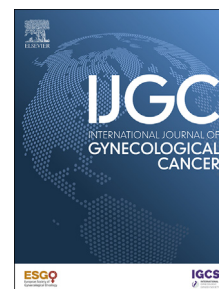


GOG-3097/ENGOT-ov81/GTG-UK/RAMP 301: a phase 3, randomized trial evaluating avutometinib plus defactinib compared with investigator's choice of treatment in patients with recurrent low grade serous ovarian cancer



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ABSTRACT

Background: There are no approved treatments specifically for low grade serous ovarian cancer; current standard of care treatment options are limited in efficacy and tolerability. The combination of avutometinib with defactinib has demonstrated efficacy and a consistent safety profile in two clinical trials in recurrent low grade serous ovarian cancer, and a lower discontinuation rate due to adverse events compared with historical rates for standard of care.

Primary Objective: To compare the progression-free survival of the combination of avutometinib with defactinib versus investigator's choice of treatment in patients with recurrent low grade serous ovarian cancer.

Study Hypothesis: Combination treatment with avutometinib—defactinib will significantly improve progression-free survival compared with investigator's choice of treatment in patients with recurrent low grade serous ovarian cancer.

Trial Design: GOG-3097/ENGOT-ov81/GTG-UK/RAMP 301 is a phase 3, randomized, international, open-label study designed to compare avutometinib with defactinib versus investigator's choice of treatment in patients with recurrent low grade serous ovarian cancer who have progressed on a previous platinum-based therapy. On confirmation of disease progression using a blinded independent central review, patients on the investigator's choice of treatment arm may cross over to the avutometinib—defactinib arm.

Major Inclusion/Exclusion Criteria: Patients must have recurrent low grade serous ovarian cancer (*KRAS* mutant or wild-type) and have documented progression (radiographic or clinical) or recurrence of low grade serous ovarian cancer after at least one platinum-based chemotherapy regimen. Unlimited additional previous lines of therapy are allowed, including previous MEK/RAF inhibitor. Patients will be excluded if they have co-existing high grade ovarian cancer or had previous treatment with avutometinib, defactinib, or any other FAK inhibitor.

Primary Endpoint: Progression-free survival according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, blinded-independent central review.

Sample Size: Approximately 270 patients will be randomized in a 1:1 fashion to either the combination avutometinib with defactinib arm ($n \sim 135$) or the investigator's choice of treatment arm ($n \sim 135$).

Estimated Dates for Completing Accrual and Presenting Results: The estimated primary completion date of RAMP 301 is 2028, and the estimated study completion date is 2031.

Trial Registration: ClinicalTrials.gov [NCT06072781](https://clinicaltrials.gov/ct2/show/study/NCT06072781)

Keywords:

Low grade serous ovarian cancer; LGSOC; clinical trial; avutometinib; defactinib; MEK; FAK; RAS; RAF

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INTRODUCTION

Low grade serous ovarian cancer is a histopathologically, molecularly, and clinically distinct malignancy comprising <10% of serous ovarian cancer diagnoses.^{1,2} It is characterized by a relatively low proliferative index, frequent alterations in the RAS/MAPK pathway (~70%, with *KRAS*, *NRAS*, *E1F1AX*, and *BRAF* being the most common alterations), presence of wild-type *BRCA* and *TP53* genes, and high levels of hormone receptor expression.³ Relative to high grade serous ovarian cancer, low grade serous ovarian cancer patients have a younger median age at diagnosis, and have a longer overall survival, resulting in a longer disease course, often complicated by disease associated morbidity. Therefore, patients with low grade serous ovarian cancer are often treated with multiple lines of therapy.^{1,2}

There are no FDA approved treatments specifically for low grade serous ovarian cancer. The current standard of care treatment options are based primarily on treatment of patients with high grade serous ovarian cancer and include chemotherapy, hormonal therapy, and antiangiogenics; single-agent MEK inhibitors have

displayed activity in patients with recurrent low grade serous ovarian cancer, but uptake of their use has been limited by availability (there are currently no FDA or EMA approved MEK inhibitors for ovarian cancer) and toxicity concerns.^{4,5} Unfortunately, the standard of care options currently available for women with recurrent low grade serous ovarian cancer are limited in efficacy (objective response rate 0–26%, median progression free survival (mPFS) 3.1–13.0 mo) and tolerability (17–36% discontinuation due to toxicity).^{6,7}

