KURZPROTOKOLL
DUO-O

Öffentlicher Titel	Phase III Studie zu Durvalumab bei neu diagnostiziertem fortgeschrittenem Ovarialkarzinom
Wissenschaftl. Titel	Eine randomisierte, doppelblinde, placebokontrollierte, multizentrische Phase III Studie mit Durvalumab in Kombination mit Chemotherapie und Bevacizumab, gefolgt von einer Erhaltungstherapie mit Durvalumab, Bevacizumab und Olaparib bei Patientinnen mit neu diagnostiziertem fortgeschrittenem Ovarialkarzinom
Kurztitel	DUO-O
Studienart	multizentrisch, prospektiv, Therapiestudie, randomisiert, Pharma-Studie, doppelblind, mehrarmig
Studienphase	Phase III
Erkrankung	Geschlechtsorgane: Krebserkrankungen der weiblichen Geschlechtsorgane: Eierstockkrebs (Ovarialkarzinom) - Erstlinie
Einschlusskriterien	- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent forms (ICFs) and in this protocol. All patients must sign both the Pre-screen ICF and main ICF: - a) The separate (Pre-screen) ICF will be provided for the mandatory tBRCA testing. - b) The main ICF for participation in the study. The main consent form includes a separate consent for the optional Genomics Initiative research component of the study (if a patient declines to participate in this research, there will be no penalty or loss of benefit to the patient and the patient will not be excluded from other aspects of the study) - ->The ICF process is described in Appendix A 3. Note that all patients, regardless of whether or not they already know whether they have a deleterious or suspected deleterious BRCA mutation present or absent based on local blood or tumour testing MUST sign the Pre-screen ICF to allow for central testing of tBRCAm status. Subject to meeting other eligibility criteria, patients can also sign the main ICF, be enrolled on the study and receive Cycle 1 of platinum-based chemotherapy. Patients will only be allocated to a tBRCAm cohort at the start of Cycle 2, once their tBRCAm status is confirmed by central testing. Patients who do nothave a valid central test result available prior to Day 1 of Cycle 2 will be withdrawn from the study and considered as screen failures - -> tBRCA mutation status - Patients must provide sufficient formallin fixed, paraffin embedded (FFPE) tumour sample suitable for the Myriad myChoice HRD Plus test Determination of tBRCAm status: Subject to local regulations, all patients must provide an FFPE tumour specimen sample for tissue-based BRCA1/2 gene testing using the clinical trial assay (CTA) known as the myChoice HRD Plus assay. The results of this test MUST be available prior to Day 1 of Cycle 2. - -> If the test results indicate that the patient has deleterious or suspected deleterious mutation in BRCA1 or BRCA2, the patient may (subject to fulfilling all other selection criteria) be eligible for enrolment in the tBRCAm single arm cohort of the study. - -> If the test results indicate that the patient has no detected deleterious or suspected deleterious mutation in BRCA1 and BRCA2 the patient may (subject to fulfilling all other selection criteria) be eligible for randomisation in one of 3 non-tBRCAm arms - -> If a valid tBRCAm test result is not obtained prior to Day 1 of Cycle 2, the patient will be withdrawn from the study and considered as a screen failure - -> The cohort allocation and randomisation procedures are provided in Section 6.3.1 - -> Patients MUST meet the following criteria prior to receiving Cycle 1 of chemotherapy - Patients must be aged >=18 years of age. For patients enrolled in Japan that are aged <20 year, a written informed consent should be obtained from the patient and her legally acceptable representative*.

- Female patients with newly diagnosed, histologically confirmed, advanced (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] Stage III or IV) high grade epithelial ovarian cancer including high grade serous, high grade endometriod, clear cell ovarian cancer or carcinosarcoma (malignant mixed Mullerian tumour [MMMT] of the ovary, provided high grade epithelial component is present); ovarian cancer = ovarian, primary peritoneal cancer and / or fallopian-tube cancer*.
- All patients must have had either*:
- -> Upfront primary surgery
- -> OR, plan to undergo chemotherapy with interval debulking surgery6 Patients must have a life expectancy of at least 12 months*.
- Patients must have normal organ and bone marrow function measured within 28 days prior to administration of Day 1 of Cycle 1 as defined below:
- -> Haemoglobin (Hb) >=10.0 g/dL
- -> Absolute neutrophil count (ANC) >=1.5 x 10^9/L
- -> Platelet count >=100 x 10^9/L
- -> Total bilirubin <=1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed to participate in the study, in consultation with their physician
- -> Aspartate aminotransferase (AST) (Serum Glutamic Oxaloacetic Transaminase (SGOT)) / Alanine aminotransferase (ALT) (Serum Glutamic Pyruvate Transaminase (SGPT)) <=2.5 × institutional ULN unless liver metastases are present in which case they must be <=5 × ULN.
- Patients must have creatinine clearance (CrCL) of >=51 mL/minute estimated using either the Cockcroft-Gault equation, a 24 hour urine test or another validated test as per local practice: Estimated CrCL = (140-age [years]) × weight (kg) × 0.85 serum creatinine (mg/dL) × 72
- Adequately controlled blood pressure (BP) (systolic blood pressure [SBP] <=150 mmHg; diastolic blood pressure [DBP] <= 100 mmHg). Patients must have a BP of <=150/100 mmHg taken in the clinic setting by a medical professional within 2 weeks prior to starting study
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1 (see Appendix G).
- Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations*.
- Patients’ body weight must be >30kg*
- Postmenopausal or evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of Day 1 of Cycle 1 and confirmed prior to treatment on Day 1
- a) Postmenopausal is defined as any of the following:
- -> Surgical sterilisation (bilateral oophorectomy or hysterectomy). Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- -> Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for women under 50 years old.
- -> Radiation-induced oophorectomy with last menses >1 year ago.
- -> Chemotherapy-induced menopause with >1 year interval since last menses.
- -> Age >50 years with >1 year interval since last menses.

