Atezolizumab With Bevacizumab and Chemotherapy vs Bevacizumab and Chemotherapy in Early Relapse Ovarian Cancer

ClinicalTrials.gov Identifier: NCT03353831

Recruitment Status: Recruiting
First Posted: November 27, 2017
Last Update Posted: December 18, 2018

See Contacts and Locations

Sponsor:
AGO Research GmbH

Collaborator:
Hoffmann-La Roche

Information provided by (Responsible Party):
AGO Research GmbH

Study Description

Brief Summary:
This is a phase III, randomized, partially blinded, multicenter trial to evaluate the efficacy and safety of atezolizumab plus bevacizumab and chemotherapy compared to placebo plus bevacizumab and chemotherapy in patients with recurrent ovarian-, fallopian tube, or primary peritoneal cancer with 1st or 2nd relapse within 6 months after platinum based chemotherapy or 3rd relapse.

<table>
<thead>
<tr>
<th>Condition or disease</th>
<th>Intervention/treatment</th>
<th>Phase</th>
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</thead>
<tbody>
<tr>
<td>Recurrent Ovarian Carcinoma</td>
<td>Drug: Bevacizumab</td>
<td>Phase 3</td>
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<tr>
<td></td>
<td>Drug: Atezolizumab</td>
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<tr>
<td></td>
<td>Drug: Chemotherapy</td>
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<td>Drug: Placebos</td>
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Detailed Description:

Approximately 664 patients will be randomized in a 1:1 ratio to the treatments as specified below:

Arm A: Chemotherapy + Bevacizumab + Placebo
Arm B: Chemotherapy + Bevacizumab + Atezolizumab

Study treatment will continue until disease progression per RECIST v1.1, unacceptable toxicity, or patient or investigator decision to discontinue treatment. Atezolizumab/placebo, chemotherapy and bevacizumab may be discontinued for toxicity independently of each other in the absence of disease progression.

For each patient, chemotherapy (PLD or Paclitaxel weekly) will be selected by the investigator prior to randomization.

Recruitment to an individual chemotherapy cohort will be closed once 50% of patients are recruited to this cohort. In such case the remaining cohort will remain open for recruitment.

Study Design

- **Study Type**: Interventional (Clinical Trial)
- **Estimated Enrollment**: 664 participants
- **Allocation**: Randomized
- **Intervention Model**: Parallel Assignment
- **Masking**: Triple (Participant, Care Provider, Investigator)
- **Primary Purpose**: Treatment
- **Official Title**: Atezolizumab in Combination With Bevacizumab and Chemotherapy Versus Bevacizumab and Chemotherapy in Recurrent Ovarian Cancer - a Randomized Phase III Trial
- **Actual Study Start Date**: September 11, 2018
- **Estimated Primary Completion Date**: July 1, 2021
- **Estimated Study Completion Date**: July 1, 2022
## Arms and Interventions

<table>
<thead>
<tr>
<th>Arm</th>
<th>Intervention/treatment</th>
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| **Placebo Comparator: Arm A: Chemotherapy + Bevacizumab + Placebo**  
  **Chemotherapy: Paclitaxel 80 mg/m² d1, 8, 14, 22 q28**  
  **or pegylated liposomal doxorubicin 40 mg/m² q28**  
  **Bevacizumab 10 mg/kg q14 + Placebos q14** | **Drug: Bevacizumab**  
  Bevacizumab will be administered by intravenous route at a dose of 10mg/kg q14 during the treatment period  
  **Drug: Chemotherapy**  
  Chemotherapy (Paclitaxel or PLD) will be administered by intravenous route at different doses during the treatment period q28  
  **Drug: Placebos**  
  Placebo will be administered by intravenous route q14 during the treatment period |
| **Experimental: Arm B: Chemotherapy + Bevacizumab + Atezolizumab**  
  **Chemotherapy: Paclitaxel 80 mg/m² d1, 8, 14, 22 q28**  
  **or pegylated liposomal doxorubicin 40 mg/m² q28**  
  **Bevacizumab 10 mg/kg q14 + Atezolizumab 840 mg q14** | **Drug: Bevacizumab**  
  Bevacizumab will be administered by intravenous route at a dose of 10mg/kg q14 during the treatment period  
  **Drug: Atezolizumab**  
  Atezolizumab will be administered by intravenous route at a dose of 840 mg q14 during the treatment period  
  **Drug: Chemotherapy**  
  Chemotherapy (Paclitaxel or PLD) will be administered by intravenous route at
Outcome Measures