Avutometinib is a first-in-class oral RAF/MEK clamp that potently inhibits MEK kinase activity and induces formation of dominant negative RAF/MEK complexes preventing phosphorylation and feedback activation of MEK by RAF protein A (ARAF), RAF protein B (BRAF), and RAF protein C (CRAF) (Figure 1). In contrast with several other MEK only inhibitors (MEKi), avutometinib blocks both MEK kinase activity and the ability of RAF to phosphorylate MEK. This RAF/MEK clamp mechanism enables avutometinib to block MEK signaling without the compensatory phosphorylation and feedback activation of MEK that compromises the efficacy of

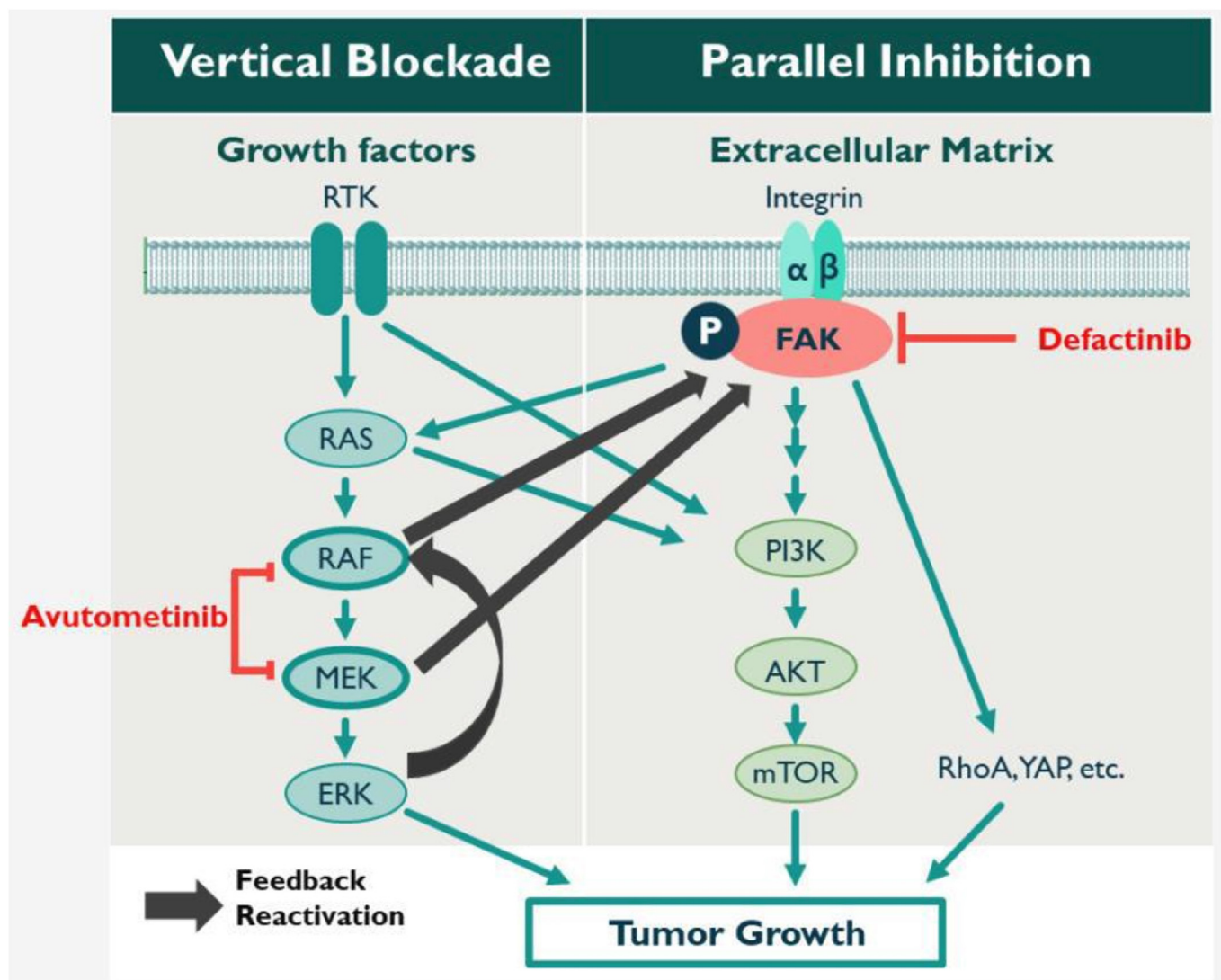


Figure 1 Avutometinib plus defactinib mechanism of action. AKT, protein kinase B; ERK, extracellular signal regulated kinase; P, phosphate; RhoA, Ras homolog family member A; RTK, receptor tyrosine kinase; YAP, yes associated protein.

MEK-only inhibitors.⁸ Defactinib is a selective inhibitor of focal adhesion kinase (FAK) and proline-rich tyrosine kinase-2 (Pyk2), the two members of the focal adhesion kinase family of non-receptor protein tyrosine kinases (Figure 1). FAK and Pyk2 integrate signals from integrin and growth factor receptors to regulate cell proliferation, survival, migration, and invasion, and have been shown to mediate resistance to multiple anticancer agents.⁹

Avutemetinib and defactinib are orally administered using an intermittent dosing schedule; avutemetinib is taken twice a week, 3 weeks on and 1 week off, and defactinib is taken twice a day, 3 weeks on and 1 week off. The combination of avutemetinib and defactinib was selected as the go-forward regimen over avutemetinib monotherapy for recurrent low grade serous ovarian cancer in the phase 2 ENGOT-ov60/GOG-3052/RAMP 201 study (RAMP 201, NCT04625270) based on a 45% objective response rate (n/N=13/29; 95% CI 26% to 64%) observed with the combination compared with a 10% objective response rate (n/N=3/30; 95% CI, 2% to 24%) observed with avutemetinib monotherapy in part A.