A randomized, double blinded, phase III study of atezolizumab versus placebo in patients with late relapse of epithelial ovarian, fallopian tube, or peritoneal cancer treated by platinum-based chemotherapy and bevacizumab

ATALANTE SYNOPSIS

ATezolizumab and **A**vastin in **LA**te recurre**NT** diseas**E**

GINECO-OV236b		ENGOT-ov29	EudraCT N°	2015-005471-24
Development Phase	Randomized Phase III	Subject	Ovarian Carcinoma in late relapse (platinum-free interval > 6 months)	

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Study title	**A RANDOMIZED, DOUBLE BLINDED, PHASE III STUDY OF ATEZOLIZUMAB VERSUS PLACEBO IN PATIENTS WITH LATE RELAPSE OF EPITHELIAL OVARIAN, FALLOPIAN TUBE, OR PERITONEAL CANCER TREATED BY PLATINUM-BASED CHEMOTHERAPY AND BEVACIZUMAB**
Study Code	**ATALANTE**: **AT**ezolizumab and **A**vastin in **LA**te recurre**NT** diseas**E**
EudraCT number	2015-005471-24
Sponsor ID	ARCAGY-GINECO: (**A**ssociation de **R**echerche contre les **CA**ncers dont **GY**nécologiques)
Participating groups	ENGOT (European Network of Gynecology Oncology Trial): GINECO (France), AGO (Germany), AGO Austria (Austria); GEICO (Spain), ISGO (Israël), NSGO (Nordic Countries), BGOG (Belgium); CEECOG (Czech Republic)
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Coordinating Investigator	Prof. Jean-Emmanuel Kurtz MD, PhD Hôpitaux Universitaires de Strasbourg, France
Statistician	Prof Bernard Asselain, MD, PhD Paris , France
Patient and site Number	405 patients recruited in approximately 100 sites
Indication	Patients with epithelial ovarian cancer (including patients with primary peritoneal and / or fallopian tube adenocarcinoma) who have first or second late relapse (platinum-free interval > 6 months)
Study Calendar	**First Patient In:** Q3 2016 **Accrual period:** 30 months **Last Patient In:** Q1 2019 **Primary analysis:**Q3 2020 **Follow-up period:** 44 months **Clinical Study Report** Q3 2023
Background	Ovarian cancer (OC) is the fifth most common cause of death from cancer in women. In the European Community, approximately 28,000 new cases of ovarian cancer and approximately 17,000 deaths are reported annually, ranking ovarian cancer as the leading cause of death from gynecological cancer. More than 70% of the patients are diagnosed with advanced disease. Despite initial therapy combining debulking surgery, standard chemotherapy with platinum and taxane regimen and bevacizumab (an anti-VEGF monoclonal antibody targeting blood vessels of the malignant tumor microenvironment), 70% of the patients with advanced OC will relapse. Late relapse (LR) or platinum-sensitive relapse (PSR) occurs more than 6 months after the last dose of platinum. Standard chemotherapy for late relapse consists of carboplatin combinations either with gemcitabine (Pfisterer J et al, 2010), paclitaxel (ICON4) or pegylated liposomal doxorubicin (PLD) (Pujade-Lauraine E, et al, 2010). Bevacizumab has been registered in EU for patients with LR treated with the carboplatin-gemcitabine regimen (OCEANS trial, Aghadjanian C et al 2012). More recently, bevacizumab has been reported to also significantly prolong median PFS of patients with PSR when combined with carboplatin and paclitaxel (GOG-0213 trial, Coleman R et al, 2015). Encouraging preliminary results of the carboplatin-PLD - bevacizumab combination (del Carmen MG et al, 2012) are being tested in a phase III trial (AGO-OVAR 2.21 trial) with carboplatin-gemcitabine-bevacizumab as comparator. **OC is an immunogenic tumor: evidence**

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	Approximately half of OC patients display a spontaneous antitumor immune response by antibodies (Stone B et al 2003, Reuschenbach M, et al 2009) and oligoclonal T-cells (Schlienger et al , 2003) which recognize autologous tumor-associated antigens (TAAs). OC exhibits an extreme degree of heterogeneity of TAAs with an average of 60 private nonsynonymous mutations per tumor which are rarely shared among different tumors. Within the tumor, a spontaneous antitumor immune response has been demonstrated in approximately 55% of the patients with OC in the form of intraepithelial tumor-infiltrating lymphocytes (TILs) (Zhang Let al, 2003) which has been repeatedly associated with a prolonged survival among ovarian cancer patients (Hwang WT et al, 2012). If the immune system is able to target OC tumors and influence survival, ovarian cancer cells can also exploit several mechanisms to evade immunologic elimination. Immune evasion mechanisms includes the recruitment of immunosuppressive cells such as regulatory T cells (Curiel TJ et al, Nat Med 2004), tumor-associated macrophages (TAMs) (Zhang QW, et al. 2012) or immature dendritic cells which have been correlated with poor survival. The immunosuppressive environment is further augmented in OC by the expression of T cell inhibitory receptors on tumor cells and immune cells. **The PD-L1/PD1 immunosuppressive pathway in Ovarian Cancer** Though data remains scarce, high IHC PD-L1 expression (score 2 & 3) has been detected in 68% of ovarian cancer patients (n=70) and that expression of PD-L1 had a strong prognostic value (Hamanashi J, 2007). The authors found also that the density of intraepithelial CD8+ T cells was inversely correlated to expression of PD-L1 by tumors, suggesting that the expression of PD-L1 on tumor cells may inhibit invasion of tumor epithelium by CD8+ T cells. In addition, PD-1 expression at the surface of intra-tumoral CD4+ FOXP3+ Tregs was found to show the highest levels in ovarian cancer (around 20% of the cells) compared to other tumor types, including melanoma, renal cell cancer or hepatoma (Kryczek et al., 2009). Thus targeting PD-1/PD-L1 pathway may inhibit Treg expression, one of the major component of ovarian cancer immunosuppression. Also Curiel et al showed that myeloid dendritic cells (MDCs) from ovarian cancer express PD-1 and that blockade of PD-1 enhanced MDC-mediated T-cell activation, including upregulation of IL-2 and interferon-gamma, and down regulation of IL-10, which resulted in enhanced T-cell immunity against autologous ovarian human tumors into NOD-SCID mice. (Curiel et al, 2003). Together with the aforementioned data on immune infiltration, these data provide the rationale for a therapeutic PD-1/PD-L1 pathway blockade in ovarian cancer. **Immune checkpoint inhibitors: anti-PD1 & anti-PD-L1 in Ovarian Cancer** In ovarian carcinoma patients, the anti-PD1 compound nivolumab has been reported to achieve 3 objectives responses out of 13 (23%) heavily pre-treated patients (Hamanishi J, ASCO 2014). Response was prolonged over 1 year in 2 out of the 3 responders (Hamanishi J, ASCO 2015). Similarly, the anti-PD1 pembrozilumab achieved 3 confirmed responses (11.5% [(95% CI, 2.4-30.2]) in 26 patients treated in a phase IB study and 3 additional patients had a tumor reduction of at least 30%. Most common AEs were fatigue (42.3%), anemia (30.8%), and decreased appetite (30.8%). Drug-related AEs occurred in 69.2% of pts (grade ≥ 3, 1/26 pts) (Varga A et al, 2015). The anti-PD-L1 avelumab has reported a 10.7% objective response and a 44% stabilization rate in 75 patients with ovarian cancer in relapse (Disis M et al, 2015). In this study, confirmed or unconfirmed responses (n=11) tend to be more frequently observed in patients with low burden of tumor, limited number of prior lines of

