ENGOT-ov46/AGO/DUO-O

Leading group: AGO

Clinical Trial Study: A phase III randomised, double-blind, placebo-controlled, multicentre study of Durvalumab in combination with chemotherapy and Bevacizumab, followed by maintenance Durvalumab, Bevacizumab and Olaparib in newly diagnosed advanced ovarian cancer patients (DUO-O)

Planned number of patients: 1056

Participating groups:

A-AGO, BGOG, GEICO, MaNGO, MITO, NSGO, PGOG, TRSGO

Study Description

Brief Summary:

This is a Phase III randomised, double-blind, multi-centre study to evaluate the efficacy and safety of durvalumab in combination with standard of care platinum based chemotherapy and bevacizumab followed by maintenance durvalumab and bevacizumab or durvalumab, bevacizumab and olaparib in patients with newly diagnosed advanced ovarian cancer.

Condition or disease	**Intervention/treatment**	**Phase**
Advanced Ovarian Cancer	Drug: BevacizumabDrug: DurvalumabDrug: OlaparibDrug: Placebo olaparibDrug: Durvalumab placeboDrug: Carboplatin+Paclitaxel	Phase 3

Detailed Description:

Eligible patients will be those patients with newly diagnosed, histologically confirmed advanced (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] Stage III-IV) ovarian, primary peritoneal cancer and/or fallopian-tube cancer. All patients should be candidates for cytoreductive surgery which could be conducted as immediate upfront primary surgery following diagnosis or can be conducted after initiation of platinum based neoadjuvant chemotherapy. All patients should be eligible to start first line platinum based chemotherapy in combination with bevacizumab.

The study aims to evaluate the efficacy and safety of standard of care (SoC) platinum-based chemotherapy and bevacizumab followed by maintenance bevacizumab either as monotherapy, or in combination with durvalumab, or in combination with durvalumab and olaparib. Therefore, this study aims to see which combination allows patients to live longer without the cancer coming back or getting worse. The study is also looking to see which combination makes patients live longer and how the treatment and the cancer affects their quality of life.

Study Design

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	1056 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	The study consists of 2 independent cohorts: 3 double-blind treatment arms cohort for patients with no BRCA mutation, and a single open label arm cohort for patients with BRCA mutation
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose:	Treatment
Official Title:	A Phase III Randomised, Double-Blind, Placebo-Controlled, Multicentre Study of Durvalumab in Combination With Chemotherapy and Bevacizumab, Followed by Maintenance Durvalumab, Bevacizumab and Olaparib in Newly Diagnosed Advanced Ovarian Cancer Patients (DUO-O).
Actual Study Start Date :	January 4, 2019
Estimated Primary Completion Date :	January 2, 2023
Estimated Study Completion Date :	August 29, 2025

Arms and Interventions

Arm	Intervention/treatment
Active Comparator: Arm 1 Platinum-based chemotherapy in combination with bevacizumab and durvalumab placebo (saline IV infusion) followed by maintenance bevacizumab, durvalumab placebo (saline IV infusion) and olaparib placebo (tablets).	Drug: Bevacizumab Bevacizumab by intravenous infusion. In tBRCAm cohort bevacizumab is optional according to local practice. Drug: Placebo olaparib Placebo tablets to match olaparib Drug: Durvalumab placebo Matching placebo for intravenous infusion Drug: Carboplatin+Paclitaxel Standard of care chemotherapy
Experimental: Arm 2 Platinum-based chemotherapy in combination with bevacizumab and durvalumab followed by maintenance bevacizumab, durvalumab and olaparib placebo.	Drug: Bevacizumab Bevacizumab by intravenous infusion. In tBRCAm cohort bevacizumab is optional according to local practice. Drug: Durvalumab Durvalumab by intravenous infusion Drug: Placebo olaparib Placebo tablets to match olaparib Drug: Carboplatin+Paclitaxel Standard of care chemotherapy

Arm	Intervention/treatment
Experimental: Arm 3 Platinum-based chemotherapy in combination with bevacizumab and durvalumab followed by maintenance bevacizumab, durvalumab and olaparib.	Drug: Bevacizumab Bevacizumab by intravenous infusion. In tBRCAm cohort bevacizumab is optional according to local practice. Drug: Durvalumab Durvalumab by intravenous infusion Drug: Olaparib Olaparib tablets Drug: Carboplatin+Paclitaxel Standard of care chemotherapy
Experimental: tBRCAm cohort Platinum-based chemotherapy in combination with bevacizumab and durvalumab followed by maintenance bevacizumab, durvalumab and olaparib. Bevacizumab is optional according to local practice.	Drug: Bevacizumab Bevacizumab by intravenous infusion. In tBRCAm cohort bevacizumab is optional according to local practice. Drug: Durvalumab Durvalumab by intravenous infusion Drug: Olaparib Olaparib tablets Drug: Carboplatin+Paclitaxel Standard of care chemotherapy

Outcome Measures

Primary Outcome Measures :

1. Progression Free Survival (PFS) - in non-tBRCAm patients [Time Frame: Approximately 6 years]

Defined as time from randomisation to first progression by investigator assessment using modified RECIST 1.1 or death (by any cause in the absence of progression)

Secondary Outcome Measures :

1. Overall Survival (OS) - in non-tBRCAm patients [Time Frame: Approximately 6 years]

Defined as the time from randomisation to death due to any cause

2. Second Progression (PFS2) - in non-tBRCAm patients [Time Frame: Approximately 6 years]

Defined as time from randomisation to second progression by investigator assessment of radiological progression, symptomatic progression or death (by any cause in the absence of progression)