¹⁰ These findings were consistent with earlier data from the phase 1 FRAME study exploring the combination of avutemetinib with defactinib in patients with recurrent low grade serous ovarian cancer (NCT03875820; 46% objective response rate, n/N=11/24, 23.0 months mPFS)¹¹ which led to an FDA breakthrough therapy designation for avutemetinib–defactinib in recurrent low grade

serous ovarian cancer (Figure 2). The safety profiles of avutemetinib–defactinib observed in RAMP 201 and FRAME were consistent: most treatment-related adverse events were grades 1–2, and a limited number of patients experienced dose reductions or discontinuations. These results led to the initiation of the ongoing confirmatory RAMP 301 study.

METHODS

Trial Design

GOG-3097/ENGOT-ov81/GTG-UK/RAMP 301 (RAMP 301) is a phase 3, randomized, international, open-label study designed to compare avutemetinib with defactinib versus investigator's choice of treatment (consisting of pegylated liposomal doxorubicin, paclitaxel, anastrozole, or letrozole) in patients with recurrent low grade serous ovarian cancer who have progressed on a previous platinum-based therapy (Figure 3).

RAMP 301 is a collaboration with GOG Foundation, ENGOT, KGOG, and ANZGOG, and is funded and sponsored by Verastem Oncology (Figure 4). Site selection and patient enrollment is ongoing at more than 30 sites identified so far.

Participants

Patients eligible for inclusion must have recurrent low grade serous ovarian cancer (*KRAS* mutant or wild-type) with documented *KRAS*

