Clinical Trial Protocol

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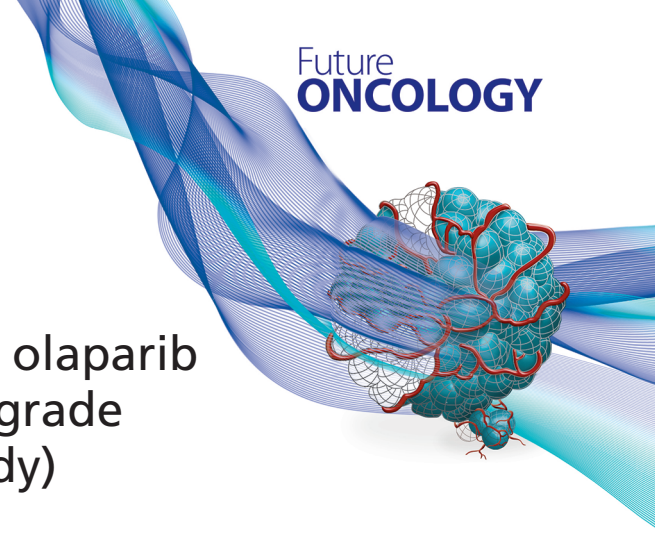

EPIK-O/ENGOT-OV61: alpelisib plus olaparib vs cytotoxic chemotherapy in high-grade serous ovarian cancer (phase III study)

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Patients with platinum-resistant or -refractory high-grade serous ovarian cancer (HGSOC) have a poor prognosis, and their management represents a substantial unmet medical need. Preclinical data and results from a phase Ib trial demonstrated the efficacy and tolerability of the combination of the α-specific phosphatidylinositol-3-kinase (PI3K) inhibitor alpelisib plus the poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib in platinum-resistant, non-*BRCA*-mutated ovarian cancer. Here, we describe the study design and rationale for the phase III, multicenter, open-label, randomized, active-controlled EPIK-O/ENGOT-OV61 trial investigating alpelisib in combination with olaparib compared with standard-of-care chemotherapy in patients with platinum-resistant or -refractory HGSOC with no germline *BRCA* mutation. Progression-free survival (blinded independent review committee) is the primary end point. Overall survival is a key secondary end point.

Clinical Trial Registration: NCT04729387 (ClinicalTrials.gov)

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Background & rationale

Epithelial ovarian cancer (OC) is the second most common cause of death from gynecologic cancers worldwide [1]. In 2020, approximately 314,000 women were diagnosed with OC worldwide, with most patients presenting with advanced disease [1–3]. High-grade serous OCs (HGSOCs) account for approximately 75% of all epithelial OCs and are responsible for up to 80% of deaths from epithelial OC [4–6]. Current standard first-line treatment for advanced HGSOC includes debulking surgery and taxane- and platinum-based chemotherapy. Bevacizumab may be added to chemotherapy and given as maintenance therapy, and poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor maintenance therapy can be given based on patients' clinical and tumor genomic characteristics [7–13]. While many women respond well to initial treatment, the majority experience relapse within 3 years of primary treatment [14,15].

Homologous recombination repair (HRR) repairs DNA double-strand breaks (DSBs) to minimize DNA alterations resulting from direct DNA damage and inaccurate repair systems [16]. Up to 50% of HGSOCs are considered deficient in HRR due to the prevalence of *BRCA1* or *BRCA2* mutations (germline, ≈14%-22%; somatic, ≈6%); *BRCA1* promoter hypermethylation (≈10–20%); and genetic and epigenetic alterations of alternative, non-*BRCA1/2* and HRR pathway genes (e.g., *RAD51C* and *RAD51D*) [4,17]. Targeting this deficiency has become a treatment strategy in HGSOC, as it confers sensitivity to DNA-damaging agents such as platinum salts and PARP inhibitors. PARP inhibitors exhibit synthetic lethality when added to HRR-deficient cells, such as those with *BRCA1/2* mutations, via two main mechanisms. First, PARP inhibition in the base excision repair pathway prevents the repair of DNA single-strand breaks, thereby converting them into the more cytotoxic DSBs, which are usually repaired via the HRR pathway in HRR-proficient cells but remain unrepaired and cause cytotoxicity in HRR-deficient cells [4,18]. Second, PARP inhibitors trap the PARP1 and PARP2 enzymes at the sites of endogenous damage, leading to inhibition of DNA replication and the formation of trapped PARP-DNA complexes, which are highly toxic to HRR-deficient cells [4,18,19]. This concept has led to the approval of multiple PARP inhibitors for the treatment of HGSOC in the last decade [20].