chemotherapy and in the setting of platinum-sensitivity. Toxicity was minimal. Considering all grades, fatigue was observed in 16% of the patients, chills in 12%, nausea in 10.7%, diarrhea in 10.7%, rash in 8% and hypothyroidism in 5.3%. Only 6 patients experienced treatment-related CTCAE grade 3 toxicity with none occurring in more than one patient (peripheral edema, localized edema, tumor pain, arthritis, myositis, increased level of lipase, CPK, glycemia and anemia).

Rationale for combining atezolizumab and bevacizumab

There are several data suggesting that atezolizumab and bevacizumab may be synergistic. Enhanced tumor angiogenesis is commonly associated with absence of tumor-infiltrating T cells in patients (Bouma-ter Steege JC et al, 2004). There is evidence in OC that tumor expression of VEGF is negatively correlated to the density of CD3+TILs (Zhang L et al 2003) and this phenotype is associated with early recurrence, consistent with prior studies showing a correlation of VEGF to early recurrence and short survival. Furthermore, in ascites, high levels of VEGF correlate to low numbers of NK T-like CD3+CD56+ cells (Bamias et al, 2008).

In addition to promoting tumor angiogenesis, there is increasing evidence that VEGF plays a role in cancer immune evasion through several different mechanisms (Ohm et al 2001). For example, experiments with activated endothelial cells suggest that in the tumor microenvironment, VEGF may reduce lymphocyte adhesion to vessel walls, thus contributing to decreased immune-cell recruitment to the tumor site (Bouzin Cet al. 2007). Indeed, emerging evidence suggests that the endothelium acts as a selective barrier, allowing certain T cell subsets, notably T regulatory (Treg) cells, to traffic more effectively contributing to tumor immune tolerance (Motz GT et al, 2014). In addition, some experiments have shown that tumour hypoxia promotes the recruitment of regulatory T (Treg) cells through induction of expression of the chemokine CC-chemokine ligand 28 (CCL28), which, in turn, promotes tumour tolerance and angiogenesis. Some immunosuppressive activities of VEGF, however, can be reversed by inhibition of VEGF signaling.

Mice exposed to pathophysiologic levels of VEGF exhibited impaired dendritic cell function (Omaya T et al, 1998), which could be restored by blockade of VEGFR2 (Huang et al 2007). Conversely, angiogenesis blockade requires CD8+T cell (Motz GT et al, 2014) supporting the notion that VEGF-A do not simply promote tumor growth through angiogenesis. Thus, peripheral immune tolerance and angiogenesis programs seem closely connected and apparently cooperate to sustain tumour growth (Facciabene A et al, 2011).

In addition, there is evidence that anti-VEGF therapy and immunotherapy act synergistically. Motz et al have suggested that the combination of anti-VEGF-A antibody and immunotherapy with adoptive T cell transfer led to a superior infiltration of tumor-reactive T cells than single approach (Motz GT et al, 2014). Indeed, in a murine melanoma model, VEGF blockade synergized with adoptive immunotherapy, as evidenced by improved anti-tumor activity, prolonged survival, and increased trafficking of T cells into tumors (Shrimali et al. 2010). These data are reminiscent of the additive benefit observed in patients by combining recombinant interferon-alpha therapy and bevacizumab, a recombinant, humanized therapeutic antibody directed against VEGF, for the treatment of metastatic renal cell carcinoma (Rini BI et al, 2010).

More evidence has come from a clinical study of subjects with melanoma combining a checkpoint inhibitor (anti–CTLA-4; ipilimumab) and bevacizumab (Hodi FS et al, 2014; Garber K, 2014). In 46 patients, the combined therapy yielded a 19.6% objective

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	response rate, stable disease in 13%. All responses were durable > 6 months and median survival was 25.1 months, much prolonged compared to ipilimumab expectation in metastatic melanoma. Activated vessel endothelium with extensive CD8+ T cell and macrophage cell infiltration was observed in post-treatment biopsies, as well as marked increases in CD4/CCR7/CD45ROm central memory cells in peripheral blood in the majority of patients. Because of the intimate relationship between angiogenesis and immunosuppression, it is thus expected that inhibiting both pathways will result in improved and more durable clinical benefit.
Study Objectives	**PRIMARY OBJECTIVE** To determine the efficacy of combining atezolizumab with carboplatin-based chemotherapy and bevacizumab compared to placebo with carboplatin-based chemotherapy and bevacizumab in patients with late (platinum-sensitive) relapse of epithelial ovarian, fallopian tube, or peritoneal cancer. The primary outcome measure is progression free survival (PFS1), where the date of progression is based on investigator assessment using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). **SECONDARY OBJECTIVES** <u>Secondary supportive objectives</u> To determine the efficacy of atezolizumab compared to placebo on: • Time from randomization to second subsequent therapy or death (TSST) • Health-related Quality of Life (HRQoL) and patient reported outcomes (PROs) as measured by EORTC QLQ-C30, and OV28. • Long term survival using the cure rate modelling • Overall survival (OS) <u>Others secondary objectives</u> To determine the efficacy of atezolizumab compared to placebo on: • Objective Response Rate (ORR) as assessed by RECIST v1.1 and Immune related RECIST (irRECIST) • PFS1 as assessed per irRECIST • Characterization of CA-125 tumor marker levels and their relation to tumor response and PFS1 as measured by RECISTv 1.1 and irRECIST • Time from randomization to first subsequent therapy or death (TFST) • Time from randomization to second progression (PFS2) To determine the efficacy of atezolizumab compared to placebo in the PD-L1-ve and PD-L1 +ve subgroups To assess the safety and tolerability of atezolizumab compared to placebo To evaluate the impact of treatment and disease on resource use as measured by different criteria including EuroQoL 5 Dimension (EQ-5D) questionnaire.