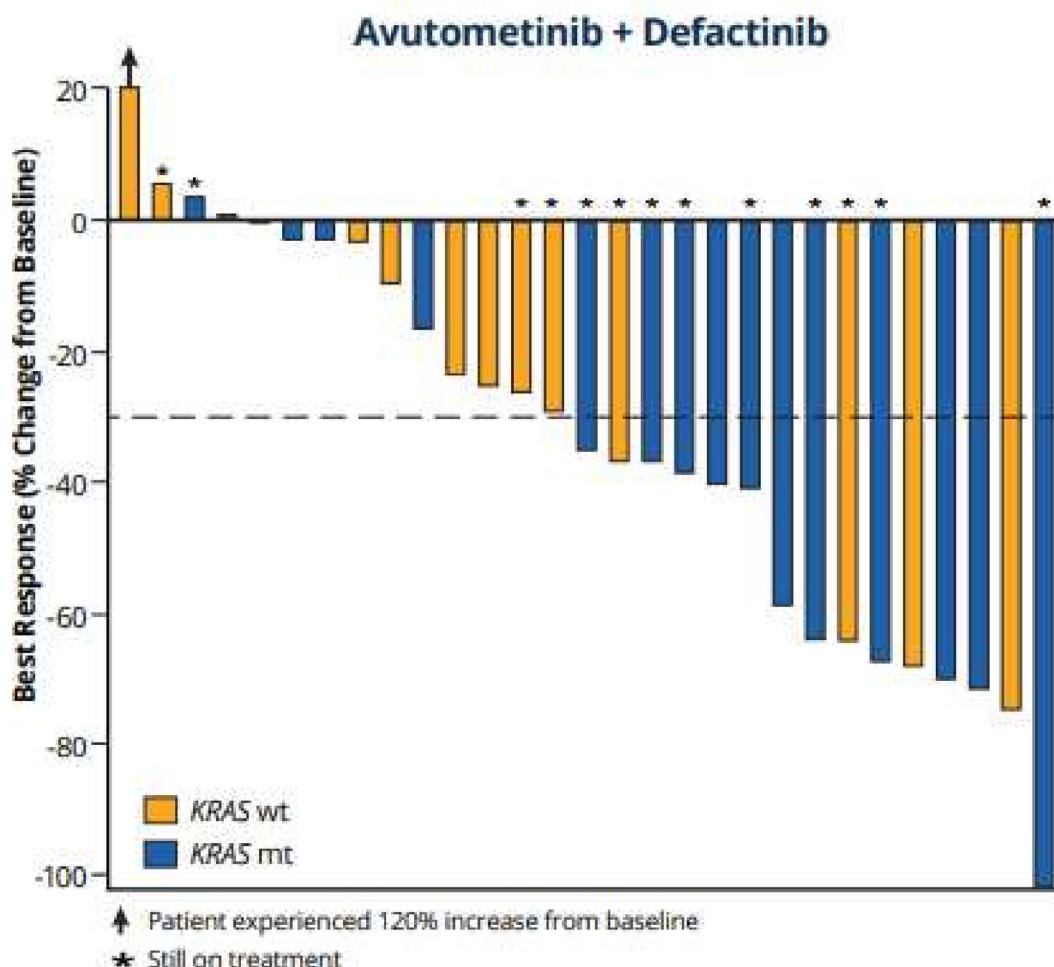


Figure 2 Per cent change in baseline tumor assessment in the RAMP 201 (part A) studies. *KRAS*, Kirsten rat sarcoma virus.

