DUO-E/GOG-3041/ENGOT-EN10: A RANDOMIZED PHASE III TRIAL OF FIRST-LINE CARBOPLATIN AND PACLITAXEL IN COMBINATION WITH DURVALUMAB, FOLLOWED BY MAINTENANCE DURVALUMAB WITH OR WITHOUT OLAPARIB, IN PATIENTS WITH NEWLY DIAGNOSED ADVANCED OR RECURRENT ENDOMETRIAL CANCER

Shannon N Westin,[1] Kathleen Moore,[2] Els Van Nieuwenhuysen,[3] Amit Oza,[4] Linda Mileshkin,[5] Aikou Okamoto,[6] Lubomir Bodnar,[7] Christos Papadimitriou,[8] Laura Barker,[9] Kassondra Meyer,[10] Akiko Suzuki,[10] Joon Rhee,[10,*] Ignace Vergote[3]

[1]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]University of Oklahoma Medical Center, Oklahoma, OK, USA; [3]BGOG and University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [4]Princess Margaret Hospital, Toronto, ON, Canada; [5]Peter MacCallum Cancer Center, Melbourne, Australia; [6]The Jikei University School of Medicine, Tokyo, Japan; [7]Warmia and Mazury Oncology Center, Olsztyn, Poland; [8]Aretaieio University Hospital, National and Kapodistrian University of Athens, Athens, Greece; [9]AstraZeneca, Cambridge, UK; [10]AstraZeneca, Gaithersburg, MD, USA; *Current affiliation, BeiGene Ltd, Emeryville, CA, USA

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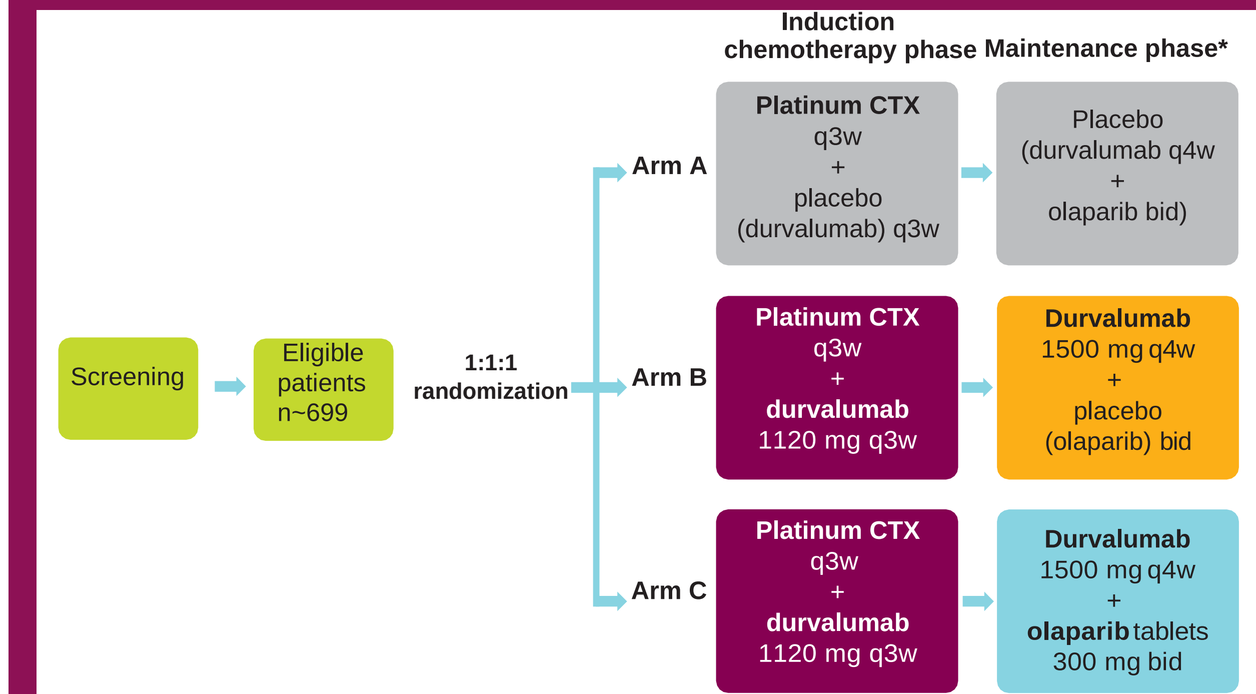
Introduction