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	EXPLORATORY OBJECTIVES 1. To explore pre-planned subgroups analyses of efficacy (PFS) based on relevant potential prognostic factors, including stratification factors, as well as on the performance or not of secondary cytoreductive surgery. 2. To explore the correlation between geriatric assessment and efficacy and tolerance of atezolizumab versus placebo for patients ≥ 70 years old. 3. To evaluate the relationship between the expression of PD-L1, tumor mutational load and intraepithelial TILs with ORR and PFS during experimental treatment and at the subsequent line of therapy 4. To assess immune-related and other potential predictive and prognostic exploratory biomarkers in de novo/archival tissue and blood and their association with disease status and/or efficacy as defined by ORR and PFS during experimental treatment and at the subsequent line of therapy 5. To evaluate the relationship between PD-L1, TILs and biomarker status in archival tissue and in de novo tumor specimens. 6. To evaluate the utility of biopsy at the time of apparent disease progression to distinguish apparent increases in tumor volume related to immunomodulatory activity of atezolizumab (i.e., pseudoprogression/tumor immune infiltration) from true disease progression as determined by confirmatory CT scan for disease progression and PFS. 7. To explore whether resistance mechanisms to atezolizumab plus bevacizumab versus placebo plus bevacizumab alone can be identified through analysis of tumor and blood samples – archival tumor, de novo tumor biopsy and blood sample at baseline (mandatory), tumor biopsy and blood sample on progression (optional). 8. To collect and store ctDNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to study treatments

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Study Population	**INCLUSION CRITERIA** I-1. Female Patients must be ≥18 years of age. I-2. Signed informed consent and ability to comply with treatment and follow-up. I-3. Patients with histologically confirmed progressive non-mucinous epithelial ovarian cancer, primary peritoneal adenocarcinoma and / or fallopian-tube adenocarcinoma I-4. Patients with PD-L1 status determined for stratification on mandatory de novo biopsy sent to central laboratory as a formalin-fixed, paraffin-embedded (FFPE) sample. - Cell pellet from pleural effusion, or ascites or lavage are not acceptable. - For core needle biopsy specimens, at least three cores should be obtained. Biopsies must be obtained in a manner that minimizes risks for the patient and maximizes the chance to get tumor tissue. In case the core biopsies do not contain significant tumor tissue, patient eligibility should be discussed with the sponsor I-5. Patients whose disease has relapsed more than 6 months from the last dose of platinum before randomization: a) criterion for relapse can be according to RECIST v1.1, CA-125 (GCIG) or clinical symptoms b) the interval between last dose of platinum and entry in the study should be free of new anti-cancer treatment, with the exception of a maintenance therapy which is allowed up to 21 days before study entry. I-6. Patients with one or 2 prior lines of chemotherapy. The last line of chemotherapy should have included platinum. I-7. Availability at the study site of representative FFPE tumor sample from surgery during front line therapy, at best before chemotherapy I-8. Patients must have normal organ and bone marrow function : a) Haemoglobin ≥ 10.0 g/dL. b) Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L. c) Platelet count ≥ 100 x 10^9/L. d) Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). e) 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 which case they must be ≤ 5 x ULN. f) Serum creatinine ≤ 1.5 x institutional ULN, g) Patients not receiving anticoagulant medication who have an International Normalized Ratio (INR) ≤1.5 and an Activated ProThrombin Time (aPTT) ≤1.5 x ULN. The use of full-dose oral or parenteral anticoagulants is permitted as long as the INR or APTT is within therapeutic limits (according to site medical standard) and if the patient is on a stable dose of anticoagulants for at least two weeks at the time of randomization. h) Urine dipstick for proteinuria < 2+. If urine dipstick is ≥2+, 24-hours urine must demonstrate ≤1 g of protein in 24 hours. i) Normal blood pressure or adequately treated and controlled hypertension (systolic BP ≤ 150mmHg and diastolic BP ≤100mmHg). I-9. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 ***For France only***: In France, a subject will be eligible for randomization in this study only if either affiliated to, or a beneficiary of, a social security category.

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EXCLUSION CRITERIA

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

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

E-3. Patients with synchronous primary endometrial cancer unless both of the following criteria are met:

a) stage < II,

b) Less than 60 years old at the time of diagnosis of endometrial cancer with stage IA or IB grade 1 or 2, or stage IA grade 3 endometrioid adenocarcinoma
OR ≥ 60 years old at the time of diagnosis of endometrial cancer with stage IA grade 1or 2 endometrioid adenocarcinoma.

c) Patients with serous or clear cell adenocarcinoma or carcinosarcoma of the endometrium are not eligible.

E-4. Other malignancy within the last 5 years except cervix or breast in situ carcinoma, breast cancer ≥ 3 years free of disease and treatment, type I stage I endometrial cancer).

E-5. Patients receiving radiotherapy within 6 weeks prior to study treatment.

E-6. Major surgery within 4 weeks of starting study treatment or patients who have not completely recovered from the effects of any major surgery. Core biopsy or other minor surgical procedure, excluding placement of a vascular access device, within 7 days prior to Day 1, Cycle 1

E-7. Previous allogeneic bone marrow transplant or previous solid organ transplantation.

E-8. 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).