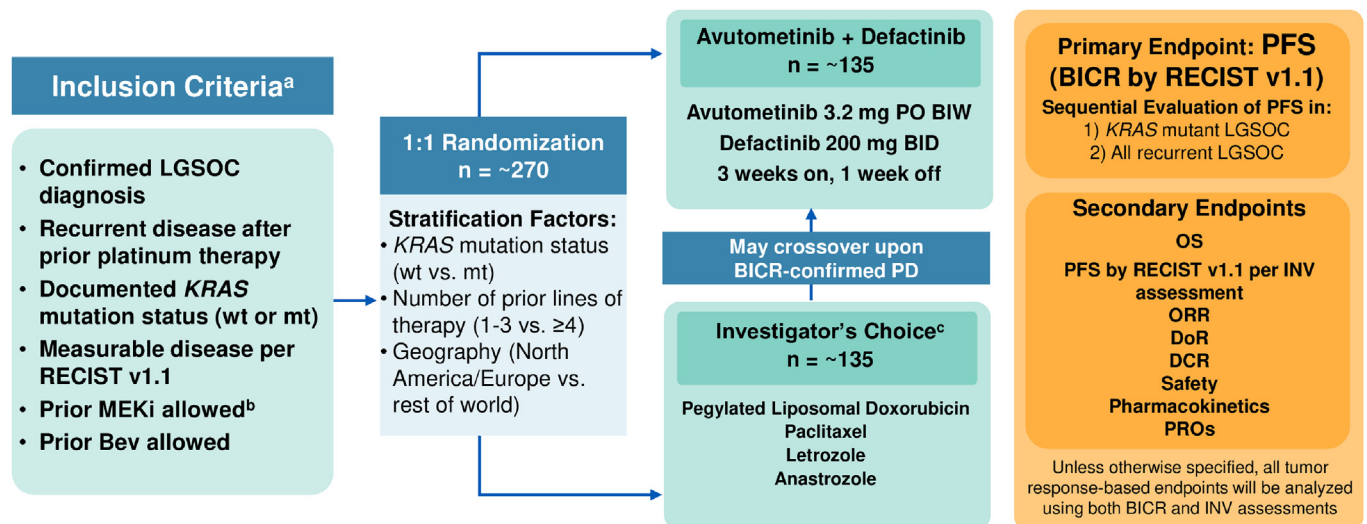


Figure 3 RAMP 301 study design. ^aKey inclusion and exclusion criteria are listed in Figure 5. ^bPrevious line of treatment with a MEK and/or RAF inhibitor is permitted. ^cPegylated liposomal doxorubicin 40 mg/m² intravenously on day 1 of each 28 day (4 week) cycle; paclitaxel 80 mg/m² intravenously on days 1, 8, and 15 of each 28 day (4 week) cycle; anastrozole 1 mg orally once daily of each 28 day (4 week) cycle; letrozole 2.5 mg orally once daily of each 28 day (4 week) cycle. Bev, bevacizumab; BICR, blinded independent central review; BID, twice daily; BIW, twice a week; DCR, disease control rate; DoR, duration of response; IV, intravenous; MEKi, MEK inhibitor; mt, mutant; ORR, objective response rate; PD, progressive disease; PFS, progression free survival; PO, oral administration; PROs, patient reported outcomes; wt, wild type.



Figure 4 RAMP 301 ovarian cancer research groups.

mutational status (local *KRAS* mutational status available from an approved diagnostic (companion diagnostic or tests with European conformity)). Archival tumor tissue or fresh biopsy tissue must be available and received by central laboratories for central confirmation of *KRAS* mutational status and low grade serous ovarian cancer diagnosis after randomization. Patients must also have measurable disease and documented progression (radiographic or clinical) or recurrence after at least one platinum based chemotherapy regimen. Previous MEK and/or RAF inhibitor is permitted. Patients will be excluded if they have co-existing high grade ovarian cancer. Patients must not have previous treatment with avutometinib, defactinib, or any other FAK inhibitor. Key inclusion and exclusion criteria are summarized in Figure 5.

Outcomes

Primary Endpoint

The primary endpoint of RAMP 301 is progression-free survival according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, per blinded independent central review.¹² Progression free survival will be estimated using Kaplan–Meier methods from time of randomization to progression of disease or death. After randomization, disease assessments will occur every 8 weeks (± 7 days) for the first 18 cycles and then every 12 weeks (± 7 days)

until disease progression, regardless of any changes to visit or cycle schedules. Post-randomization chest CT is only required when there is baseline disease or when there is suspected disease or symptoms. Survival follow-up will be performed every 12 weeks (± 14 days) after the 30 day safety follow-up visit for up to 5 years after the last patient is enrolled.

Secondary Endpoints

Efficacy. Unless otherwise specified, all tumor response based endpoints will be analyzed using both blinded independent central review and investigator assessments. Time based endpoints will be estimated using Kaplan–Meier methods (overall survival, progression free survival by investigator, duration of response). Overall survival will be calculated from time of randomization to death due to any cause. Progression-free survival by investigator assessment will be calculated from time of randomization to progression of disease or death. Overall response rate will be calculated as the proportion of patients achieving confirmed complete response or partial response. The overall response rate will be assessed according to RECIST V.1.1¹² as assessed by the investigator. The primary analysis of overall response rate will occur at the same time as the primary analysis of progression-free survival. Duration of response will be calculated for those