- There is a high unmet need for advances in endometrial cancer (EC) treatment that provide progression-free survival (PFS) and overall survival (OS) benefits.
- Durvalumab is a human immunoglobulin G1 monoclonal antibody that blocks the binding of programmed cell death ligand 1 (PD-L1) to its receptors, resulting in a T-cell-mediated immune response to tumor cells[1]
  - FDA approval of anti-programmed cell death-1 (anti-PD-1) antibody pembrolizumab as monotherapy in patients with high level microsatellite instability (MSI-H) or in combination with lenvatinib in microsatellite stable patients has raised interest in the use of immune checkpoint inhibitors in EC
  - Clinical trials have demonstrated antitumor activity of durvalumab[2] and anti-PD-1 antibody therapies[3,4] in patients with EC. The GARNET trial showed that the anti-PD-1 antibody dostarlimab led to durable overall response rates (ORR) in patients with and without MSI-H EC, suggesting patients may benefit from immune checkpoint blockade regardless of MSI status.[4]
- Standard of care treatment for newly diagnosed advanced EC includes platinum-based chemotherapy, for which a response rate of ~51–62% has been shown.[5–7]
- Platinum sensitivity is emerging as a potential predictor of PARP inhibitor sensitivity based on recent studies of olaparib in platinum-sensitive, germline *BRCA1* and/or *BRCA2* mutated ovarian and pancreatic cancers,[8–10] so it is hypothesized that a proportion of platinum-sensitive EC may also be sensitive to PARP inhibition.
- Molecular features known to predict increased benefit from PARP inhibitor treatment, such as homologous recombination deficiency and homologous recombination repair gene mutations, have been found in EC; however, it is not yet known which EC tumors are sensitive to PARP inhibition.[11–13]
- The potential to increase activity by combining a PARP inhibitor with PD-L1 immune checkpoint blockade is based on the hypothesis that pharmacological inhibition of PARP by olaparib will result in enhanced immunogenicity, which can be further enhanced with an immune checkpoint inhibitor, such as durvalumab.
- This hypothesis is supported by preclinical studies in mouse models of cancer, demostrating that administration of PARP inhibitors to sensitive tumor types results in increased T-cell infiltration and immune activation within tumors.[14]
- The DUO-E/GOG-3041/ENGOT-EN10 trial (NCT04269200, EUDRACT 2019-004112-60) will investigate the efficacy and safety of durvalumab in combination with platinum-based chemotherapy followed by durvalumab maintenance with or without olaparib in patients with newly diagnosed advanced or recurrent EC.

Study design

- DUO-E is a multicenter, randomized, double-blind, placebo-controlled Phase III study of durvalumab in combination with platinum-based chemotherapy, followed by maintenance durvalumab with or without olaparib, compared with platinum-based chemotherapy alone, in patients with newly diagnosed advanced or recurrent EC.
- The study will be performed according to the ENGOT-GOG Model C.[15]
- Approximately 699 patients from ~210 sites will be randomized.
- Key inclusion and exclusion criteria are shown in Table 1.
- As shown in Figure 1, patients will be randomized 1:1:1 (n=~233 per arm) to:
  - Arm A: carboplatin/paclitaxel + durvalumab placebo, followed by maintenance durvalumab placebo + olaparib placebo
  - Arm B: carboplatin/paclitaxel + durvalumab, followed by maintenance durvalumab + olaparib placebo
  - Arm C: carboplatin/paclitaxel + durvalumab, followed by maintenance durvalumab + olaparib.
- To continue onto the maintenance phase, patients should receive six cycles of platinum-based chemotherapy with or without durvalumab (Figure 1)
  - Carboplatin AUC (area under the free carboplatin plasma concentration versus time curve) 5 or AUC 6 and paclitaxel 175 mg/m^2 every 3 weeks (q3w)
  - Intravenous (IV) durvalumab 1120 mg q3w or durvalumab placebo.

Figure 1: Study design



*Patients who achieve and maintain disease control (complete response, partial response or stable disease) during the chemotherapy phase will receive maintenance therapy. bid, twice daily; CTX, chemotherapy; q4w, every 4 weeks.