E-9. Prior treatment with CD137 agonists or immune checkpoint blockade therapies, anti−PD1, or anti−PDL1 therapeutic antibodies or anti-CTLA 4.

E-10. Treatment with systemic immunostimulatory agents (including but not limited to interferon-alpha (IFN-α) and interleukin-2 (IL-2) within 4 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1

E-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

a) 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.

b) Prophylactic anti-emetic corticosteroids will be avoided if possible in patients treated with pegylated liposomal doxorubicin-carboplatin or gemcitabine-carboplatin regimen. The use of corticosteroids is allowed as premedication for paclitaxel-based regimen and/or premedication in case of carboplatin hypersensitivity.

E-12. History of autoimmune disease, including but not limited to 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-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Are eligible patients with: a) a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone b) controlled Type 1 diabetes mellitus on a stable insulin regimen E-13. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis. Radiation pneumonitis in the radiation field (fibrosis) detected on screening chest CT scan is permitted E-14. 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. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. E-15. Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1 E-16. 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. Influenza vaccination should be given during influenza season only (example approximately October to March in the Northern Hemisphere). Patients must not receive live, attenuated influenza E-17. Current or recent (within 10 days prior to randomization) chronic use of aspirin > 325 mg/day. E-18. Prior history of hypertensive crisis (CTC-AE grade 4) or hypertensive encephalopathy. E-19. Inadequately controlled HTN (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg on antihypertensive medications) E-20. Clinically significant (e.g. active) cardiovascular disease, including: a) Myocardial infarction or unstable angina within ≤ 6 months of randomization, b) New York Heart Association (NYHA) ≥ grade 2 congestive heart failure (CHF), c) Poorly controlled cardiac arrhythmia despite medication (patients with rate controlled atrial fibrillation are eligible), d) Peripheral vascular disease grade ≥ 3 (e.g. symptomatic and interfering with activities of daily living [ADL] requiring repair or revision) E-21. Resting ECG with QTc > 470 msec on 2 or more time points within a 24 hour period or family history of long QT syndrome. E-22. Left ventricular ejection fraction defined by MUGA/ECHO below the institutional lower limit of normal (only applicable for patients intended to be treated with pegylated liposomal doxorubicin). E-23. Previous Cerebro-Vascular Accident (CVA), Transient Ischemic Attack (TIA) or Sub-Arachnoids Hemorrhage (SAH) within 6 months prior to randomization. E-24. History or evidence of hemorrhagic disorders within 6 months prior to randomization. E-25. Evidence of bleeding diathesis or significant coagulopathy (in the absence of coagulation).

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	E-26. 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. E-27. History or evidence upon neurological examination of central nervous system (CNS) disease, unless adequately treated with standard medical therapy (e.g. uncontrolled seizures). E-28. Significant traumatic injury during 4 weeks prior to randomization. E-29. Non-healing wound, active ulcer or bone fracture. Patients with granulating incisions healing by secondary intention with no evidence of facial dehiscence or infection are eligible but require 3 weekly wound examinations. E-30. History of VEGF therapy related abdominal fistula or gastrointestinal perforation. E-31. Current, clinically relevant bowel obstruction, including sub-occlusive disease, related to underlying disease. E-32. Patients with evidence of abdominal free air not explained by paracentesis or recent surgical procedure. E-33. Evidence of any other disease, metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment related complications. E-34. Women of childbearing potential (<2 years after last menstruation and not surgically sterile) not willing to use highly-effective means of contraception (Appendix 1) during the study and for 6 months after the last dose of study medication. E-35. Pregnant or lactating women. E-36. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins. E-37. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or to any component of the atezolizumab formulation. E-38. Known hypersensitivity reaction or allergy to drugs chemically related to bevacizumab, carboplatin, gemcitabine, paclitaxel, pegylated liposomal doxorubicin, or their excipients that contraindicates the subject's participation.

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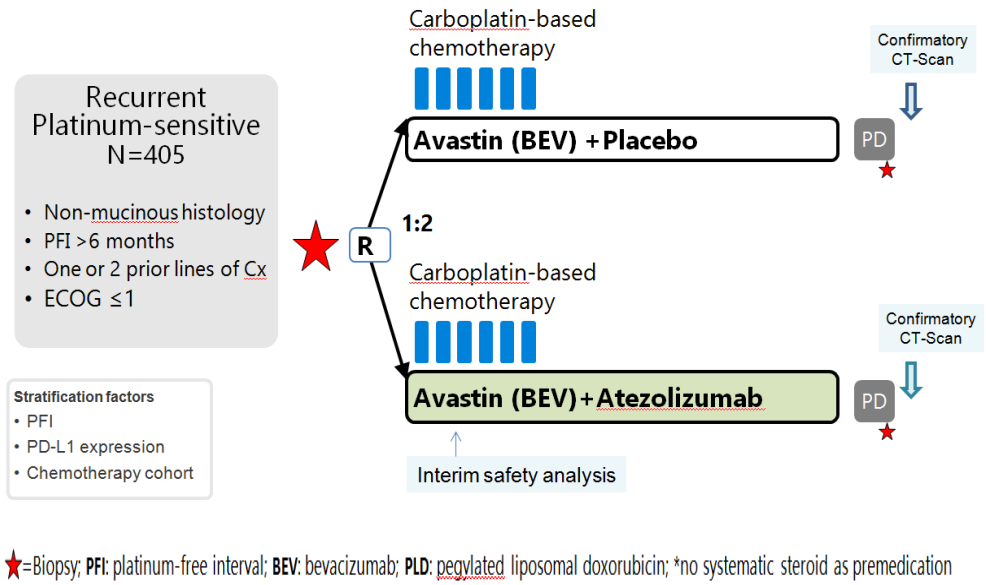
Study Design



★=Biopsy; **PFI**: platinum-free interval; **BEV**: bevacizumab; **PLD**: pegylated liposomal doxorubicin; *no systematic steroid as premedication

This is a phase III, randomized, double-blinded, comparative, multi-centre study to assess the efficacy of atezolizumab in combination with platinum-based chemotherapy plus bevacizumab administered concurrent to chemotherapy and in maintenance, in patients presenting epithelial ovarian cancer (including patients with primary peritoneal and / or fallopian tube adenocarcinoma) who have platinum-sensitive relapse (platinum-free interval > 6 months).