Primary Outcome Measures:

1. Overall Survival (OS) [Time Frame: time from randomization to death from any cause, assessed up to 40 months]
   - regular patient contacts during the trial regarding life status

2. Progression-free survival [Time Frame: time from randomization to progressive disease (PD) or death, whichever occurs earlier, assessed up to 40 months]
   - Progressive Disease is based on investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Secondary Outcome Measures:

1. Patient reported outcomes (QLQ and PRO-CTCAE) [Time Frame: every 4 weeks during the first 3 months, then every 12 weeks until PD#1, assessed up to 40 months]
   - questionnaires to be completed by patients and collected frequently during the trial

2. Objective Response Rate (ORR) [Time Frame: time from randomization to progressive disease (PD) or death, whichever occurs earlier, assessed up to 40 months]
   - Both criteria are based on investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

3. Duration of Response (DOR) [Time Frame: time from randomization to progressive disease (PD) or death, whichever occurs earlier, assessed up to 40 months]
   - Both criteria are based on investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

Other Outcome Measures:

1. Time from randomization to first subsequent therapy (TFST) [Time Frame: at every visit during the trial up to a maximum of 40 months]

2. Time from randomization to second subsequent therapy (TSST) [Time Frame: at every visit during the trial up to a maximum of 40 months]
Eligibility Criteria

Information from the National Library of Medicine

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, Learn About Clinical Studies.

Ages Eligible for Study: 18 Years and older (Adult, Older Adult)
Sexes Eligible for Study: Female
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Patients with histologically diagnosed ovarian, fallopian tube, or primary peritoneal cancer
2. Relapsed disease
3. Patients with up to three prior therapies. In patients with 1 or 2 prior treatment lines, the treatment free interval after platinum has to be less than 6 months; in addition patients with three prior lines of chemotherapy who are not considered for platinum-containing chemotherapy lines are also eligible
4. Measurable disease, evaluable disease in combination with GCIG CA-125 criteria, or histologically proven relapse/progression
5. Patient agrees and is able to provide a recent tumour biopsy (not older than 3 months) or agrees and has a tumour lesion amenable for taking a new tumor biopsy.
6. Availability of a representative archival FFPE tumor sample (preferable from primary diagnosis)
7. Patient has not progressed on the chosen/planned chemotherapy (PLD or Paclitaxel) in any prior line
8. Patients previously treated with bevacizumab are eligible, with the exclusion of those patients that has suspended bevacizumab for more than 2 subsequent cycles or permanently discontinued bevacizumab during their previous treatment due to toxicity. A washout period of at least 20 days after last bevacizumab treatment must be adhered.
9. Females aged ≥ 18 years at signing at time of signing informed consent form
10. Signed written informed consent and ability to comply with the study protocol, in the investigator's judgement
11. Adequate hematological, renal and hepatic function within 28 days prior to first administration of study treatment: Hemoglobin ≥ 9.0 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), Aspartate aminotransferase /Serum Glutamic Oxaloacetic Transaminase (ASAT/SGOT) and Alanine
aminotransferase /Serum Glutamic Pyruvate Transaminase (ALAT/SGPT) ≤ 2.5 x ULN, unless liver metastases are present, in case of liver metastases values must be ≤ 5 x ULN, Serum creatinine ≤ 1.5 x institutional ULN, Patient not receiving anticoagulant medication who has an International Normalized Ratio (INR) ≤ 1.5 and an Activated ProThrombin Time (aPTT) ≤ 1.5 x ULN, Urine dipstick for proteinuria < 2+. If urine dip-stick is ≥ 2+, 24-hours urine must demonstrate ≤ 1 g of protein in 24 hours.

