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DUETTE: a phase II randomized, multicenter study to investigate the efficacy and tolerability of a second maintenance treatment in patients with platinum-sensitive relapsed epithelial ovarian cancer, who have previously received poly(ADP-ribose) polymerase (PARP) inhibitor maintenance treatment

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ABSTRACT

Background With the success of poly(ADP-ribose) polymerase (PARP) inhibitor therapy in the first-line and second-line treatment settings, a new patient population is emerging with platinum-sensitive relapsed ovarian cancer, who have previously received a PARP inhibitor in the maintenance setting and for whom no second maintenance standard of care exists. DUETTE (NCT04239014) will evaluate the combination of ceralasertib (a potent, selective inhibitor of the serine/threonine kinase ataxia telangiectasia and Rad3-related protein (ATR) + olaparib, or olaparib monotherapy, compared with placebo, in this patient population of unmet need.

Primary Objective The primary objective is to assess the efficacy of ceralasertib + olaparib combination, and olaparib monotherapy, compared with placebo, as second maintenance therapy in platinum-sensitive relapsed ovarian cancer.

Study Hypothesis This study will test the hypothesis that ceralasertib + olaparib, or olaparib monotherapy, is tolerable, and effective at prolonging progression-free survival compared with placebo.

Trial Design This is a phase II, multicenter study where patients will be randomized in a 1:1:1 ratio to receive either (Arm 1) ceralasertib + olaparib, (Arm 2) olaparib monotherapy, or (Arm 3) placebo. The olaparib and placebo arms will be double-blinded, whereas the ceralasertib + olaparib arm will be open label. Patients will be stratified according to *BRCA* status, and response to platinum-based chemotherapy.

Major Inclusion/Exclusion Criteria Eligible patients will have histologically diagnosed high-grade epithelial ovarian cancer, with platinum-sensitive relapse on, or after, completion of at least 6 months of any prior PARP inhibitor maintenance therapy (a minimum of 12 months is required if the patient received PARP inhibitor maintenance following first-line chemotherapy). If the prior

PARP inhibitor used was olaparib then patients must have received treatment without significant toxicity or the need for a permanent dose reduction. Disease relapse in the second-line or third-line setting is allowed. Patients who have received secondary debulking surgery are potentially eligible if they meet all other inclusion criteria.

Primary Endpoints The primary endpoint is progression-free survival determined by blinded independent central review according to RECIST 1.1, with sensitivity analysis of progression-free survival using investigator assessments according to RECIST 1.1.

Sample Size 192 patients.

Estimated Dates for Completing Accrual and Presenting Results December 2022.

Trial Registration NCT04239014.

INTRODUCTION

Epithelial ovarian cancer is the most lethal gynecologic malignancy.¹ Worldwide, every year there are over 295 414 new cases diagnosed and 184 799 deaths from epithelial ovarian cancer.¹ Cytoreductive surgery and platinum-based chemotherapy are considered the treatment of choice for patients with newly diagnosed advanced ovarian cancer.² At first and subsequent relapse, if the time since last dose of platinum chemotherapy (treatment free interval–platinum; TFIp) is ≥ 6 months, standard treatment includes a further four to six cycles of platinum-based chemotherapy.² Recurrent disease follows a frequent relapse–response pattern, before eventually becoming resistant to treatment.² Consequently, maintenance treatment is an important strategy to prevent or delay relapse in epithelial ovarian cancer.

The efficacy of the poly(ADP-ribose) polymerase (PARP) inhibitors as maintenance treatment, in PARP