Approximately 405 patients will be randomized using an Interactive Voice Response System /Interactive web system (IVR/IWR system) in a 1:2 ratio to the treatments as specified below:

A. **Arm A: Placebo** + bevacizumab & platinum-based chemotherapy.

   The placebo arm will include one of 3 following regimens up to investigator choice (chosen prior to randomization)

   1. Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m2, d1 & d8) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w until disease progression or
   2. Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + placebo (1200mg, d1) x 6 cycles every 3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w until disease progression or
   3. Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + placebo (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + placebo (1200mg, d1) q3w until disease progression.

B. **Arm B: Atezolizumab** + bevacizumab & platinum-based chemotherapy

   The atezolizumab arm will include one of 3 following regimens up to investigator choice (chosen prior to randomization)

   1. Carboplatin (AUC = 4, d1) combined with gemcitabine (1000 mg/m², d1 & d8) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles

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	q3wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w until disease progression or 2. Carboplatin (AUC = 5, d1) combined with paclitaxel (175 mg/m², d1) and bevacizumab (15mg/kg, d1) + atezolizumab (1200mg, d1) x 6 cycles every 3wk (1200mg, d1) q3w until disease progression or 3. Carboplatin (AUC = 5, d1) combined with pegylated liposomal doxorubicin (PLD) (30 mg/m², d1) and bevacizumab (10mg/kg, d1 & 15) + atezolizumab (800mg, d1& 15) x 6 cycles every 4wk followed by maintenance with bevacizumab (15 mg/kg, d1) + atezolizumab (1200mg, d1) q3w until disease progression. **Before randomization to the study:** • A tumor biopsy should have been obtained within 2 months from randomization and sent to the central lab • PD-L1 status should be known **Randomization will be stratified by 3 factors**: 1. Platinum-free interval (6-12 months vs > 12 months) *When several disease progression criteria are met before randomization, the date of RECIST v1.1 disease progression on imaging will be chosen in priority as date of relapse to calculate the platinum-free interval* 2. PD-L1 expression : ✓ negative ✓ positive ✓ non informative *PD-L1 positivity will be defined as ≥ 1% of immune cells (ICs) expressing PD-L1 which will be referred to IC1/2/3 according to PD-L1 scoring algorithm* 3. Chemotherapy cohort chosen by the investigator ✓ carboplatin-gemcitabine ✓ carboplatin-PLD ✓ carboplatin-paclitaxel
Investigational medicinal and comparator products, dosage and mode of administration	Atezolizumab and placebo are available as glass vial of 1200 mg. Patients will be administered study treatment as I.V. infusion at a fixed dose of 1200mg q3weeks or 800mg q2 weeks according to the companion chemotherapy regimen schedule. Atezolizumab/placebo is provided in a single-use, 20-cc USP/Ph. Eur. Type 1 glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab/placebo solution. Bevacizumab is provided in this trial. Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid ready for parenteral administration. Each 400-mg (25-mg/mL) glass vial contains 16 mL of bevacizumab with a vehicle consisting of sodium phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP. Vials contain no preservative and are for single use only intended for use solely in clinical trials.
Duration of the study	Patients should continue to receive study treatment until objective radiological disease progression as per RECIST v1.1 as assessed by the investigator if they do not

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	meet any other discontinuation criteria. Once patient have been discontinued from study treatment, other treatment options will be at the discretion of the investigator. Even after objective radiological disease progression, study treatment may be continued as long as patients are experiencing clinical benefit as assessed by investigator.
Statistical Considerations	***Primary endpoint will be the Progression Free Survival (PFS1)*** ▪ *First progression-free survival definition (PFS1)* PFS1 is defined as the time from randomization until the date of the first objective radiological disease progression according to investigator assessment of RECIST version 1.1 or death. ▪ *Control (placebo) arm median PFS assumption* The median PFS1 of the control arm (placebo arm with bevacizumab concurrent to chemotherapy and in maintenance) is extrapolated from the 2 large phase III trials run in patients with platinum-sensitive relapse of ovarian cancer. The median PFS of patients treated with carboplatin-gemcitabine + bevacizumab in the OCEANS study (Agadjanian C et al) was 12.4 months whereas it was 13.8 months for those included in the carboplatin-paclitaxel-bevacizumab arm of the GOG-0213 trial (Coleman R et al). In the study reported by Del Carmen et al exploring the carboplatin-PLD-bevacizumab combination in platinum-sensitive disease, the observed median PFS (14 months) falls within the range of the 2 previous studies. Thus the median PFS in the control arm is expected to be close to 13 months. ▪ *Sample size calculation* With the addition of atezolizumab compared to placebo, it is expected to increase the median PFS from 13 months to 18.57 months, corresponding to a 30% reduction of the risk of progression (average HR of 0.70) and a difference of median PFS of 5.57 months which is considered by patients as clinically relevant (Herzog T et al. 2014) According to Freedman's method accepting a type I error (two tailed) of 5% and a 80% power, 405 patients (270 +135 in a 2:1 randomization) have to randomized and 278 events observed for the primary analysis. Target recruitment is 405 patients. However up to an additional 10% of the total number (40 patients) may be enrolled in order to account for patient dropout or withdrawal rate. The expected accrual time is 30 months. The total duration of the trial up to primary endpoint analysis would be of approximately 48 months. All patients will be followed until end of study. ***Supportive secondary outcome measures*** ▪ *Time to start of second subsequent therapy or death (TSST)* TSST is defined as the time from the date of randomization to the earliest date of second subsequent anti-cancer therapy start date following study treatment discontinuation, or death. ▪ *Patient reported outcome variables* Details of the analysis on the QoL based on EORTC QLQ-C30 & OV28 and EQ-5D-5L will be outlined in the Statistical and Analysis Plan (SAP).