Olaparib

Olaparib is a PARP inhibitor, approved by the US FDA for treatment of OC in multiple settings [21]. In the first-line setting based on the phase III SOLO-1 study, olaparib was approved by the FDA as a maintenance treatment option for patients with newly diagnosed advanced OC and a germline or somatic *BRCA* mutation following a complete or partial response to platinum-based chemotherapy. The results of SOLO-1 reported a progression-free survival (PFS) benefit of 42.2 months for olaparib compared with placebo (median, 56.0 vs 13.8 months, respectively; hazard ratio, 0.33; 95% CI, 0.25–0.43) after 5 years of follow-up [11,21,22]. The PAOLA-1 study tested the addition of olaparib maintenance therapy to bevacizumab in patients with advanced OC, regardless of their *BRCA* mutation status, and demonstrated a significant PFS benefit of 5.5 months with olaparib plus bevacizumab compared with bevacizumab alone (median, 22.1 vs 16.6 months, respectively; hazard ratio, 0.59; 95% CI, 0.49–0.72; $p < 0.001$) [23]. The greatest benefit of olaparib + bevacizumab is in patients whose cancers are BRCA mutated or homologous recombination deficiency (HRD) positive/BRCA-wt which is reflected in the FDA approval of this combination [21]. Additional phase III trials of olaparib, niraparib and rucaparib have demonstrated significant benefits with these PARP inhibitors in multiple settings of advanced OC, and these results have led to the incorporation of PARP inhibitors into the management of patients with OC [13,24–26].

Despite initial response to treatment, approximately >75% of patients with advanced HGSOC will develop relapsed cancer that is incurable [7]. The platinum-free interval (PFI) generally guides subsequent treatment. Recognizing that response rates to platinum therapy fall on a continuum, the Fifth Ovarian Cancer Consensus Conference of the Gynecologic Cancer InterGroup categorized platinum sensitivity into four subsets based on the duration of the PFI: <1 month, 1–6 months, 6–12 months and >12 months, corresponding to the widely used definitions of platinum refractory, resistant, partially sensitive and fully sensitive, respectively [27]. While acknowledging the subjectivity and heterogeneity of these categories, these definitions continue to be incorporated in the management of patients and the design of clinical studies in OC [28]. Eventually, nearly all patients with OC will develop platinum-resistant cancer as the duration of response shortens with each subsequent administration of a platinum agent [29,30].

Although there is significant heterogeneity, patients with platinum-resistant HGSOC have a poor prognosis, with a median overall survival (OS) of approximately 12–15 months [31]. Non-platinum cytotoxic chemotherapy (with or without the antiangiogenic drug bevacizumab) remains the standard-of-care treatment in this setting [32]. The AURELIA study in patients with platinum-resistant recurrent OC demonstrated a median PFS of 6.7 months with chemotherapy (paclitaxel, PLD or topotecan) + bevacizumab versus 3.4 months with chemotherapy alone (hazard ratio, 0.48; 95% CI, 0.38–0.60; $p < 0.001$) [8]. Thus far, immune checkpoint inhibitors have not impacted standard of care in this patient population.

PARP inhibitors are a treatment option in platinum-resistant OC, but only for patients with *BRCA*-mutated (BRCA-mut) tumors [33]. For patients with BRCA-wt tumors and platinum-resistant disease, PARP inhibitors exhibit very low activity as monotherapy [34]. For example, the ORR in platinum-resistant, BRCA-wt tumors was only 4% based on a phase II study of olaparib monotherapy [34,35]. In the QUADRA study, the overall response to the PARP inhibitor niraparib in platinum-resistant, BRCA-wt tumors was only 3%, regardless of whether tumors