inhibitor-naïve patients with platinum-sensitive relapsed ovarian cancer who have partial or complete response following their last platinum-containing regimen, is well-established. In the first-line maintenance setting, the landmark SOLO1 (NCT01844986) study showed a statistically significant 70% reduction in the risk of disease progression or death, translating to an absolute improvement in progression-free survival in the region of 3 years, for olaparib maintenance over placebo in patients with *BRCA*-mutant (*BRCAm*) advanced ovarian cancer who were in response following first-line platinum-based chemotherapy.³ These results have led to regulatory approval for olaparib in this indication in a number of countries including the European Union, the USA, and Canada. In addition, positive results have been announced for two studies (PRIMA (NCT02655016) and PAOLA-1 (NCT02477644)) evaluating the benefit of PARP inhibitor maintenance therapy in the first-line maintenance setting in an all-comers population.^{4,5} In platinum-sensitive relapsed epithelial ovarian cancer, data from a randomized phase II study (Study 19 (NCT00753545))⁶ initially showed that maintenance treatment with olaparib led to a significant progression-free survival improvement versus placebo (HR 0.35, 95% CI 0.25 to 0.49; $p < 0.001$), with benefit demonstrated in patients irrespective of *BRCA* status. Subsequently, the randomized phase III study (SOLO2/ENGOT-Ov21 (NCT01874353)) demonstrated that investigator-assessed progression-free survival following olaparib maintenance therapy was significantly longer compared with the placebo group (HR 0.30, 95% CI 0.22 to 0.41; $p < 0.0001$), with a 12-month benefit in median overall survival (HR 0.74, 95% CI 0.54 to 1.00) in a *BRCAm* population.⁷

Rationale

This success of the PARP inhibitor as first- and second-line maintenance treatments is heralding a new change to the standard of care for ovarian cancer. Consequently, a new patient population is emerging with platinum-sensitive relapsed epithelial ovarian cancer who have previously received a PARP inhibitor and for whom no second maintenance standard of care exists.

Ceralasertib (formerly known as AZD6738) is a potent, selective inhibitor of the serine/threonine kinase ataxia telangiectasia and Rad3-related protein (ATR). Olaparib and ceralasertib inhibit key DNA repair targets within different DNA damage response pathways and individually may be able to reduce the rate of DNA repair in cells, thereby increasing DNA damage and causing cell death.⁸ Therefore, the mechanistic rationale for the combination of these compounds is that the simultaneous inhibition of two repair pathways (ie, olaparib inducing DNA damage during S-phase and S/G2 cell cycle checkpoint, and ceralasertib inhibiting S-phase repair and abrogation of S/G2 checkpoint) leads to actively replicating cancer cells accumulating DNA double-strand breaks and to cell death in the M-phase.⁹

In addition, the benefit of a second maintenance therapy with olaparib monotherapy is unknown, as the current standard of care in this patient population is no further treatment until next progression. As such, this provides a window of opportunity to intervene with a second maintenance approach in an area of unmet need.

Study Hypothesis

DUETTE will assess the hypothesis that the combination of ceralasertib + olaparib, or olaparib monotherapy, is tolerable, and

effective at prolonging progression-free survival compared with placebo, in patients with platinum-sensitive relapsed epithelial ovarian cancer who have previously received any PARP inhibitor in the maintenance setting, with response or stable disease following completion of platinum-based chemotherapy regimen.

METHODS

Trial Design

DUETTE is a phase II, randomized, multicenter clinical trial to investigate the efficacy and tolerability of a second maintenance treatment in patients with platinum-sensitive relapsed epithelial ovarian cancer, who have previously received PARP inhibitor maintenance treatment and who have benefited (partial or complete response or stable disease) from further platinum-based chemotherapy. Patients will be randomized in a 1:1:1 ratio to receive either (Arm 1) ceralasertib + olaparib, (Arm 2) olaparib monotherapy, or (Arm 3) placebo (Figure 1).

Patients will be recruited globally from approximately 120 study sites in the USA, Canada, the Middle East, and Europe.

Participants

Eligible patients will have histologically diagnosed high-grade epithelial ovarian cancer, with platinum-sensitive relapse on or after completion of at least 6 months of prior PARP inhibitor maintenance therapy (a minimum of 12 months is required if the patient received PARP inhibitor maintenance following first-line chemotherapy). If the prior PARP inhibitor used was olaparib then patients must have received treatment without significant toxicity or the need for a permanent dose reduction. Disease relapse in the second-line or third-line setting is allowed. Patients who have received secondary debulking surgery are potentially eligible if they meet all other inclusion criteria. Patients must have adequate hematological and end-organ function, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. Patient with uncontrolled, intercurrent illness, malignant bowel obstruction, symptomatic uncontrolled brain metastases, leptomeningeal carcinomatosis, or significant unresolved toxicity from prior treatments are ineligible.