12. Patients must have adequately controlled blood pressure (BP), with a systolic BP of ≤ 140 mmHg and diastolic BP of ≤ 90 mmHg for eligibility. Patients must have a BP of ≤ 140/90 mmHg taken in the clinic setting by a medical professional within 2 weeks prior to starting study.

13. Estimated life expectancy of at least 3 months

14. ECOG performance status 0 - 1

15. Negative urine or serum pregnancy test within 7 days of study treatment in women of childbearing potential (WOCBP), confirmed prior to treatment on day 1

16. For women of childbearing potential: agreement to re-main abstinent (refrain from heterosexual intercourse) or use a contraceptive method with a failure rate of < 1% per year during the treatment period and for at least 5 months after administration of the last dose of atezolizumab/placebo and 6 months after the last dose of bevacizumab, paclitaxel, or PLD, whichever is later.

17. For countries where this will apply to: a patient will be eligible for randomization in this study only, if either affiliated to, or a beneficiary of a social security category.

18. Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures, that include the completion of patient-reported outcomes questionnaires.

Exclusion Criteria:

1. Non-epithelial tumor origin of the ovary, the fallopian tube or the peritoneum (i.e. germ cell tumors)

2. Ovarian tumors of low malignant potential (e.g. borderline tumors)

3. Malignancies other than ovarian cancer within 5 years prior to randomisation, with the exception of those with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%) and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, non melanoma skin carcinoma, ductal carcinoma in situ, or Stage I uterine cancer)

4. More than three prior systemic anticancer regimens; maintenance therapies (e.g. with bevacizumab, olaparib or niraparib) are not calculated as separate line.

5. Prior systemic anticancer therapy within 28 days before randomization (except bevacizumab: 20 days).

6. Prior radiotherapy to the pelvis or the abdomen.

7. Administration of other simultaneous chemotherapy drugs, any other anticancer therapy or anti-neoplastic hormonal therapy, or simultaneous radiotherapy during the trial treatment period (hormonal replacement therapy is permitted).

8. Prior treatment with CD137 or immune checkpoint blockade therapies, anti-PD1, or anti-PD-L1 therapeutic antibodies or anti-CTLA 4

10. Treatment with systemic immunostimulatory agents (including but not limited to interferon-alpha and interleukin-2 within 4 weeks or five half-lives of the drug (whichever is longer) prior to Cycle 1, Day 1
11. Treatment with systemic corticosteroids or other systemic immunosuppressive medications (including but not limited to prednisone, dexamethasone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [TNF] agents) within 2 weeks prior to Cycle 1, Day 1, or anticipated requirement for systemic immunosuppressive medications during the trial
12. the use of inhaled corticosteroids for chronic obstructive pulmonary disease, mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension, and low-dose supplemental corticosteroids for adrenocortical insufficiency are allowed
13. Prophylactic antiemetic corticosteroids shall be avoided if possible in patients treated with pegylated liposomal doxorubicin regimen. The use of corticosteroids is allowed as premedication for paclitaxel regimen and/or premedication in case of any hypersensitivity
14. Patients with a history of allergic reaction to IV contrast requiring steroid pre-treatment should have screening and subsequent tumor assessments performed using magnetic resonance imaging (MRI)
15. Administration of a live, attenuated vaccine within 4 weeks prior to Cycle 1, Day 1 or anticipation that such a live attenuated vaccine will be required during the study or within 5 months after the last dose of atezolizumab/placebo. Influenza vaccination should be given during influenza season only. Patients must not receive live, attenuated influenza vaccination
16. Major surgery within 4 weeks of starting study treatment or patient who has not completely recovered from the effects of any major surgery. Core biopsy or other minor surgical procedure within 7 days prior to Day 1, Cycle 1 is permitted.
17. Previous allogeneic bone marrow transplant or previous solid organ transplantation
18. Current treatment with anti-viral therapy for HBV.
19. History of idiopathic pulmonary fibrosis (including pneumonitis), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan. History of radiation pneumonitis in the radiation field (fibrosis) detected on screening chest CT scan is permitted
20. Previous Cerebro-Vascular Accident (CVA), Transient Ischemic Attack (TIA) or Sub-Arachnoids Hemorrhage (SAH) within 6 months prior to randomization
21. History or evidence of thrombotic or hemorrhagic disorders within 6 months prior to randomization
22. History or clinical suspicion of brain metastases or spinal cord compression. CT/MRI of the brain is mandatory (within 4 weeks prior to randomization) in case of suspected brain metastases. Spinal MRI is mandatory (within 4 weeks prior to randomization) in case of suspected spinal cord compression
23. History of autoimmune disease, including but not limited to dermatomyositis, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener’s granulomatosis, Sjögren’s syndrome, Guillain-Barre syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
24. Any prior history of hypertensive crisis (CTCAE grade 4) or hypertensive encephalopathy
25. Immunocompromised patients, e.g., patients who are known to be serologically positive for human
immunodeficiency virus (HIV). Patients with active hepatitis B (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C