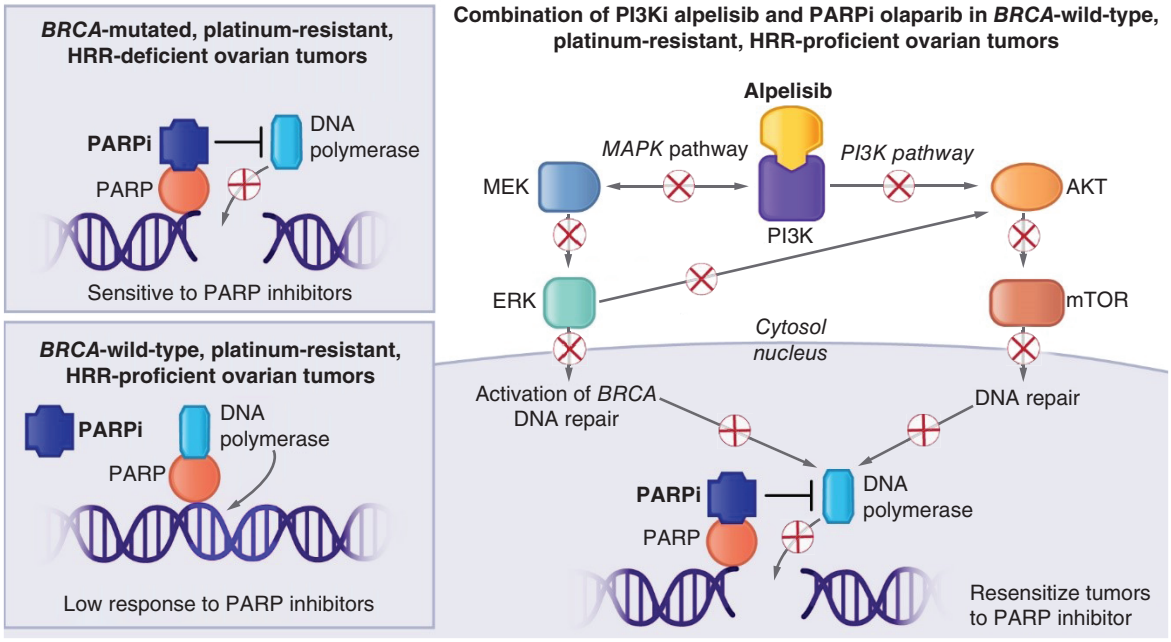

Figure 1. Mechanistic rationale for combined PI3K and PARP inhibition.
HRR: Homologous recombination repair; PARP: Poly(adenosinediphosphateribose) polymerase; PI3K: α-specific phosphatidylinositol-3-kinase.

were HRD-positive or -negative using the Myriad myChoice HRD test [36]. In this regard, this population of patients with BRCA-wt, platinum-resistant HGSOC presents a significant unmet need.

Alpelisib

Alpelisib (BYL719) is an orally bioavailable, α-specific phosphatidylinositol-3-kinase (PI3K) inhibitor that selectively inhibits p110α with 50-fold greater potency than other PI3K isoforms (β, δ, γ) [37,38]. Alpelisib inhibits both mutated and wt PI3K. In preclinical studies, alpelisib exhibited a dual mechanism of action by inhibiting p-Akt and degrading p110α protein levels in a dose-dependent manner [39]. Alpelisib, in combination with fulvestrant, has demonstrated a significant improvement in PFS and a tolerable safety profile in men and postmenopausal women with *PIK3CA*-mutated, hormone-receptor positive, HER2-negative advanced breast cancer following progression during or after endocrine therapy and is approved in multiple countries [37]. When PI3K inhibitors were used as a single agent in solid tumors (including OC), limited responses were observed; however, early-phase combination trials have demonstrated that combination therapies are more effective than monotherapies [40,41].

Preclinical & clinical data supporting synergism between olaparib & alpelisib

The PI3K pathway is a central oncogenic pathway that regulates cellular proliferation, metabolism, growth, survival and apoptosis [42]. Elevated PI3K signaling is a hallmark of cancer, and PI3K activity is stimulated by various oncogenes and growth factor receptors [43]. PI3K inhibition can lead to downregulation of *BRCA1* or *BRCA2* and abrogation of HRR, and potential sensitization to PARP inhibitors [44,45]. Preclinical studies in triple-negative breast cancer cell lines (MDA-MB-468) showed that inhibition of PI3K led to DNA damage, downregulation of *BRCA*1/2 and an increase in PARP activity (based on increased poly[ADP-ribose] levels), indicating that cells undergoing PI3K suppression become more dependent on this DNA repair mechanism and therefore susceptible to PARP inhibition [44]. Mechanistically, downregulation of *BRCA*1/2 is mediated by extracellular signal-regulated kinase-dependent activation of the ETS1 transcription factor, which suppresses *BRCA* gene transcription, thereby causing a deficiency in HRR and concomitant PARP inhibitor sensitivity [44,45]. Therefore, the addition of a PI3K inhibitor, like alpelisib, may sensitize HRR-proficient HGSOC to PARP inhibitor therapy (Figure 1) [4].

Besides abrogation of HRR and sensitization to PARP inhibitor therapy, another proposed mechanism of synergism between PI3K inhibitors and PARP inhibitors is relevant to the metabolic effects of PI3K inhibition. Specifically, PI3K inhibitors, including alpelisib, have been shown to cause a significant decrease in glycolysis (at the