Inclusion Criteria	Exclusion Criteria
- Age $\geq$ 18 years - Histologically proven LGSOC (ovarian, fallopian, peritoneal) - Documented mutational status of <i>KRAS</i> by a validated tumor-tissue based diagnostic test - Documented disease progression or recurrence of LGSOC - Prior treatment with $\geq$ 1 platinum-based regimen - Suitable candidate for treatment with at least one of the Investigator's Choice Therapies (pegylated liposomal doxorubicin, paclitaxel, letrozole, anastrozole) - Adequate recovery from toxicities related to prior treatment $\geq$ 1 measurable lesion per RECIST v1.1 - ECOG performance status $\leq$ 1 - Adequate organ function - Agreement to use highly effective method of contraception (for patients with reproductive potential)	- High-grade serous ovarian cancer or mixed histology not described in inclusion criteria - LGSOC in conjunction with serous borderline tumor is permitted - Prior treatment with avutemetinib, defactinib, or other FAK inhibitors - Prior MEK and/or RAF inhibitor is permitted - Suitable for debulking surgery according to physician - Systemic anti-cancer therapy within 4 weeks of the first dose of study intervention or participation in concurrent investigational therapy or device clinical trial - Major surgery within 4 weeks - Symptomatic brain metastases requiring steroids or other interventions, known leptomeningeal metastases, or spinal cord compression - Active skin disorder that has required systemic therapy within 1 year of first dose - History of medically significant rhabdomyolysis - Symptomatic bowel obstruction within 3 months - Concurrent ocular disorders - Concurrent heart disease or severe obstructive pulmonary disease

Figure 5 Key inclusion and exclusion criteria for RAMP 301.

patients with a confirmed complete response or partial response from the time of first response to progression of disease. Disease control rate will be calculated for those patients with a complete response, partial response, or stable disease documented at $\geq$ week 24. Changes over time in health-related quality of life will be analyzed descriptively based on data collected from EORTC QLQ-C30, EORTC QLQ-QV28, and EQ-5D-5L questionnaires.

The primary analysis of all secondary efficacy endpoints will be performed at the time of the primary analysis of the primary endpoint, except for overall survival. An interim analysis of overall survival will take place at the time of the primary analysis of the primary endpoint. The final analysis of overall survival will take place approximately 5 years after the last patient is enrolled. Given the anticipated high crossover rate and natural history of the disease, it is not anticipated that this study will be fully powered to detect a statistically significant overall survival effect.

Safety and Tolerability. Safety assessments will include the monitoring of adverse events/ serious adverse events, clinical laboratory tests, physical examinations, ophthalmic examinations (avutemetinib plus defactinib arm only), ECGs, and echocardiograms or multi-gated acquisition scans. All concomitant medications and/or procedures will be recorded during the study period. Incidence and severity of adverse events, including laboratory abnormalities, vital signs, and physical examination abnormalities, will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.5.0. A special grading system will be used for the assessment of ocular toxicities.

Pharmacokinetics. Sparse pharmacokinetic samples will be collected for patients randomized to the avutemetinib plus

defactinib arm. Pharmacokinetic exposures for both avutemetinib and defactinib will be determined using population pharmacokinetic modeling and will be applied to explore the exposure response (efficacy and adverse events) relationship.

Patient Reported Outcomes. All patient reported outcomes should be administered before any other assessments. The patient reported outcome instrument will be provided in the local language in accordance with local guidelines. The EORTC QLQ-30 assesses the health-related quality of life of cancer patients participating in clinical trials.¹³ This instrument is comprised of five functional scales (physical, role, emotional, social, and cognitive), eight single item scales (fatigue, pain, nausea/ vomiting, appetite loss, constipation, diarrhea, insomnia, and dyspnea) in addition to subscales evaluating global health/quality of life and financial health.

The EORTC QLQ-OV28 assesses concerns pertinent to ovarian cancer patients participating in clinical trials, including abdominal and gastrointestinal symptoms, peripheral neuropathy, other chemotherapy side effects, hormonal and menopausal symptoms, body image, attitude to disease/treatment, and sexual functioning.¹⁴

The EQ-5D-5L is a standardized measure of health that comprises five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression¹⁵). The instrument also quantifies a patient's self-rated health on a 0–100 point analog scale with 0 being 'the worst health you can imagine' and 100 being 'the best health you can imagine.'

Sample Size

A total of approximately 270 patients will be randomized in a 1:1 fashion. Randomization will be stratified by *KRAS* mutation status

(mutant vs wild-type), geography (North America/Europe vs rest of the world) and number of previous therapies (1–3 vs 4 or more).

