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THE POWER OF SHARED PURPOSE: Transforming Gynecologic Cancer Care

A Phase 3, Randomized Trial Evaluating Avutometinib Plus Defactinib Compared With Investigator's Choice of Therapy (ICT) in Patients With Recurrent Low-Grade Serous Ovarian Cancer (LGSOC): GOG-3097/ENGOT-ov81/NCRI/RAMP 301

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POSTER 2120

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BACKGROUND

Unmet Need in Patients With LGSOC

- LGSOC is a rare, histopathologically, molecularly, and clinically distinct cancer requiring long-term, well-tolerated continued treatment and broadly driven by the RAS/MAPK pathway[1,2]
- It is poorly sensitive to chemotherapy[3] and affects younger women (median, 43 to 47 years of age), many of whom endure years of ineffective treatments and poor quality of life[2]
- Current LGSOC treatment options are limited in efficacy and tolerability—there are no approved therapies specifically indicated for LGSOC[4]

Mechanism of Action (Figure 1)

- **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 (ARAF, BRAF, and CRAF)[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]

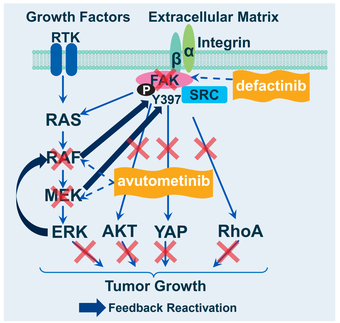

Figure 1. Avutometinib + Defactinib Mechanism of Action.

STUDY RATIONALE

- 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; **Figure 2A**)[12-14]
  - Results of the FRAME study led to US FDA Breakthrough Therapy Designation and rationale for the phase 2 registrational ENGOT-ov60/GOG-3052/RAMP 201 (NCT04625270) study[15-17]
- In Part A of RAMP 201, a confirmed ORR of 45% (n/N=13/29; 95% CI, 26-46) was observed along with tumor reduction in 86% of patients treated with avutometinib + defactinib (**Figure 2B**)[15,16,18]
  - The combination of avutometinib + defactinib demonstrated exceptionally high responses in heavily pretreated recurrent LGSOC, regardless of *KRAS* status, number of prior lines of therapy, or best response to last treatment in the recurrent/metastatic setting
  - The safety profile was consistent with previously reported safety results for avutometinib ± defactinib; the majority of AEs experienced were grade 1-2, and a limited number of patients experienced dose reductions (17%); 12% of patients discontinued avutometinib or defactinib due to ≥ 1 treatment emergent adverse event
- **The confirmatory phase 3 GOG-3097/ENGOT-ov81/NCRI/RAMP 301 (RAMP 301) study is further assessing the safety and efficacy of avutometinib in combination with defactinib versus ICT in patients with recurrent LGSOC who have at least progressed on a prior platinum-based therapy**

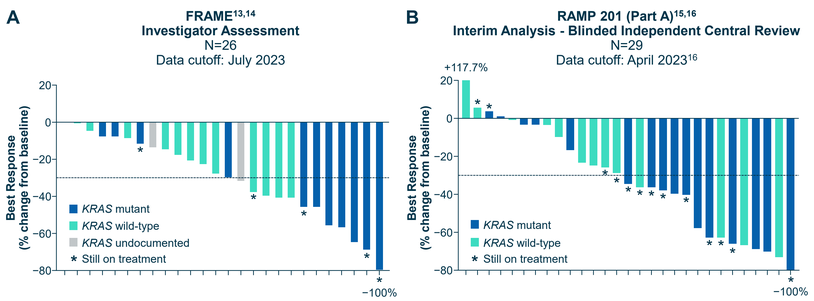

Figure 2. Percent Change in Baseline Tumor Assessment in the (**A**) FRAME and (**B**) RAMP 201 (Part A) Studies.

STUDY DESIGN

Study Objective and Endpoints

- RAMP 301 (NCT06072781) is a phase 3, randomized, international, open-label study designed to compare avutometinib plus defactinib versus ICT in patients with recurrent LGSOC who have at least progressed on a prior platinum-based therapy[19] (**Figure 3**)
- The primary endpoint of the study is PFS according to RECIST v1.1, per BICR
- Secondary endpoints of the study include
  - OS
  - PFS per RECIST v1.1 per investigator assessment
  - ORR
  - DOR
  - Disease control rate (defined as CR/PR or SD at ≥24 weeks)
  - Safety and tolerability
  - Pharmacokinetics
  - PROs/quality of life: EORTC QLQ-C30 and EORTC QLQ-OV28 questionnaires

RAMP 301 Study Design

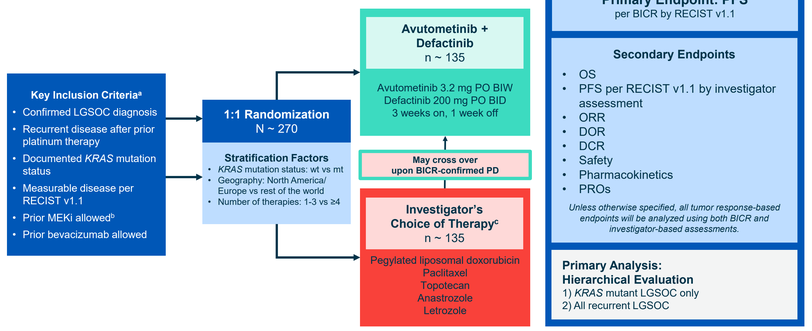

Figure 3. RAMP 301 Study Design. [a]Key inclusion and exclusion criteria are listed below in Table 1. [b]One prior line of treatment with a MEK and/or RAF inhibitor is permitted only if there was prior clinical benefit (objective response or SD ≥6 months) and not received within 6 months of signing informed consent. [c]Pegylated liposomal doxorubicin: 40 mg/m^2 IV on Day 1 of each 28-day (4-week) cycle; paclitaxel: 80 mg/m^2 IV on Days 1, 8, and 15 of each 28-day (4-week) cycle; topotecan: 4 mg/m^2 IV on Days 1, 8, and 15 of each 28-day (4 week) cycle; anastrozole: 1 mg PO once daily of each 28-day (4-week) cycle; letrozole: 2.5 mg PO once daily of each 28-day (4-week) cycle.