Author contact details: swestin@mdanderson.org

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Table 1. Key patient eligibility criteria

Inclusion criteria	Exclusion criteria
Aged ≥18 years	Prior treatment with PARP inhibitors
Newly diagnosed, histologically confirmed stage III*/IV† EC, or recurrent,‡ histologically confirmed EC	Prior immune checkpoint inhibitors or prior treatment with an agent directed to a stimulatory or coinhibitory T-cell receptor other than an anti-PD-1, anti-PD-L1 or anti-PD-L2 agent
Mandatory provision of tumor sample for the testing of biomarkers, such as MMR status	Known brain metastases or spinal cord compression
Naïve to first-line systemic anticancer treatment (for patients with recurrent disease, prior chemotherapy is allowed only if it was administered in the adjuvant setting and there is ≥12 months between last chemotherapy dose and subsequent relapse)	History of leptomeningeal carcinomatosis
ECOG performance status 0–1	
Adequate organ and bone marrow function	
Postmenopausal or confirmed not pregnant	

*Measurable disease using RECIST v1.1 following surgery or diagnostic biopsy; †With or without disease following surgery or diagnostic biopsy; ‡Measurable or non-measurable disease using RECIST v1.1, where the potential for cure by surgery alone or in combination is poor
anti-PD-L2, anti-programmed cell death ligand 2; ECOG, Eastern Cooperative Oncology Group; MMR, tumor tissue mismatch repair; RECIST, Response Evaluation Criteria in Solid Tumors.

- Patients without disease progression (RECIST v1.1) during the chemotherapy phase will receive (Figure 1):
  - Maintenance durvalumab placebo + olaparib placebo (Arm A), or
  - Maintenance IV durvalumab 1500 mg q4w + olaparib placebo (Arm B), or
  - Maintenance IV durvalumab 1500 mg q4w + olaparib tablets 300 mg bid (Arm C).
- Study treatment will be administered until investigator-assessed radiological disease progression (RECIST v1.1), unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Objectives

- The primary objective is to evaluate PFS defined as time from randomization to objective disease progression or death by investigator assessment using RECIST v1.1.
- The key secondary and exploratory objectives are presented in Table 2.

Table 2. Primary, secondary and exploratory objectives

Objectives	Endpoints
Primary	PFS*
Key secondary	OS PFS2† ORR‡ Duration of response§ Time to first subsequent therapy or death Time to second subsequent therapy or death Time to study treatment discontinuation or death Pharmacokinetic and immunogenicity analysis of durvalumab with or without olaparib Health-related quality of life Safety and tolerability
Key exploratory	Tumor predictive biomarkers Resistance analysis

*Investigator-assessed using RECIST v1.1; †Time to second disease progression or death, as assessed by the local investigator; ‡Proportion of patients who have complete or partial response, as assessed by the local investigator; §Time from response to disease progression or death (in the absence of disease progression); PFS2, time to second progression.

Assessments

Efficacy

- Computed tomography (CT) or magnetic resonance imaging (MRI) scans at baseline, then every 9 weeks ± 1 week for the first 18 weeks from randomization, and then every 12 weeks ± 1 week until radiological disease progression (RECIST v1.1).

Safety

- Adverse events (AEs) will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
  - AEs will be documented until 30 days following the discontinuation of olaparib or until 90 days following the discontinuation of durvalumab, whichever is later.
- Details of health-related quality of life assessments and statistical analyses can be found in the Supplementary Methods.

Enrollment

- Patient enrollment began in Q2 2020.
- For more information on participating locations, please see clinicaltrials.gov (NCT04269200).

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Supplementary materials to:
DUO-E/GOG-3041/ENGOT-EN10: a randomized Phase III trial of first-line carboplatin and paclitaxel in combination with durvalumab, followed by maintenance durvalumab with or without olaparib, in patients with newly diagnosed advanced or recurrent endometrial cancer

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This supplementary materials document has been provided by the study authors to give readers additional information about the DUO-E trial.

Methods

Health-related quality of life (HRQoL) assessments

- HRQoL will be assessed using the following questionnaires:
  - European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-EN24 questionnaires
  - European QoL five-dimension five-level (EQ-5D-5L) questionnaire
  - Patient-reported outcomes version of the CTCAE (PRO-CTCAE)
  - Patient global impression of severity of cancer symptoms (PGIS), change (PGIC), treatment tolerability (PGI-TT) and benefit/risk (PGI-BR).

Statistical analyses

- The following endpoints will be analyzed using a log-rank test:
  - Progression-free survival
  - Overall survival
  - Second progression-free survival
  - Time to first subsequent therapy or death
  - Time to second subsequent therapy or death
  - Time to study treatment discontinuation or death
    - Hazard ratios and confidence intervals will be will be estimated using a stratified Cox proportional hazards model.
- Objective response rate will be analyzed using logistic regression

- Time to deterioration in EORTC QLQ-C30 and EORTC QLQ-EN24 endpoints will be examined comparing treatment versus control arm. Additional patient reported outcome data will be summarized descriptively.
- Safety and tolerability data will be summarized using appropriate descriptive measures.