Randomization and Treatment Plan

Randomization

Approximately 270 patients will be randomized in a 1:1 ratio to receive either combination avutometinib–defactinib or the investigator’s choice of treatment (pegylated liposomal doxorubicin, paclitaxel, letrozole, or anastrozole). Before randomization, the investigator will determine which investigator’s choice of treatment option would be appropriate for the patient based on the medical history, previous treatment(s), availability, and approval within a given country, and other relevant factors. These investigator’s choice of treatment options have received marketing approval in the US, Canada, Europe, and other regions for recurrent epithelial ovarian cancer and have been broadly adopted as treatment options for patients with low grade serous ovarian cancer and are NCCN compendium listed for treatment of this disease. These investigator’s choice of treatment options are also consistent with what have been studied in two previously conducted randomized controlled trials in recurrent low grade serous ovarian cancer.¹⁶ Patients will remain on treatment until disease progression or intolerable toxicity.

Treatment Schedule

Avutometinib will be dosed at 3.2 mg orally taken twice weekly (eg, Monday/Thursday, Tuesday/Friday) for 3 weeks (21 days) followed by 1 week (7 days) off treatment, in a 4 week cycle. Defactinib will be dosed at 200 mg orally taken twice per day for 3 weeks (21 days) followed by 1 week (7 days) off treatment, in a 4 week cycle.

Pegylated liposomal doxorubicin will be dosed at 40 mg/m² intravenously on day 1 of each 28 day (4 week) cycle. Paclitaxel will be dosed at 80 mg/m² intravenously on days 1, 8, and 15 of each 28 day (4 week) cycle. Anastrozole will be dosed at 1 mg orally once daily of each 28 day (4 week) cycle. Letrozole will be dosed at 2.5 mg orally once daily of each 28 day (4 week) cycle.

Crossover

Patients randomized to the investigator’s choice of treatment arm who have locally determined assessment of progressive disease (according to RECIST V.1.1) confirmed by blinded independent central review may, at the investigator’s discretion, be considered for crossover to receive the investigational combination avutometinib plus defactinib.

The end of treatment 30-day safety follow-up visit, per the investigator’s choice of treatment schedule of assessments, will be completed. Patients will re-consent before any crossover specific assessments or procedures not considered standard of care. Assessments performed as part of the 30-day safety follow-up visit may not need to be repeated if performed within the 28-day crossover screening window. Avutometinib plus defactinib treatment must be initiated no less than 28 days and no more than 8 weeks after blinded independent central review confirmation of disease progression.

Statistical Methods

Progression-free survival will be tested sequentially using a stratified log rank test to control the overall type 1 error rate at 0.025

one sided for the primary endpoint. Progression-free survival will be tested first in the subset of patients with *KRAS* mutant recurrent low grade serous ovarian cancer at the one sided 0.025 alpha level.

Interim Analysis

An interim analysis will be conducted after a predefined number of progression-free survival events have been observed in patients with *KRAS* mutated recurrent low grade serous ovarian cancer and the overall population. The purpose of the interim analysis will be a possible sample size adjustment based on a conditional power approach. Conditional power will be calculated by assuming that for the patients after the interim analysis, the distribution of the time to the primary event for each treatment group would be the same as the observed one at the interim. The conditional power of the study for the original sample size will be calculated. Conditional power will be calculated for all patients and for patients with *KRAS* mutant recurrent low grade serous ovarian cancer.

DISCUSSION

Relative to high grade serous ovarian cancer, low grade serous ovarian cancer has a lower incidence, younger median age of presentation, and longer median overall survival but recurrent low grade serous ovarian cancer is ultimately fatal for most patients. Patients with low grade serous ovarian cancer have historically been excluded from most ovarian cancer studies due to low grade serous ovarian cancers’ relative resistance to standard therapies. Previous studies of chemotherapy and endocrine therapy have resulted in disappointing response rates. The phase II GOG study of selumetinib, the MILO study of binimetinib, and the GOG 281/low grade serous ovarian cancer phase III study of trametinib^{4,5,16} have shown encouraging initial signals in support of single agent continuous MEK inhibitors for patients with recurrent low grade serous ovarian cancer, but with challenging toxicity and still limited efficacy. Most patients with recurrent low grade serous ovarian cancer treated with a single agent MEK inhibitor do not experience significant disease shrinkage (response rates of 15–26%).⁵ The FRAME and interim results of the RAMP-201 studies of combination therapy with avutometinib plus defactinib have demonstrated unprecedented response rates of 45–46% in patients with recurrent low grade serous ovarian cancer. Importantly, to date, the combination of avutometinib and defactinib (dosed intermittently, 3 weeks on and 1 week off) has demonstrated a well tolerated toxicity profile, even in heavily pretreated patients. This randomized phase 3 study seeks to change the standard of care for patients with recurrent low grade serous ovarian cancer and to potentially establish the first therapy specifically approved for low grade serous ovarian cancer.