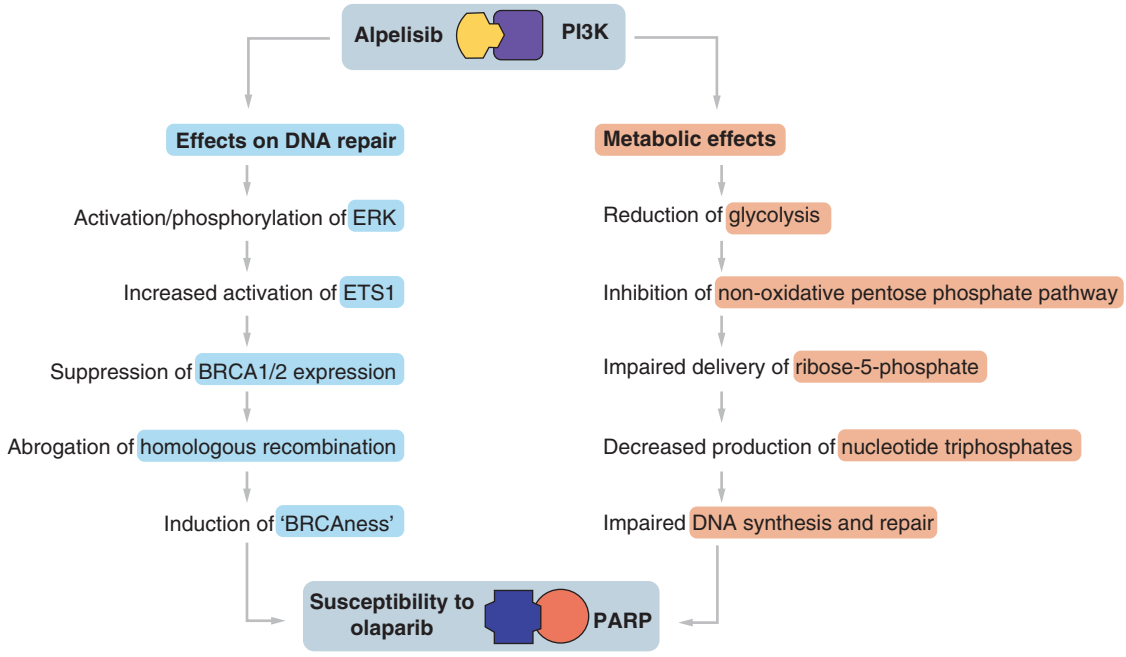

Figure 2. Mechanistic rationale between combined PI3K and PARP inhibition.
PARP: Poly(adenosine diphosphateribose) polymerase; PI3K:α-specific phosphatidylinositol-3-kinase.

step catalyzed by aldolase A), leading to a drop in glyceraldehyde 3-phosphate (Ga3P) [46]. Ga3P is a very important product that, under conditions of enhanced glycolysis, enters the nonoxidative pentose-phosphate pathway and is used to generate the ribose 5-phosphate required for base ribosylation and, finally, the synthesis of DNA and RNA. In other words, PI3K blockade leads to inhibition of glycolysis, inhibition of the non-oxidative pentose phosphate pathway, impaired delivery of ribose 5-phosphate, low base ribosylation and a significant drop in the production of nucleotide triphosphates required for DNA synthesis. This can result in DNA damage and increased dependence on DNA repair mechanisms, which can in turn potentially increase vulnerability to PARP inhibition [46]. This is important because studies have also shown that increasing glycolysis reduces sensitivity to olaparib; similarly, blocking of glycolysis resensitizes tumors to PARP inhibitor therapy [47]. Therefore, the ability of PI3K inhibitors to inhibit glycolysis may clinically enhance PARP inhibitor sensitivity (Figure 2).

In vivo synergism with PARP and PI3K inhibition in OC was demonstrated in luciferized patient-derived xenograft (PDX) models, which were generated from tumor cells isolated from the ascites or pleural fluid of patients undergoing clinical procedures and characterized at molecular and clinical levels [48,49]. In preclinical studies, the combination of alpelisib/olaparib demonstrated efficacy and tolerability in PDX models of OC [49]. Efficacy studies showed that this combination induced inhibition of tumor growth in multiple ovarian PDX models, including (1) *BRCA1/2*-wt, PARP inhibitor- and platinum-resistant and HRR-proficient; (2) *BRCA1/2*-wt, PARP inhibitor- and platinum-sensitive and HRR-deficient; and (3) *BRCA1* mut, PARP inhibitor- and platinum-resistant with acquired HRR proficiency. Furthermore, as a proof of mechanism, alpelisib inhibited HRR in HRR-proficient models, as evidenced by a decrease in RAD51 foci-positive cells after treatment with alpelisib/olaparib compared with treatment with olaparib alone [4,49]. Target engagement studies showed downregulation of phosphorylated AKT, a downstream effector target of PI3K, following treatment with alpelisib/olaparib in HGSOC tumor cells [49].

The alpelisib/olaparib combination was clinically evaluated in a multicenter, open-label, dose-escalation and dose-expansion phase Ib trial. This study evaluated olaparib (100–200 mg orally twice daily) in combination with alpelisib (200–300 mg orally once daily) in a cohort of 34 patients with recurrent HGSOC of any histology but with a known germline *BRCA* mutation status, or recurrent triple-negative breast cancer of any histology with a known germline *BRCA* mutation status [49]. The dose-escalation phase enrolled 28 patients, and six patients with OC were enrolled in an expansion cohort; 30 had OC (two did not receive study treatment due to ineligibility) and four had breast cancer. Of the 28 patients with OC included in the analysis, 36% had a partial response, 50% had stable disease, 11% had progressive disease and 4% were not evaluable. Of the 14 patients with stable disease,