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	▪ *Long term survival* The cure rate model is a statistical methodology allowing to estimate by treatment arm a proportion of « cured » patients or reaching a plateau, and a survival function for the patients who will not be « cured ». (Yin G. et al., 2005) ▪ Overall Survival (OS) Overall survival is defined as the time from randomization until death due to any cause. ***Others secondary outcome measures*** ▪ Objective response rate (ORR) The ORR will be assessed as per RECIST v1.1 criteria and as per irRECIST criteria. ▪ *First progression-free Survival (PFS1) according to irRECIST criteria* The PFS1 will also be evaluated according to the irRECIST criteria. ▪ *Time to earliest progression by CA-125 or RECIST V.1.1* Progression according to CA-125 will be assessed according to GCIG criteria ▪ *Time to start of first subsequent therapy or death* TFST is defined as the time from the date of randomization to the earliest date of anti-cancer therapy start following study treatment discontinuation, or death. ▪ *Second Progression Free Survival (PFS2)* Time from randomization to second progression is defined as the time from the date of randomization to the earliest of the progression event subsequent to that used for the primary variable PFS, or date of death. The date of second progression will be recorded by the investigator and defined according to local standard clinical practice and may involve any of the following: objective radiological, CA-125 or symptomatic progression or death. ▪ *PD-L1 sub groups* PD-L1 expression will be assessed by immunochemistry on immune cells of the tumor de novo biopsy obtained before entry in ATALANTE. PD-L1 positivity will be defined as ≥1% of immune cells (ICs) expressing PD-L1 which will be referred to IC1/2/3 according to PD-L1 scoring algorithm. ▪ *Safety and Tolerability* Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs and ECG. AE will be described according to MedDRA terms and graded according to CTCAE version 4.03. ▪ *Pharmacoeconomy* Frequency and estimates of resource use, including length of stay and number of hospital admissions, will be derived from the resource use information. ***Analysis*** ▪ *Populations* All efficacy analysis will be performed on the ITT population including all randomized patients analyzed according to the randomization scheme. Health-related quality of life analysis will be performed according to the specific Statistical Analysis Plan (SAP). Several approaches will be used to deal with missing questionnaires.

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	The safety data will be analyzed on the safety analysis set including all randomized patients having received at least one dose of study treatment. ▪ *Interim safety analyses* The tolerability profile of the atezolizumab -bevacizumab-carboplatin-based chemotherapy regimens will be assessedfirst, after 36 evaluable patients and second after 45 evaluable patients included in the ATALANTE trial. ▪ *Primary efficacy analysis* As the effect of atezolizumab is expected to be delayed and to increase with time, the proportional hazards assumption, necessary for a correct use of the logrank test or the classical Cox model, has great chances not to be ascertained. So, the primary analysis will use a Cox model including a potential time dependent treatment effect. H(t,Z) = h0(t) exp (b1*Z +b2* f (Z ,t)) Where Z is the treatment arm (0 vs 1), b1 the non time-dependent coefficient, and b2 the time dependent coefficient associated with a potential modification of the treatment effect with time. The simpler function for the time-dependent treatment effect is f (Z,t) = Z *t, leading to the following model: H(t,Z) = h0(t) exp (b1*Z +b2* Z * t) In a first step, the overall likelihood of the model will be tested, adjusted on the stratification parameters: If the overall treatment effect is significant (two tailed 5%), atezolizumab will be considered as effective and then the hazards proportionality assumption (corresponding to no time dependent treatment effect) will be tested (b2 = 0) in a second step: If there is a significant deviation from the proportional hazards assumption, then the time dependent effect will be represented by a graph of the variations of the HR with time derived from the model. If there is no significant deviation from the proportional hazards assumption (no time-dependent effect of the treatment), then we will consider a constant HR, and the use of classical Cox model (H(t,Z) = h0(t) exp (b*Z)) will give an overall estimate of the HR observed in the trial. This conditional procedure will not increase the overall type I error, as testing the proportionality of the hazards will depend on an overall significant treatment effect in the first step of the analysis. ▪ *Exploratory endpoints analysis* Subgroup PFS analyses will be conducted to assess consistency of treatment effect across potential or expected prognostic factors, including stratification factors. An analysis will not be performed if there are too few events available for a meaningful analysis of a particular subgroup (less than 20 events in a subgroup).

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	<u>Biomarkers</u> Appropriate summaries of exploratory outcome variables and data listings will be produced and compared across the two treatment arms. Graphical methods will be widely used in exploring the characteristics and relationships of outcome variables.

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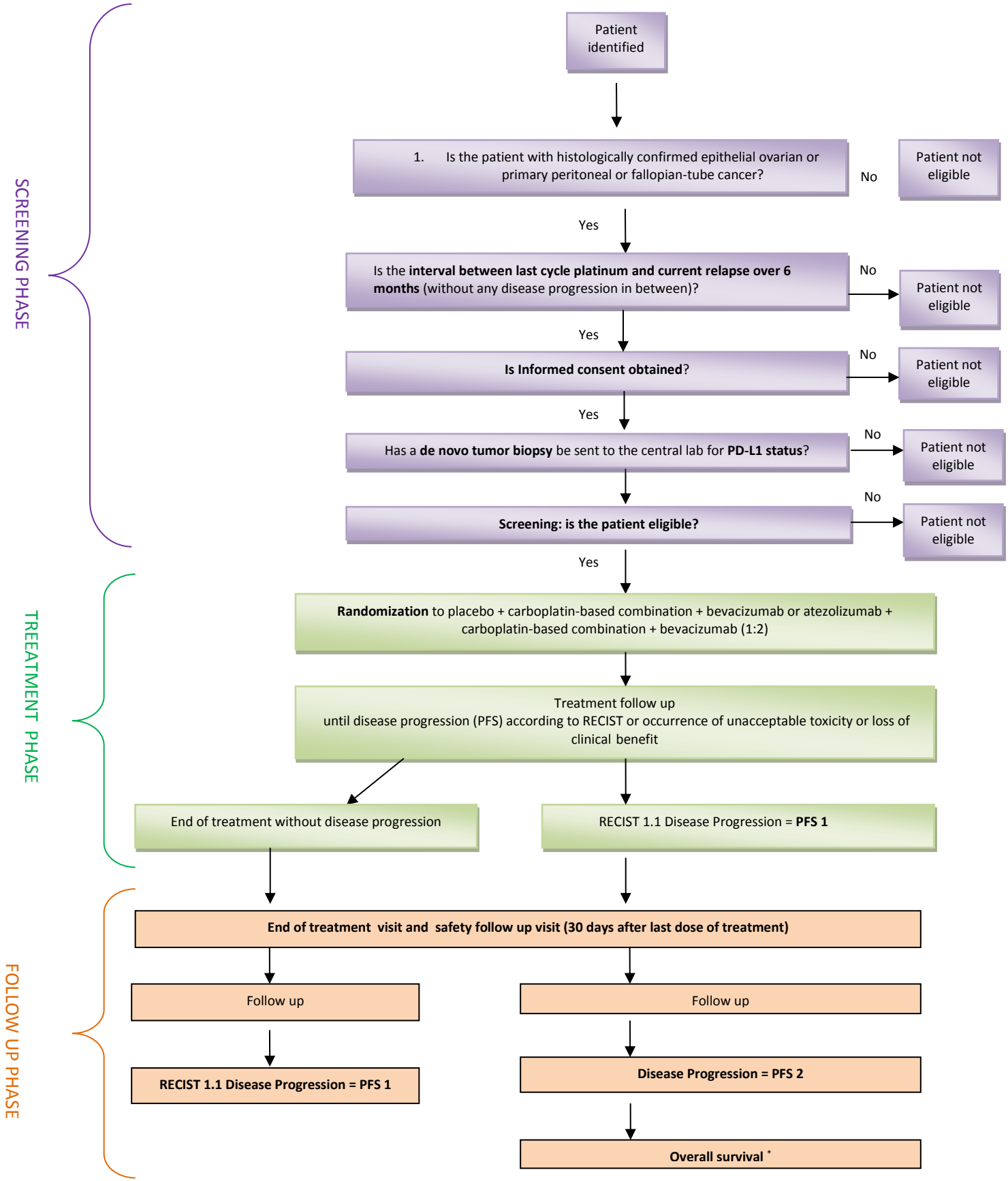
Flow Chart



