dose date.

TABLE A3. DOR by BICR and PFS in the Avutometinib (4.0 mg two times per week) Monotherapy Group: Parts A and B

Clinical Outcome	All Patients, n = 69	*KRAS* mt, n = 30	*KRAS* wt, n = 39
DOR, median (95% CI), months	NE	NE	NE
PFS, median (95% CI), months	14.8 (9.1 to 27.5)	24.5 (11.0 to 29.3)	11.0 (9.0 to NE)

NOTE. NE = Could not be estimated on the basis of number of patients with loss of response.
Abbreviations: BICR, blinded independent central review; DOR, duration of response; mt, mutant; *KRAS*, Kirsten rat sarcoma virus; NE, not evaluable or unknown; PFS, progression-free survival; wt, wild-type.

TABLE A4. RAMP 201 Investigators and Institutions

Investigator	Research Group	Institution
Susana Banerjee	GTG-UK	Royal Marsden NHS Foundation Trust
Charlie Gourley	GTG-UK	Western General Hospital - Edinburgh Cancer Centre
Andrew Clamp	GTG-UK	The Christie NHS Foundation Trust
Rowan Miller	GTG-UK	University College London Cancer Institute
Diane Provencher	ENGOT	Centre de recherche du Centre Hospitalier de l'Universite de Montreal
Valentina Guarneri	MaNGO	U.O.C. Oncologia 2Istituto Oncologico Veneto I.R.C.C.S.
Nicoletta Colombo	MaNGO	Divisone Ginecologia Oncologica Medica
Ana Oaknin	GEICO	Hospital Universitario Vall d'Hebron
Maria Jesus Rubio	GEICO	Hospital Universitario Reina Sofia
Alfonso Cortes Salgado	GEICO	Hospital Universitario Ramon y Cajal
Jose Alejandro Perez Fidalgo	GEICO	Hospital Clinico Universitario de Valencia
Véronique D'Hondt	GEICO	ICM Val d Aurelle
Isabelle Ray-Coquard	GEICO	Centre Leon Berard
Laura Mansi	GEICO	Hospital Jean Minjoz
Manuel Rodrigues	GEICO	Institut Curie
Toon Van Gorp	BGOG	UZ Leuven Campus Gasthuisberg
Christine Gennigens	BGOG	CHU de Liège
Rachel Grisham	GOG	Memorial Sloan Kettering Cancer Center
Charles Anderson	GOG	Oncology Associates of Oregon, P.C., USO
Christine Lee	GOG	Texas Oncology, P.A., USO
Bradley Monk	GOG	Arizona Oncology Associates, PC-HAL, USO
Emily Prendergast	GOG	Minnesota Oncology Hematology, P.A., USO
Anna Priebe	GOG	Texas Oncology, P.A., USO
Lynne Knowles	GOG	Texas Oncology, P.A., USO
Kari Ring	GOG	University of Virginia Health System
Robert Holloway	GOG	Advent Cancer Institute
Hye Sook Chon	GOG	H. Lee Moffitt Cancer Center & Research Institute, Inc
Alessandro D. Santin	GOG	Yale University School of Medicine
Premal Thaker	GOG	Washington University School of Medicine
John Moroney	GOG	The University of Chicago Medical Center
Carolyn Muller	GOG	University of New Mexico Comprehensive Cancer Center
Peter Rose	GOG	Cleveland Clinic
David M. O'Malley	GOG	Ohio State University
David Miller	GOG	UT Southwestern Medical Center
Erika Hamilton	GOG	Tennessee Oncology PLLC
Kathleen Moore	GOG	Stephenson Cancer Center
Mitul Gandhi	GOG	Virgina Cancer Specialists, USO
Antonio Santillan-Gomez	GOG	Texas Oncology, USO
Gregg Newman	GOG	Sansum Clinic, USO
Anu Thummala	GOG	Comprehensive Cancer Centers Of Nevada, USO
Erin Salinas	GOG	Northwest Cancer Specialists, P.C., USO
Carol Tweed	GOG	Maryland Oncology Hematology, PA, USO
Kristi Mcintyre	GOG	Texas Oncology Presbyterian, USO