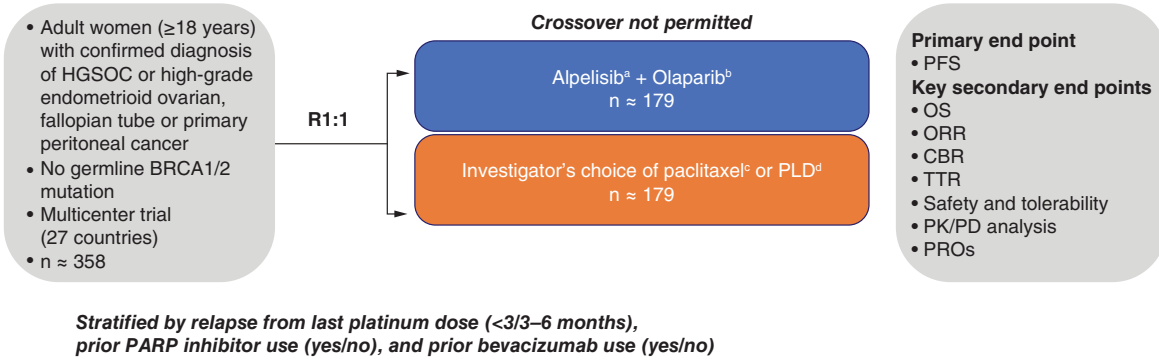

Figure 3. EPIK-O/ENGOT-OV61 study design and schedule.
[a]200 mg orally once daily starting cycle 1, day 1 in a 28-day cycle.
[b]200 mg orally twice daily starting cycle 1, day 1 in a 28-day cycle.
[c]80 mg/m^2 intravenously weekly in a 28-day treatment cycle starting on cycle 1, day 1.
[d]40–50 mg/m^2 intravenously every 28 days in a 28-day treatment cycle starting on cycle 1, day 1.
CBR: Clinical benefit rate; DOR: Duration of response; HGSOC: High-grade serous ovarian cancer; ORR: Overall response rate; OS: Overall survival; PARP: Poly(ADP-ribose) polymerase; PLD: Pegylated liposomal doxorubicin; PFS: Progression-free survival; PK/PD: Pharmacokinetic/pharmacodynamic; PRO: Patient-reported outcome; TTR: Time-to-response.

eight had stable disease for 6 months or more. The overall response rate (ORR) in OC was similar for populations with germline BRCA-mut (n = 9 [33%]) and germline BRCA-wt (n = 16 [31%]) platinum-resistant or -refractory disease treated with alpelisib/olaparib [49]. In the overall population in the phase Ib study, median duration of response was 5.5 months (range, 0.5–13.1 months), and median PFS was 7.2 months (95% CI, 4.9–9.0 months). Importantly, targeted next-generation sequencing revealed that objective responses to alpelisib/olaparib occurred regardless of the presence or absence of HRR and PI3K pathway alterations in the tumors. The most common treatment-related grade 3/4 adverse events (considering all dose levels) were hyperglycemia (15.6%), nausea (9.4%) and increased alanine aminotransferase concentration (9.4%), none of which were unexpected based on data from previous trials [49]. No treatment-related deaths were reported [49]. The ORR of 31% in BRCA-wt patients receiving alpelisib/olaparib is particularly notable as two separate phase II clinical trials in patients with BRCA-wt, platinum-resistant OC treated with olaparib monotherapy demonstrated an ORR of <5% and approximately 13% [34,50].

Taken together, these preclinical data and findings from the phase Ib study – as well as the continued unmet need in patients with BRCA-wt, platinum-resistant HGSOC – support further investigation of the combination of alpelisib/olaparib in patients with BRCA-wt, platinum-resistant HGSOC (irrespective of *PIK3CA* mutation status).

EPIK-O/ENGOT-OV61

The EPIK-O/ENGOT-OV61 study (NCT04729387) is investigating the efficacy and safety of alpelisib/olaparib compared with standard-of-care single-agent cytotoxic chemotherapy in patients with platinum-resistant or -refractory HGSOC with BRCA-wt.

Design

Study design

EPIK-O/ENGOT-OV61 is a pivotal phase III, multicenter, open-label, randomized study (Figure 3). Patients will be randomized 1:1 to receive alpelisib (200 mg orally once daily on a continuous schedule for 28-day cycles) plus olaparib (200 mg orally twice daily on a continuous schedule for 28-day cycles) in Arm 1 or the investigator's choice of cytotoxic chemotherapy in Arm 2. The doses for alpelisib and olaparib are based on the maximum tolerated dose identified in the phase I study [49]. There are two cytotoxic chemotherapy options: paclitaxel (80 mg/m^2 intravenously weekly during a 28-day cycle [days 1, 8, 15 and 22]) or PLD (40–50 mg/m^2 intravenously once every 28-day cycle). The choice of cytotoxic chemotherapy for each patient is specified by the investigators. No switching between chemotherapy agents is allowed in Arm 2 once the first dose of chemotherapy is administered. For Arm 1 (alpelisib/olaparib arm), prophylactic use of a non-sedating antihistamine is recommended starting on

cycle 1, day 1 for approximately 8 weeks to prevent rash associated with PI3K inhibition. Patients with ≥1 risk factor for development of severe hyperglycemia (prediabetes/diabetes and/or BMI ≥30 and/or age ≥75 years) are recommended to initiate a sodium-glucose cotransporter-2 inhibitor alone or in combination with metformin prophylactically, at the discretion of the investigator. Crossover between arms is not permitted. Randomization will be stratified by three factors: relapse from last platinum dose (<3/3–6 months), prior PARP inhibitor use (yes/no) and prior bevacizumab use (yes/no). Patients will continue to receive study treatment until disease progression, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 as assessed by blinded independent review committee (BIRC); unacceptable toxicity or discontinuation of study treatment due to any other reason.