Primary Endpoint

The primary endpoint is progression-free survival determined by blinded independent central review according to RECIST 1.1, with sensitivity analysis of progression-free survival using investigator assessments according to RECIST 1.1. Secondary endpoints include overall survival, time to second objective disease progression, objective response rate, duration of response, safety, and tolerability. Exploratory objectives will be to explore genetic and non-genetic drivers of innate and acquired PARP inhibitor resistance and predictive biomarkers of response.

Sample Size

Approximately 192 patients will be randomized in a 1:1:1 ratio to the three treatment arms.

Assuming the true treatment effect of olaparib compared with placebo has a HR of 0.53 (this translates to an approximate 3.5-month improvement in median progression-free survival over an assumed 4-month median progression-free survival for placebo), 90 progression-free survival events must be observed for the study

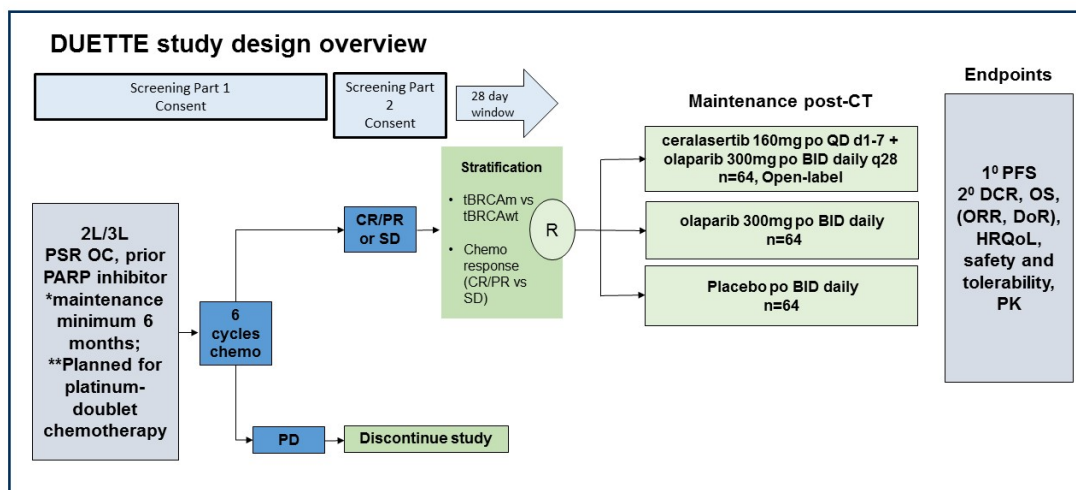


Figure 1 DUETTE study design overview. 1^o, primary; 2^o, secondary; 2L, second line; 3L, third line; BID, twice daily; tBRCAm, tumor breast cancer susceptibility gene-mutant; tBRCAwt, tumor breast cancer susceptibility gene-wildtype; chemo, chemotherapy; CR, complete response; CT, chemotherapy; DCR, Disease Control Rate; DoR, duration of response; HRQoL, health-related quality of life; OC, ovarian cancer; ORR, objective response rate; OS, overall survival; PARP, polyadenosine 5'diphosphoribose (poly(ADP ribose)) polymerase; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetic(s); po, oral; PR, partial response; PSR, platinum-sensitive relapsed; q28, every 28 days; QD, once daily; R, randomization; SD, stable disease.

to have 83% power to show a statistically significant difference in progression-free survival at the two-sided 4.5% level. The smallest treatment difference that would be statistically significant at the primary analysis is a progression-free survival HR of 0.65.