Key Inclusion Criteria	Key Exclusion Criteria
• Age ≥18 years • Histologically proven LGSOC (ovarian, fallopian, peritoneal) • Documented mutational status of *KRAS* by an approved diagnostic test (eg, CDx, CE marked) from tumor tissue • Suitable for at least one of the ICTs (PLD, paclitaxel, topotecan, letrozole, anastrozole) • Adequate recovery from toxicities related to prior treatment • Recurrent LGSOC (*KRAS*-mutant and wild-type) • Prior treatment with ≥1 platinum-based regimen • ≥1 measurable lesion per RECIST v1.1 • ECOG PS ≤1 • Adequate organ function • Agreement to use highly effective measures of contraception (for patients with reproductive potential)	• Co-existing, high-grade ovarian cancer or another histology – LGSOC in conjunction with serous borderline tumor is permitted • Prior treatment with avutometinib, defactinib, or other FAK inhibitors is not allowed – 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 • Suitable for debulking surgery according to their physician • Systemic anticancer therapy within 4 weeks of the first dose of study intervention • Major surgery within 4 weeks • Symptomatic brain metastases or spinal cord compression • Active skin disorder that has required systemic therapy within 1 year of signing informed consent • History of medically significant rhabdomyolysis • Symptomatic bowel obstruction within 3 months • Concurrent ocular disorders • Concurrent heart disease or severe obstructive pulmonary disease

Table 1. Key Inclusion and Exclusion Criteria. A full listing can be found on ClinicalTrials.gov at https://classic.clinicaltrials.gov/ct2/show/NCT06072781.

Patient Assessments

- **Diagnostic Assessments**
  - Local *KRAS* mutational status available from an approved diagnostic (eg, CDx, CE marked)
  - LGSOC diagnosis
  - Archival tumor tissue (<5 years old) or fresh biopsy tissue must be available and received by central labs for central confirmation of *KRAS* mutational status and LGSOC diagnosis
- **Efficacy Assessments**
  - Post-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
- **Safety Assessments**
  - Safety assessments are ongoing after informed consent which may include AEs/SAEs, lab tests, physical examinations, and ECHOs
- **Patient-Reported Outcomes**
  - EORTC QLQ-C30 and EORTC QLQ-OV28, provided in local language, will be administered after randomization up to C1D1 before any visit-related assessments, at C3D1, C5D1, then every 4 cycles (C9D1, C13D1, etc)

TRIAL STATUS

- Enrollment of ~ 270 patients is ongoing
- This international study is in collaboration with the GOG Foundation and ENGOT and the following ovarian cancer research organizations

GOG FOUNDATION + ENGOT (European Network of Gynaecological Oncological Trial groups)

United States	GOG FOUNDATION	France	ARCAGY GINECO	Denmark	NSGO
UK	NCRI	Italy	MaNGO, Mito	South Korea	Korean Gynecologic Oncology Group
Spain	GEICO	Canada	GOG FOUNDATION	Australia	ANZGOG
Belgium	BGOG	Germany	AGO Arbeitsgemeinschaft Gynäkologische Onkologie e.V.		

AGO, Arbeitsgemeinschaft Gynäkologische Onkologie; ANZGOG, Australia New Zealand Gynaecological Oncology Group; BGOG, Belgium and Luxembourg Gynaecological Oncology Group; ENGOT, European Network for Gynaecological Oncological Trial groups; GEICO, Grupo Español de Investigación en Cáncer de Ovario; GINECO, Groupe d'Investigateurs National des Etudes des Cancers Ovariens et du sein; GOG, Gynecologic Oncology Group; KGOG, Korean Gynecologic Oncology Group; MaNGO, Mario Negri Gynecologic Oncology; MITO, Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies; NCRI, National Cancer Research Institute; NSGO, Nordic Society of Gynaecological Oncology.

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ABBREVIATIONS

AEs, adverse events; **AKT**, protein kinase B; **BICR**, blinded independent central review; **BID**, twice daily; **BIW**, twice a week; **CDx**, companion diagnostic; **CE**, Conformité Européenne; **CR**, complete response; **DCR**, disease control rate; **DOR**, duration of response; **ECHOs**, echocardiograms; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **EORTC**, European Organisation for Research and Treatment of Cancer; **ERK**, extracellular signal-regulated kinase; **FAK**, focal adhesion kinase; **FDA**, Food and Drug Administration; **IV**, intravenous; **MAPK**, mitogen-activated protein kinase; **mDOR**, median duration of response; **mPFS**, median progression-free survival; **MEK**, MAPK kinase; **MEKi**, MEK inhibitor; **mt**, mutant; **ORR**, objective response rate; **OS**, overall survival; **P**, phosphate; **PD**, progressive disease; **PFS**, progression-free survival; **PLD**, pegylated liposomal doxorubicin; **PO**, oral administration; **QLQ**, Quality of Life Group Questionnaire; **PR**, partial response; **RAF**, rapidly accelerated fibrosarcoma; **RAS**, rat sarcoma virus; **RECIST**, response evaluation criteria in solid tumors; **RhoA**, Ras homolog family member A; **RTK**, receptor tyrosine kinase; **SD**, stable disease; **wt**, wild type; **YAP**, yes-associated protein.

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