26. Persistent toxicities (≥ CTCAE grade 2) with the exception of alopecia, caused by previous cancer treatment. Neurotoxicity CTCAE grade 2 is permitted in case the patient is planned for PLD treatment

27. Severe infection requiring oral or IV antibiotics within 4 weeks prior to randomization, including but not limited to active tuberculosis or hospitalization for complications of infection, bacteremia, or severe pneumonia. Patients receiving prophylactic antibiotics (e.g., to prevent an urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.

28. Current or recent (within 10 days prior randomization) chronic use of aspirin > 325 mg/day

29. Clinically significant (e.g. active) cardiovascular disease, including:
   - Myocardial infarction or unstable angina within ≤ 6 months of randomization
   - New York Heart Association (NYHA) ≥ grade 2 congestive heart failure (CHF)
   - Poorly controlled cardiac arrhythmia despite medication (patients with rate controlled atrial fibrillation are eligible)
   - Peripheral vascular disease grade ≥ 3 (e.g. symptomatic and interfering with activities of daily living [ADL] requiring repair or revision)
   - Resting ECG with QTc >470 msec or family history of long QT syndrome

30. Left ventricular ejection fraction defined by ECHO below the institutional lower limit of normal

31. Evidence of bleeding diathesis or significant coagulopathy (in the absence of anticoagulation)

32. Non-healing wound, active ulcer or bone fracture

33. History of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, GI perforation, or intra-abdominal abscess, or evidence of rectosigmoid involvement by pelvic examination, bowel involvement on computed tomography, or clinical symptoms of bowel obstruction

34. Patients with evidence of abdominal free air

35. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment related complications

36. Known hypersensitivity or allergy to drugs containing Chinese hamster (CHO) ovary cells or history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins

37. Known hypersensitivity reaction or allergy to drugs chemically related to bevacizumab, paclitaxel, pegylated liposomal doxorubicin, or their excipients that contraindicates the subject's participation

38. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. This includes also any psychiatric disorder that prohibits obtaining informed consent

39. Pregnancy, lactation, or intention to become pregnant during the study or within 5 months after the last dose of Atezolizumab/placebo.
## Bevacizumab

Additional relevant MeSH terms:

<table>
<thead>
<tr>
<th>Term</th>
<th>Term</th>
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<tbody>
<tr>
<td>Ovarian Neoplasms</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Carcinoma, Ovarian Epithelial</td>
<td>Bevacizumab</td>
</tr>
<tr>
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<td>Atezolizumab</td>
</tr>
<tr>
<td>Neoplasms by Site</td>
<td>Liposomal doxorubicin</td>
</tr>
<tr>
<td>Neoplasms</td>
<td>Doxorubicin</td>
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<td>Ovarian Diseases</td>
<td>Antibodies, Monoclonal</td>
</tr>
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<td>Antineoplastic Agents, Phytogenic</td>
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<td>Endocrine System Diseases</td>
<td>Mitosis Modulators</td>
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<td>Molecular Mechanisms of Pharmacological Action</td>
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<td>Antineoplastic Agents, Immunological</td>
</tr>
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</tr>
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