Key eligibility criteria

Key eligibility criteria are summarized in Box 1. Briefly, women aged ≥18 years are eligible to enroll if they have received 1–3 prior systemic therapies and have a histologically confirmed diagnosis of HGSOC or high-grade endometrioid ovarian, fallopian tube or primary peritoneal cancer, germline BRCA-wt and no known somatic *BRCA* mutation, measurable disease and platinum-resistant or -refractory disease. If no measurable disease is present, the disease must be assessable by Gynecologic Cancer InterGroup criteria (GCIG) for CA-125. Patients should have received bevacizumab previously unless they are not candidates for bevacizumab due to a medical reason. Patients receiving bevacizumab are at an increased risk of bowel perforation, hypertension, bleeding and concurrent cardiovascular comorbidity or other events [8,51]. Patients with primary platinum-refractory disease (i.e., those who never responded to platinum and experienced progression during initial platinum-based chemotherapy) are not eligible for the study as they are characterized by a distinctly poorer prognosis, making it difficult to group and analyze them within the trial. Participants with non-measurable disease will be limited to 20% of the overall study population. Prior PARP inhibitor exposure is allowed. Signed informed consent is required.

Planned sample size & study period

Approximately 358 patients will be recruited in EPIK-O/ENGOT-OV61 at an estimated 135 sites in 27 countries. Assuming that enrollment will continue at a stepwise rate: (1) 8 participants per month for the first 6 months; (2) 18 participants per month from 6 months to 12 months; and (3) 28 participants per month after 12 months, as well as a 20% overall dropout rate by the time of the final PFS analysis, a total of 358 participants will need to be randomized to observe the targeted 224 PFS events. The study began enrollment in July 2021, and the estimated study completion date is early 2025.

Study procedures

Radiological tumor assessments will be performed by BIRC per RECIST 1.1. Baseline imaging assessments will be performed at screening, within 28 days prior to randomization. Computed tomography (CT) or MRI of the chest, abdomen and pelvis and CT or MRI of other metastatic sites, if suspected, are required at baseline. These same imaging assessments will be required every 8 weeks (±7 days) for the first 18 months and every 12 weeks (±7 days) thereafter until disease progression, death, withdrawal of consent or loss to follow-up. For metastatic lesions documented at baseline, the same schedule of CT or MRI will be followed. Tumor evaluation at the end-of-treatment is required for patients who discontinue study treatment before the first scheduled post-baseline tumor assessment at week 8 and for patients whose prior assessment was performed >21 days prior to the end-of-treatment visit and did not demonstrate progressive disease.

Safety will be monitored throughout the study using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Physical examination, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, body weight, electrocardiogram, cardiac function evaluation, laboratory testing and pregnancy testing will be assessed during the study.

The Functional Assessment of Cancer Therapy–Ovarian, EQ-5D-5L and Brief Pain Inventory-Short Form questionnaires will be administered electronically at screening; every 8 weeks after randomization during the first 18 months and every 12 weeks thereafter only if end-of-treatment occurs for reasons other than death, withdrawal of consent, loss to follow-up or disease progression; at the end-of-treatment; 30 days after the last dose (safety follow-up); and 8 weeks after progression. All patient-reported outcome measure questionnaires will be administered prior to study drug administration during visits.

In approximately 30 patients in the alpelisib/olaparib combination arm, post-dose pharmacokinetic blood samples will be collected at steady state over the course of a 24-h period on cycle 1, day 8 to compare exposure

Box 1. General inclusion and exclusion criteria (EPIK-O/ENGOT-OV61 trial) .

Inclusion criteria

- Women ≥18 years old
- Histologically confirmed diagnosis of high-grade serous or high-grade endometrioid ovarian cancer, fallopian tube cancer or primary peritoneal cancer
- No germline *BRCA1/2* mutation
- Either ≥1 measurable lesion per RECIST 1.1 criteria or, if no measurable lesion is present, disease assessable by GCIG for CA-125
- ECOG performance status of 0 or 1
- Platinum therapy-resistant or -refractory disease[†,‡]
- 1–3 prior systemic therapies
- Prior PARP exposure allowed
- Prior use of bevacizumab required unless ineligible for bevacizumab (due to medical reasons, per investigator's discretion)
- Adequate bone marrow and organ function as defined by laboratory values
- Documented informed consent