*In case of lost to follow up, overall survival data will be obtained from hospital records and / or public death registries where available.

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Patient screening and treatment initiation

PATIENT SCREENING	**Inform consent**	**X**				
	PD-L1 status obtained centrally from tumor de novo biopsy at current relapse (mandatory) within 2 months before randomization	**X**				
	Screening to be done within 28 days before randomization		RANDOMIZATION	**Tests to be repeated if not done within 7 days before treatment starts**	**Tests to be done before 1st dose administration**	TREATMENT INITIATION
	Medical history	X				
	Inclusion/Exclusion criteria	X				
	Platinum-free interval (6-12 vs > 12 months)	X				
	Tumor assessment (chest and abdomino-pelvic CT scan or MRI)[a]	X				
	Availability of FFPE archival tumor tissue from debulking surgery during front line therapy, at best before chemotherapy	X				
	Height	X				
	Body weight, blood pressure	X		X		
	Physical examination[b], ECOG performance status (0-1)	X		X		
	Symptoms/Adverse events	X		X		
	Concomitant medications	X		X		
	Urinalysis	X		X		
	Haematology / coagulation[c] / serum biochemistry[d]	X		X		
	CA-125	X		X		
	Pregnancy test (if applicable)	X		X		
	ECG	X		X		
	ECHO/MUGA[e]	X				
	TSH, free T3, free T4	X				
	HBV, HCV, and EBV serology	X				
	HIV test	X				
	Auto-antibody testing[f]				X	
	QoL (EORTC QLQ-C30 & OV28,EQ-5D-5L)				X	
	Geriatric questionnaires (ADL, IADL, HADS) if patient is ≥70 years				X	
	Resource use (Pharmaco-economic)				X	
	Blood sample for ctDNA analysis and potential biomarkers (mandatory)				X	

a: PET- scan cannot be used to assess disease response or progression in the absence of validated data in ovarian cancer patients treated with immunotherapy
b: including dental examination
c Coagulation tests : aPTT, INR
d Biochemistry tests at baseline : albumin,creatinine, sodium, potassium, calcium, total bilirubin, lactic dehydrogenase [LDH], aspartate transaminase [AST], alanine transaminase [ALT], Alkaline Phosphatase [ALP], C-reactive protein
e: Only for patients planned to be treated with pegylated liposomal doxorubicin (PLD)
f: Auto-antibody testing : antinuclear auto anti-bodies (ANA) and anti –Neutrophil cytoplasmic antibodies (ANCA)

SYNOPSIS

On treatment study schedule up to disease progression or loss of clinical benefit, or occurrence of unacceptable toxicity or study withdrawal

PERIOD		Start of treatment	FIRST 24 WEEKS INCLUDING CHEMOTHERAPY FOR 6 CYCLES	FROM WEEK 24 TO DISEASE PROGRESSION (PD) OR "MAINTENANCE PERIOD"	PFS1 RECIST V1.1 To be confirmed ≥ 4 weeks (irRECIST)	FROM PD TO TREATMENT DISCONTINUATION
Day		**1**	**Day 1 of next visit period every 3 weeks for carboplatin-gemcitabine and carboplatin-paclitaxel or every 4 weeks with carboplatin-PLD regimen**	**Day 1 of next visit period every 6 weeks**		**Day 1 of next visit period every 6 weeks**
Visit Window			±3d	±7d		±7d
Vital signs (Include body weight, blood pressure)		X[a]	X	X		X
Physical examination, ECOG performance status		X[a]	X	X		X
Symptoms/Adverse Events		X[a]	X	X		X
Concomitant medications		X[a]	X	X		X
Urinalysis[c]		X[a]	X	X		X
Haematology/coagulation test (aPTT, INR)[b]/biochemistry[d]		X[a]	X	X		X
TSH, free T3, freeT4			Week 12 and 24	every 12 weeks		every 12 weeks
Tumor Assessment	CA-125	X[a]	Week 12 and 24	every 12 weeks		collected
	CT/MRI (chest, abdomen, pelvis)		Week 12 and 24 [e]	every 24 weeks[e]	X[e]	collected
QoL (EQ-5D-5L, EORTC QLQ-C30 & OV28)		X[f]	X[f]	every 12 weeks[f]		**every 12 weeks**
Resource use (Pharmacoeconomic)		X	X	X		X
Pregnancy test (if applicable)		X[ab]				
ECG		X[ab]	X[g]			
ECHO/MUGA[h]			X			
HBV, HCV, and EBV serology		X[b]				
Auto-antibody testing		X[b]				
Atezolizumab or placebo		X	X	X	X[i]	X[i]
Blood sample for ctDNA and potential biomarker analysis before treatment start (mandatory)		X	X (cycle 2)			
Tumor sample on progression when feasible (optional)[j]					X[j]	
Blood sample on progression (optional)					X	