Assuming the true treatment effect of the olaparib combination arm (ceralasertib + olaparib) compared with placebo has a HR of 0.38 (this translates to an approximate 6.5-month improvement in median progression-free survival for the combination treatment over an assumed 4-month median progression-free survival for placebo), 90 progression-free survival events must be observed for the study to have 96% power to show a statistically significant difference in progression-free survival at the two-sided 0.5% level. The smallest treatment difference that would be statistically significant at the primary analysis is a progression-free survival HR of 0.55.

An interim futility analysis will be triggered when approximately 25 patients (75 patients overall) have been recruited into each of the treatment arms and have been assessed for at least 8 weeks. Assuming progression-free survival is exponentially distributed, and the placebo treatment group has a median progression-free survival of 4 months, it is expected that the proportion of patients with non-progressive disease at Week 8 will be 72.6%. If the 80% two-sided exact upper limit of the CI for the proportion of patients with non-progressive disease in the ceralasertib + olaparib arm or olaparib monotherapy arm is less than 72.6%, with consideration of this analysis in context with the totality of the clinical data (safety and efficacy) available, the Independent Data Monitoring Committee may recommend recruitment cessation.

An initial overall survival analysis will be performed at the same time as the primary analysis of progression-free survival; a further analysis of overall survival will be performed when the overall survival data are approximately 60% mature (approximately 115 deaths).

Randomization and Blinding

Patients will be randomized in a 1:1:1 ratio to the following three treatment arms (64 patients per arm):

- ▶ Arm 1 (ceralasertib + olaparib): ceralasertib 160 mg once daily, orally, on Days 1 to 7 plus olaparib 300 mg twice daily, orally, continuous (28-day cycle).
- ▶ Arm 2 (olaparib monotherapy): olaparib 300 mg twice daily, orally continuous.
- ▶ Arm 3 (placebo): placebo to match olaparib twice daily, orally continuous.

The olaparib and placebo arms will be double-blinded, whereas the ceralasertib + olaparib arm will be open label.

Patients will be stratified according to tumor *BRCA* status (mutant (deleterious or suspected deleterious mutation in *BRCA1* or *BRCA2*) or wild-type (including variants of uncertain significance in *BRCA1* or *BRCA2*)) and response to most recent platinum-based chemotherapy (responders or stable disease).

Correlative Studies

In addition to collecting archival tumor tissue sample, contemporaneous core needle biopsies (three passes) before starting chemotherapy is mandatory on this study. Comparison of the archival tumor sample from the time of primary tumor diagnosis (or prior to first PARP inhibitor treatment) and the contemporaneous tumor sample will be used to assess mechanisms of PARP inhibitor resistance, for example, *BRCA* reversion mutations, and for other exploratory purposes. An additional biopsy at time of disease progression on study is particularly encouraged to ascertain mechanisms of treatment resistance.

Blood samples for exploratory biomarker analyses will be collected at sequential time points. Testing may include (but is not limited to) assessment of mutations in circulating tumor DNA, correlation of baseline circulating tumor DNA with clinical outcome

measures, and correlation between tumor and plasma mutation status and future diagnostic development.

Statistical Analysis

The primary analysis will include all randomized patients. Standard statistical methods will be used to evaluate the primary endpoint, as well as secondary and exploratory endpoints, including parametric and non-parametric tests for comparisons between treatment groups. Progression-free survival will be analyzed using pairwise log rank tests, and pairwise HRs and CIs will be estimated from a Cox proportional hazards model, stratified by *BRCA* status and response to platinum-based chemotherapy. Ceralasertib + olaparib versus placebo comparison will be tested at the two-sided 0.5% level and olaparib versus placebo at two-sided 4.5% to strongly control the overall type 1 error. The efficacy of the combination therapy versus olaparib monotherapy will be evaluated but not formally tested. A sensitivity analysis will be performed based on the investigator-recorded assessment of disease progression by RECIST 1.1.