Key exclusion criteria

- Prior treatment with any PI3K, mTOR or AKT inhibitor
- Known hypersensitivity to any of the study drugs
- Concurrently using other anticancer therapy
- Surgery ≤14 days prior to starting study treatment or not recovered from major side effects
- Not recovered from all toxicities related to prior anticancer therapies to baseline or NCI CTCAE version 4.03 grade ≤1[§]
- Prior exposure to murine antibodies or had therapeutic paracentesis or pleurocentesis ≤28 days prior to starting study drug[¶]
- Known somatic *BRCA* mutation[#]
- Liver impairment and Child–Pugh score B or C
- In a state of small- or large-bowel obstruction or has other impairment of GI function or GI disease
- Received radiotherapy ≤4 weeks or limited-field radiation for palliation ≤2 weeks prior to randomization
- Concurrent malignancy or malignancy within 3 years of starting study treatment[††]
- CNS involvement
- Established diagnosis of uncontrolled diabetes mellitus type 1 or 2
- Known history of acute pancreatitis ≤1 year of screening or past medical history of chronic pancreatitis
- Currently documented pneumonitis/interstitial lung disease
- Clinically significant uncontrolled heart disease and/or hypertension
- Women of childbearing potential
- Currently receiving or has received systemic corticosteroids ≤2 weeks prior to starting study drug

[†]Platinum-resistant disease is defined as progression 1–6 months after completion of platinum-based therapy. Platinum-refractory disease is defined as progression during treatment or within 4 weeks of the last dose.
[‡]Patients with primary platinum-refractory disease (never responded to platinum and progressed during initial platinum-based chemotherapy) are not eligible.
[§]Patients with any grade of alopecia are allowed to enter the study.
[¶]Only applicable to patients with non-measurable disease by RECIST 1.1.
[#]Testing for somatic *BRCA* mutation is not a requirement for eligibility.
[††]Adequately treated basal- or squamous-cell carcinoma, non-melanomatous skin cancer or curatively resected cervical cancer are allowed.
CNS: Central nervous system; CTCAE: Common Terminology Criteria for Adverse Events; ECOG: Eastern Cooperative Oncology Group; GCIG: Gynecological Cancer InterGroup criteria; GI: Gastrointestinal; NCI: National Cancer Institute; RECIST: Response Evaluation Criteria in Solid Tumors.

with historical data. Plasma samples will be taken pre-dose and at 1, 2, 3, 4, 6, 8 and 24 h post-dose of alpelisib. Exploratory biomarker analyses may include investigations of aberrations in the PI3K pathway, HRR status and other DNA damage/repair pathways, among others.

Germline *BRCA* mutation status will be assessed during molecular screening with the FDA-approved Myriad BRACAnalysis CDx test peformed through either a local laboratory or a designated central laboratory.

Outcome measures/end points

The study end points are summarized in Table 1. The primary end point is PFS, defined as the time from randomization to the date of first documented progression or death due to any cause. If a patient has not had an

Table 1. Summary of EPIK-O end points.

End point	Measures
Primary	• PFS[†]
Key secondary	• OS
Other secondary	• Incidence, type and severity of adverse events per CTCAE version 4.03 • Dose interruptions, dose reductions, dose intensity and duration of exposure for study treatments • Time to definitive deterioration of ECOG performance status from baseline • ORR, CBR, DOR and time to response[†] • PK profile of alpelisib and olaparib (including but not limited to AUC_{tau}, AUC_{last}, C_{max} and T_{max}) • Change from baseline in FACT-O trial outcome index
Exploratory	• PFS2 • PK/PD analysis • Molecular analysis of liquid biopsy and tumor tissue (somatic *BRCA*, HRR deficient status, ctDNA) • Change from baseline in PROs (EQ-5D-5L, worst pain item in BPI-SF)

[†]Based on BIRC assessment per RECIST 1.1.

AUC: Area under the curve; BIRC: Blinded Independent review committee; BPI-SF: Brief Pain Inventory-Short Form; CBR: Clinical benefit rate; C_{max}: Maximum plasma concentration; CTCAE: Common Terminology Criteria for Adverse Events; ctDNA: Circulating tumor DNA; DOR: Duration of response; ECOG: Eastern Cooperative Oncology Group; FACT-O: Function Assessment of Cancer Therapy-Ovarian; HRR: Homologous recombination repair; ORR: Overall response rate; OS: Overall survival; PD: Pharmacodynamic; PFS: Progression-free survival; PFS2: Progression after the next line of antineoplastic therapy; PK: Pharmacokinetic; PRO: Patient-reported outcome; RECIST: Response Evaluation Criteria in Solid Tumors; T_{max}: Time to reach peak plasma concentration.

event at the time of analysis, PFS will be censored at the date of last adequate tumor assessment (RECIST 1.1). PFS will be based on BIRC assessment according to RECIST 1.1. Due to the pelvic location of the primary tumor and the frequent occurrence of peritoneal disease, imaging may not always be reliable for documentation of disease progression. Thus, as a supplemental analysis, PFS will also be assessed based on clinical disease progression as assessed by BIRC using the GCIG criteria for CA-125 progression.