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[a] Tests to be repeated if not done within 7 days of treatment starts.
[b] Test to be repeated during treatment only if clinically indicated.
[c] At baseline and during bevacizumab treatment. If bevacizumab treatment is discontinuated, only if clinically indicated
[d] Biochemistry tests:
- At screening only: albumin and lactic dehydrogenase [LDH], sodium, potassium, calcium, C-reactive protein,
At screening and during study treatment: creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT]
[e] **CT/MRI (chest, abdomen, pelvis) must be performed systematically at baseline, landmark PFS (at 12, 24, 48; 72 and 96 weeks)** and then the imaging will be performed according local standard practices until progression according to RECIST v1.1. From week 24 , at the 12 weeks planned interval visit without systematic imaging, imaging can be done if required by any evidence of progressive disease (PD), such as clinical progression and/or CA-125 level increase (by GCIG criteria). **A confirmatory imaging is required to confirm disease progression at least 4 weeks after the first imaging showing disease progression.**

Tumor assessment visit every 12 weeks	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96
- Physical examination	x	x	x	x	x	x	x	x
- CA-125	x	x	x	x	x	x	x	x
- CT scan / MRI	x	x	If required	x	If required	x	If required	x

[f] Questionnaires to be done before treatment start, before every cycle of chemotherapy and every 12 weeks until next subsequent treatment. When the patient has shifted from study treatment to next subsequent treatment, QoL / PRO questionnaires should be collected every 4 weeks (+/-1 week) during 12 weeks and then every 12 weeks until PFS2 or a maximum of 3 years, at best before the patient knows the disease assessment results
[g]: To be done after cycle 3 for patients treated with carboplatin-pegylated liposomal doxorubicin (PLD)
[h]: Only for patients planned to be treated with PLD combination. To be repeated if clinically indicated and if cumulated dose of anthracyclin exceed 450 mg/m^2
[i]: Even after objective radiological disease progression, study treatment may be continued as long as patients are experiencing clinical benefit as assessed by investigator.
[J]: When feasible in case of tumor tissue sample (biopsy for diagnosis of relapse or at debulking surgery)

SYNOPSIS

Treatment discontinuation and follow up schedule

Visits		ON STUDY TREATMENT	OFF STUDY TREATMENT VISITS		FOLLOW UP FOR PFS 1 (if off study treatment is prior to RECIST PD)	PFS1 RECIST V1.1 To be confirmed ≥ 4 weeks (irRECIST)	FOLLOW UP FOR PFS 2		PFS2	FOLLOW UP FOR OVERALL SURVIVAL
			End of treatment	Safety FU (+ 30 d after last treatment dose)	**Visit to be done Every 12 weeks until disease progression**		**Next treatment start**	**Follow up according to the investigator**		**Follow up according to the investigator**
Visit Window			±7d	±7d	±7d					
Physical examination, ECOG performance status			X	X	X					
Vital signs (Include BP), Body weight,			X	X						
Adverse Events			X	X	X[i]			X[i]		X[i]
Concomitant medications			X	X						
Urinalysis & Haematology/coagulation[a]/biochemistry[b]			X	X						
TSH, free T3, freeT4				X						
ECG, pregnancy test, HBV, HCV, and EBV serology, auto-antibody testing[a]				X						
Tumor Assessment	CA-125				every 12 weeks[e]		collected	collected		
	CT/MRI (chest, abdomen, pelvis)				every 24 weeks[c]	X[d]	collected	Collected[f]		
QoL (EQ-5D-5L, EORTC QLQ-C30 & OV28)			X	X	every 12 weeks[g]		**every 4 weeks during 3 months**	**every 12 weeks[g]**		
Resource use (Pharmacoeconomic)			X	X						
Tumor sample on progression when feasible (optional)						X[h]				
Blood sample on progression (optional)						X				
Subsequent cancer therapy								X[j]		X[j]
Overall survival										X

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[a] To be done only if clinically indicated.
[b] Biochemistry tests: creatinine, total bilirubin, alkaline phosphatase [ALP], aspartate transaminase [AST], alanine transaminase [ALT].
[c] **CT/MRI (chest, abdomen, pelvis) must be performed systematically at landmark PFS (at 12, 24, 48; 72; 96 weeks)** and then the imaging will be performed according to local standard practices, until progression according to RECIST v1.1, even in case of treatement dicontinuation due to toxicity. From week 24, at the 12 weeks planned interval visit without systematic imaging, imaging can be done if required by any evidence of progressive disease (PD), such as clinical progression and/or CA-125 level increase (by GCIG criteria).
[d] A diagnosis of first radiologic progression by RECIST v1.1, should be confirmed by **an additional CT scan performed at least 4 weeks after (immune related RECIST)**

Tumor assessment visit every 12 weeks	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72	Week 84	Week 96
- Physical examination	x	x	x	x	x	x	x	x
- CA-125	x	x	x	x	x	x	x	x
- CT scan / MRI	x	x	If required	x	If required	x	If required	x

[e] CA 125 samples must be performed every 12 weeks until progression (PFS1) or during a maximum of 96 weeks and then CA-125 samples will be taken according to local practice.
[f] Including PET-scan and ultrasound
[g] Questionnaires will be collected every 12 weeks, at best before the patient knows the disease assessment results. When the patient has shifted from study treatment to next subsequent treatment, QoL / PRO questionnaires should be collected every 4 weeks (+/-1 week) during 12 weeks and then every 12 weeks until PFS2 or a maximum of 3 years
[h] When feasible in case of tumor tissue sample (biopsy for diagnosis of relapse or at debulking surgery)
[I] Occurrence of auto-immune disease should be declare as serious adverse event (SAE)
[j]: Subsequent cancer therapy will be collected until death or the end of the study or a maximum of 3 years .