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Patient Consent for Publication Not applicable.

Ethics Approval The study is currently undergoing activation at a number of sites, and thus the complete list of institutional review board approved sites is not currently available. This can be provided if needed once sites are activated. This manuscript is a trials in progress manuscript intended to familiarize colleagues about the availability of this phase III study globally.

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Data Availability Statement All data relevant to the study are included in the article.

Provenance and Peer Review Commissioned; internally peer reviewed.

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REFERENCES

- Gershenson DM. Low-grade serous carcinoma of the ovary or peritoneum. *Ann Oncol*. 2016;27(Suppl 1):i45–i49.
- Grisham RN, Slomovitz BM, Andrews N, et al. Low-grade serous ovarian cancer: expert consensus report on the state of the science. *Int J Gynecol Cancer*. 2023;33:1331–1344.
- Manning-Geist BL, Liu YL, Devereaux KA, et al. Microsatellite Instability-High Endometrial Cancers with MLH1 Promoter Hypermethylation Have Distinct Molecular and Clinical Profiles. *Clin Cancer Res*. 2022;28:4302–4311.
- Monk BJ, Grisham RN, Banerjee S, et al. MLO/ENGOT-ov11: Binimetinib Versus Physician's Choice Chemotherapy in Recurrent or Persistent Low-Grade Serous Carcinomas of the Ovary, Fallopian Tube, or Primary Peritoneum. *J Clin Oncol*. 2020;38:3753–3762.
- Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. *Lancet*. 2022;399:541–553.
- Grisham RN, Manning-Geist BL, Chui MH. The highs and lows of serous ovarian cancer. *Cancer*. 2023;129:2613–2620.
- Welsh SJ, Corrie PG. Management of BRAF and MEK inhibitor toxicities in patients with metastatic melanoma. *Ther Adv Med Oncol*. 2015;7:122–136.
- Gonzalez-Del Pino GL, Li K, Park E, et al. Allosteric MEK inhibitors act on BRAF/MEK complexes to block MEK activation. *Proc Natl Acad Sci U S A*. 2021;118:e2107207118.
- Jones SF, Siu LL, Bendell JC, et al. A phase I study of VS-6063, a second-generation focal adhesion kinase inhibitor, in patients with advanced solid tumors. *Invest New Drugs*. 2015;33:1100–1107.
- Banerjee SN, Ring KL, Van Nieuwenhuysen E, et al. Initial efficacy and safety results from ENGOT-ov60/GOG-3052/RAMP 201: A phase 2 study of avutemetinib (VS-6766) ± defactinib in recurrent low-grade serous ovarian cancer (LGSOC). *J C O*. 2023;41:5515.
- Banerjee S, Grochot R, Shinde R, et al. 725MO Phase I study of the combination of the dual RAF/MEK inhibitor VS-6766 and the FAK inhibitor defactinib: Results of efficacy in low grade serous ovarian cancer. *Ann Oncol*. 2021;32.

12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228–247.
13. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst*. 1993;85:365–376.
14. Greimel E, Bottomley A, Cull A, et al. An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ-OV28) in assessing the quality of life of patients with ovarian cancer. *Eur J Cancer*. 2003;39:1402–1408.
15. Feng YS, Kohlmann T, Janssen MF, et al. Psychometric properties of the EQ-5D-5L: a systematic review of the literature. *Qual Life Res*. 2021;30:647–673.
16. Farley J, Brady WE, Vathipadiekal V, et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. *Lancet Oncol*. 2013;14:134–140.