The key secondary end point is OS, which is defined as the time from randomization to the date of death due to any cause. Patients without an OS event will be censored at the latest date they were known to be alive. Other secondary end points include ORR, clinical benefit rate, time-to-response, duration of response, time-to-definitive deterioration in quality of life, time-to-definitive deterioration in ECOG performance status, pharmacokinetics and safety. Exploratory end points include progression after the next line of antineoplastic therapy (PFS2), pharmacodynamic data and biomarker analyses.

Statistics

Primary and secondary efficacy analyses will be performed in the intent-to-treat population, comprising all randomized patients. Safety will be assessed in the population of all patients who received treatment, defined as all randomized patients who received at least one dose of the study treatment. The primary efficacy analysis of PFS comparing alpelisib/olaparib with standard-of-care single-agent cytotoxic chemotherapy will be evaluated with a stratified log-rank test. PFS will be estimated using the Kaplan–Meier method. A stratified Cox regression model will be used to estimate the hazard ratio and its 95% CI.

An interim futility analysis is planned after approximately 90 of the 224 targeted PFS events (≈40%) have been documented and before the final PFS analysis. A hierarchical testing procedure will be adopted for OS analyses, and the statistical tests for OS will be performed only if the primary efficacy end point of PFS is statistically significant. All participants will continue survival follow-up until the final OS analysis.

Conclusion

Preclinical experiments and a phase Ib trial demonstrated promising antitumor activity and tolerability with the combination of alpelisib/olaparib in patients with platinum-resistant BRCA-wt OC. Inhibition of the PI3K pathway by alpelisib may induce a state of HRD in HRR-proficient HGSOC and thereby sensitize platinum-resistant cancers to olaparib, which blocks the base excision DNA repair pathway, thereby causing cytotoxicity in HRR-deficient cells. In preclinical studies, alpelisib has been shown to augment the effect of olaparib in HRR-proficient tumors. The phase III EPIK-O/ENGOT-OV61 trial will investigate the efficacy and safety of alpelisib plus olaparib compared with standard-of-care single-agent cytotoxic chemotherapy in patients with no germline *BRCA* mutation detected and platinum-resistant or -refractory HGSOC. Patients with platinum-resistant HGSOC have a poor prognosis, especially BRCA-wt patients, due to limited medical treatment options (e.g., lack of efficacy of PARP inhibitors). Despite enormous effort over the last 20 years, there has been no appreciable increase in PFS

or OS. This study's results will help to determine whether the combination of a PI3K and PARP inhibitor is an active and tolerable treatment option for these patients, thus fulfilling an unmet medical need.

Executive summary

Study rationale

- Patients with platinum-resistant high-grade serous epithelial ovarian cancer (HGSOC) and with no germline *BRCA* mutation (BRCA-wt) have a poor survival outcome.
- The current standard-of-care for patients with BRCA-wt and platinum-resistant HGSOC is cytotoxic chemotherapy.
- Tumors in platinum-resistant, BRCA-wt, epithelial ovarian cancer are not responsive to single-agent poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors.

Background & rationale

- Preclinical studies of the combination of alpelisib/olaparib have shown efficacy and tolerability in ovarian cancer models.
- Phosphatidylinositol-3-kinase (PI3K) inhibition by alpelisib renders BRCA-wt platinum-resistant ovarian cancer cells deficient in homologous recombination repair (HRR).
- PARP inhibition by olaparib blocks the base excision repair pathway, which causes cytotoxicity in HRR-deficient cells.
- In preclinical studies, PI3K inhibition by alpelisib augmented the PARP inhibitor effect of olaparib.
- Findings from the phase Ib trial evaluating alpelisib/olaparib support further investigation of the use of this combination in patients with platinum-resistant or -refractory HGSOC with BRCA-wt.

EPIK-O/ENGOT-OV61 study design & eligibility criteria

- EPIK-O/ENGOT-OV61 is a phase III, multicenter, randomized, open-label, active-controlled study to assess the efficacy and safety of alpelisib in combination with olaparib compared with single-agent cytotoxic chemotherapy in patients with platinum-resistant or -refractory HGSOC with no detected germline *BRCA* mutation.

Objectives

- The primary objective is to evaluate progression-free survival in patients receiving alpelisib in combination with olaparib compared with standard-of-care cytotoxic chemotherapy (paclitaxel or pegylated liposomal doxorubicin).
- The key secondary objective is overall survival between the two treatment arms.

Conclusions

- Platinum-resistant epithelial ovarian cancer represents a disease area with significant unmet medical needs, with a median overall survival of 12–15 months.
- In patients with platinum-resistant or -refractory BRCAwt HGSOC, the combination of alpelisib/olaparib may offer improved efficacy compared with single-agent cytotoxic chemotherapy.

Author contributions

All authors made substantial contributions to the conception or design of the work, drafting the work or revising it critically for important intellectual content, provided final approval of the version to be published and agreed to be accountable for all aspects of the work.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval and have followed the principles outlined in the Declaration of Helsinki for all human experimental investigations. In addition, informed consent has been obtained from the participants involved.

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