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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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 methyltransferase 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 durvalumab1 and anti-PD-1 antibody therapies2–4 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-EC, suggesting patients may benefit from immune checkpoint blockade regardless of MSI status.5
- Standard of care treatment for newly diagnosed advanced EC includes platinum-based chemotherapy, for which a response rate of 51–62% has been shown.6–7
- Platinum-sensitivity is emerging as a potential predictor of PARP inhibitor sensitivity based on recent studies of olaparib in platinum-sensitive, germ line 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.11,12
- 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 demonstrating 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 + olaparib placebo
  - Arm B: carboplatin/paclitaxel + 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)
  - Carboptatin AUC (area under the free carboplatin plasma concentration versus time curve) 5 or AUC 6 and paclitaxel 175 mg/m² q3w
  - Intravenous (IV) durvalumab 1120 mg q4w or durvalumab placebo.

Efficacy

- 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.

Assessments

- Tumor predictive biomarkers
- Resistance analysis

Table 1. Key patient eligibility criteria

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
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<tr>
<td>Aged ≥18 years</td>
<td>Prior treatment with PARP inhibitors</td>
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<tr>
<td>Newly diagnosed, histologically confirmed stage IVA-IVc EC, or recurred, histologically confirmed EC</td>
<td>Known brain metastases or spinal cord compression</td>
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<td>Adequate organ and bone marrow function</td>
<td>History of leptomeningeal carcinomatosis</td>
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<td>Postmenopausal or confirmed not pregnant</td>
<td>Nausea 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 (therapeutic dose and subsequent relapse)</td>
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<tr>
<td>Adequate organ and bone marrow function</td>
<td>ECOG performance status 0–1</td>
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<td>Patients without disease progression (RECIST v1.1) during the chemotherapy phase will receive (Figure 1):</td>
<td>Adequate organ and bone marrow function</td>
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<tr>
<td>Maintenance durvalumab placebo + olaparib placebo (Arm A), or</td>
<td>Adequate organ and bone marrow function</td>
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<tr>
<td>Maintenance IV durvalumab 1500 mg q4w + olaparib placebo (Arm A), or</td>
<td>Adequate organ and bone marrow function</td>
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<tr>
<td>Maintenance IV durvalumab 1500 mg q4w + olaparib tablets 300 mg bid (Arm C).</td>
<td>Adequate organ and bone marrow function</td>
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- For more information on participating locations, please see clinicaltrials.gov (NCT04269200).

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