DISCUSSION

DUETTE strives to improve outcomes in patients with platinum-sensitive relapsed ovarian cancer, by addressing the role of a second maintenance treatment in patients who have received prior PARP inhibitor treatment. Given the success of PARP inhibitor as first- and second-line maintenance treatments, this is an emerging patient population of unmet need. There is currently no standard of care defined for this patient population. While studies have demonstrated a progression-free survival benefit from bevacizumab maintenance in the platinum-sensitive relapse setting,¹⁰ these trials did not include patients who had received prior PARP inhibitor therapy, and many clinicians will opt to reserve bevacizumab for use in the platinum-resistant setting where treatment options are more limited.

Following progression on PARP inhibitor maintenance therapy, many of these patients are found to retain sensitivity to platinum-based chemotherapy. It is not known whether these patients will benefit from an additional period of PARP inhibitor maintenance therapy given alone or in combination with another DNA damage response agent. The concept of DNA damage response as a therapeutic strategy, as seen with olaparib, has led to interest in combining PARP inhibitors with other DNA damage response-targeted agents that impair the ability of tumor cells to stall the cell cycle (checkpoint) to process and repair trapped PARP1 DNA lesions.⁹ Potential targets include ATR, the key serine/threonine-specific protein kinase involved in initiating and co-ordinating the DNA damage replication stress response and S/G2 cell cycle checkpoint.⁹

DUETTE will evaluate the combination of ceralasertib + olaparib, and olaparib monotherapy, as second maintenance treatment in platinum-sensitive relapsed ovarian cancer. It is predicted that ATR kinase inhibition through the use of ceralasertib combined with PARP inhibition may be synergistic and impair cancer cell survival. In addition, this treatment combination has shown promising results in pre-clinical PARP- or platinum-resistant cancer models and is expected to overcome the resistance mechanisms associated with DNA damage response rewiring,¹¹ increased protection of DNA replication forks,¹² or SLFN11-loss¹³ associated with PARP inhibitor resistance. The ceralasertib + olaparib combination is less likely to overcome resistance mechanisms associated with *BRCA* reversions¹⁴ or decreased PARP trapping.¹⁵ By selecting patients with ovarian cancer who have tumor response or

stable disease following platinum-based chemotherapy, it is expected that the study population will be enriched for non-*BRCA* reversion, PARP inhibitor resistance mechanisms. Translational studies incorporated into this trial will further explore these PARP inhibitor resistance mechanisms and biomarkers of response in tumor and in blood.

The benefits of a second maintenance with olaparib are also being evaluated in the OReO study (NCT03106987; ENGOT-ov38/OReO), a phase IIIb study of olaparib maintenance retreatment in patients with epithelial ovarian cancer previously treated with a PARP inhibitor and responding to repeat platinum chemotherapy. A small number of clinical trials are currently also investigating the role of second maintenance treatment for this patient population, examining combination strategies such as cediranib + olaparib (EVOLVE (NCT02681237)), bevacizumab + atezolizumab + platinum chemotherapy (ATALANTE (NCT02891824)), atezolizumab + niraparib + platinum chemotherapy (ANITA (NCT03598270)), and tremelimumab + olaparib (NCT02571725; NCT04034927). However, a number of recent PARP inhibitor-combination maintenance trials actually exclude patients who have received prior PARP inhibitor therapy (TOPACIO (NCT02657889) and MEDIOLA (NCT02734004)). The results of these trials, including translational studies, are still awaited and are yet to define a standard of care for second maintenance treatment.

DUETTE is uniquely positioned in this setting to elucidate whether second maintenance treatment can transform survival in a platinum-sensitive relapsed ovarian cancer population who have specifically received prior PARP inhibitor treatment. Importantly, correlative analyses will explore mechanisms of PARP inhibitor resistance and predictive biomarkers in order to inform therapeutic development. DUETTE will potentially change practice by defining the role of ceralasertib + olaparib, or olaparib monotherapy, in this emerging patient population for whom no standard of care exists, and for whom more effective treatment options are urgently needed.

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Competing interests AMO is on the steering committee of GSK, AstraZeneca (AZ), Clovis, Tesaro, and Merck (uncompensated), and is PI on clinical trials for AZ, GSK, and Clovis. BL, EP, and GD are employees of AZ.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article

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Clinical trial

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