3. Health-related quality of life - in non-tBRCAm patients [Time Frame: Approximately 3 years]

Change from baseline in the physical functioning subscale of the EORTC-QLQ-C30

4. pathological Complete Response (pCR) - in non-tBRCAm patients [Time Frame: Approximately 3 months after randomisation]

Defined as the proportion of patients with pCR in patients undergoing IDS

5. The pharmacokinetics (PK) and immunogenicity of durvalumab and olaparib as determined by peak concentration - in non-tBRCAm patients [Time Frame: Approximately 18 months]

Determination of durvalumab concentration in serum and olaparib concentration in plasma in a subset of patients

6. Objective Response Rate (ORR) - in non-tBRCAm patients [Time Frame: Approximately 6 years]

Defined as the number (%) of patients with at least one investigator-assessed visit response of CR or PR as per RECIST 1.1

7. Duration of response (DoR) - in non-tBRCAm patients [Time Frame: Approximately 6 years]

Defined as the time form the date of first documented response (CR/PR) until the first progression or death in the absence of disease progression

8. Time to first subsequent therapy (TFST) - in non-tBRCAm patients [Time Frame: Approximately 6 years]

Time elapsed from randomisation to first subsequent therapy or death

9. Time to second subsequent therapy (TSST) - in non-tBRCAm patients [Time Frame: Approximately 6 years]

Time elapsed from randomisation to second subsequent therapy or death

10. Time to discontinuation or death (TDT) - in non-tBRCAm patients [Time Frame: Approximately 30 months]

Time elapsed from randomisation to study treatment discontinuation or death

11. PFS - in tBRCAm patients [Time Frame: Approximately 6 years]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

12. PFS2 - in tBRCAm patients [Time Frame: Approximately 6 years]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

13. ORR - in tBRCAm patients [Time Frame: Approximately 6 years]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

14. ORR pre-surgery in IDS group - in tBRCAm patients [Time Frame: Approximately 6 years]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

15. duration of response (DoR) - in tBRCAm patients [Time Frame: Approximately 6 years]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

16. Time to first subsequent therapy (TFST) - in tBRCAm patients [Time Frame: Approximately 6 years]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

17. Time to second subsequent therapy (TSST) - in tBRCAm patients [Time Frame: Approximately 6 years]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

18. Time to discontinuation or death (TDT) - in tBRCAm patients [Time Frame: Approximately 30 months]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

19. Health-related quality of life - in tBRCAm patients [Time Frame: Approximately 3 years]

Change from baseline in the physical functioning subscale of the EORTC-QLQ-C30

20. Proportion of patients with pCR in patients undergoing IDS - in tBRCAm patients [Time Frame: Approximately 3 months after cohort allocation]

To assess the potential additional clinical benefit of durvalumab added to SoC and olaparib in the first line treatment of tBRCAm patients

<u>Other Outcome Measures:</u>

1. Safety and tolerability of drugs by assessment of AEs/SAEs [Time Frame: Approximately 6 years]

Graded according to the National Cancer Institute (NCI CTCAE)

Eligibility Criteria

Ages Eligible for Study:	18 Years to 150 Years (Adult, Older Adult)
Sexes Eligible for Study:	Female
Gender Based Eligibility:	Yes
Gender Eligibility Description:	All female patients newly diagnosed with advanced ovarian cancer
Accepts Healthy Volunteers:	No

Criteria

Key Inclusion Criteria:

Female patients with newly diagnosed, histologically confirmed, advanced (Stage III-IV) high grade epithelial ovarian cancer including high grade serious, high grade endometriod, clear cell ovarian cancer or carcinosarcoma, primary peritoneal cancer and / or fallopian-tube cancer

- Patients must be aged ≥18 years of age. For patients enrolled in Japan that are aged <20 year
- All patients should be candidates for cytoreductive surgery either: upfront primary surgery OR plan to undergo chemotherapy with interval debulking surgery
- Evidence of presence or absence of BRCA1/2 mutation in tumour tissue
- Mandatory provision of tumour sample for centralised tBRCA testing
- ECOG performance status 0-1
- Patients must have preserved organ and bone marrow function
- Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test

Key Exclusion Criteria:

Non-epithelial ovarian cancer, borderline tumors, low grade epithelial tumors or mucinous histology

- Prior systemic anti-cancer therapy for ovarian cancer
- Inability to determine the presence or absence of a deleterious or suspected deleterious BRCA mutation
- Prior treatment with PARP inhibitor or immune mediated therapy
- Planned intraperitoneal cytotoxic chemotherapy
- Active or prior documented autoimmune or inflammatory disorders
- Patients considered a poor medical risk due to a serious, uncontrolled intercurrent illness

- Clinically significant cardiovascular disease
- Patients with known brain metastases
- History of another primary malignancy except for:
    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study treatment and of low potential risk for recurrence (patients who have received prior adjuvant chemotherapy for early stage breast cancer may be eligible, provided that it was completed ≥3 years prior to registration, and that the patient remains free of recurrent or metastatic disease)
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease
    - Endometrial cancer FIGO Stage IA, Grade 1 or Grade 2
- Persistent toxicities CTCAE Grade >2 caused by previous cancer therapy
- Patients with a known hypersensitivity to olaparib, durvalumab or any of the excipients of these products and to the combination/comparator agents
- Breast feeding women