Ausschlusskriterien

- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the post menopausal range for women under 50 years old

- Radiation-induced oophorectomy with last menses >1 year ago.
- Chemotherapy-induced menopause with >1 year interval since last menses
- Age >50 years with >1 year interval since last menses.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
- Patients with myelodysplastic syndrome/acute myeloid leukaemia or with features suggestive of MDS/AML*.
- Patients with known brain metastases.
- History of leptomeningeal carcinomatosis
- History of active primary immunodeficiency
- Active infection including tuberculosis (TB) (clinical evaluation that includes clinical history of TB, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive hepatitis B virus [HBV] surface antigen [HBsAg] result), hepatitis C (HCV), or human immunodeficiency virus (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc], followed by a negative hepatitis B virus DNA test and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
- Prior history of hypertensive crisis (Common Terminology Criteria for Adverse Events [CTCAE] Grade 4) or hypertensive encephalopathy*.
- Clinically significant (e.g. active) cardiovascular disease*, including: Myocardial infarction or unstable angina within <=6 months of randomisation, New York Heart Association (NYHA) Grade >=2 congestive heart failure (CHF)
- -> Poorly controlled cardiac arrhythmia despite medication (patient with rate controlled atrial fibrillation are eligible), or any clinically significant abnormal finding on resting electrocardiogram (ECG), Peripheral vascular disease Grade >=3 (eg, symptomatic and interfering with activities of daily living [ADL] requiring repair or revision)
- Previous cerebrovascular accident (CVA), transient ischemic attack (TIA) or intracranial bleeds (ie, intra-cerebral haemorrhage, sub-arachnoid haemorrhage or subdural haemorrhage) within 6 months prior to randomization*.
- Clinically significant ECG abnormality
- Non-healing wound, active ulcer or bone fracture
- Persistent toxicities CTCAE Grade >2 caused by previous cancer therapy
- Pre-existing sensory or motor neuropathy Grade >=2*16 Evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation)
- History of abdominal fistula or gastrointestinal perforation or active gastrointestinal bleeding within 6 months prior to randomisation
- Current signs or symptoms of bowel obstruction, including sub-occlusive disease, related to underlying disease
- Patient with evidence of abdominal free air not explained by paracentesis or recent surgical procedure
- History of allogenic organ transplantation including previous allogenic bone marrow transplant or double umbilical cord blood transplantation (dUCBT)*

- Patients considered a poor medical risk due to a serious, uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure (CHF), uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent
- Patients unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication*.
- Patients with a history of CTCAE Grade 4 proteinuria (Nephrotic Syndrome) prior to the Day 1 of Cycle 1
- Prior systemic anti-cancer therapy for ovarian cancer
- Prior treatment with PARP inhibitor or prior exposure to immune-mediated therapy, including but not limited to, anti- cytotoxic T lymphocyte-associated (CTLA-4), anti-programmed cell death protein 1 (PD-1), anti- programmed death-ligand 2 (PD-L1), or anti-programmed death-ligand 2 (PD-L2) antibodies, including therapeutic anticancer vaccines
- Planned intraperitoneal cytotoxic chemotherapy
- Other concurrent systemic anticancer therapy apart from the protocol specified. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) or bisphosphonates, if indicated, is acceptable*
- Current or prior use of immunosuppressive medication within 14 days before randomisation*. The following are exceptions to this criterion:
- -> Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
- -> Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication or as a premedication for paclitaxel) or as prophylaxis for CINE (chemotherapy-induced nausea or vomiting)
- Receipt of live attenuated vaccine within 30 days prior to Day 1 of Cycle 1*.
- (Note: Patients, if enrolled, should not receive live vaccine whilst receiving study treatment and up to 30 days after the last dose of study treatment.)
- Participation in another clinical study with an investigational product administered in the last 12 months
- Patients with a known hypersensitivity to olaparib, durvalumab or any of the excipients of these products
- Patients with a known hypersensitivity to the combination/comparator agents
- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).
- Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions and requirements
- Previous randomisation in the present study
- Breast feeding women

Alter	18 Jahre und älter
Sponsor	Astra Zeneca
Registrierung in anderen Studienregistern	ClinicalTrials.gov NCT03737643 (primäres Register) EudraCT 2017-004632-11
Links	Studiendokumente zum Download (roXtra)