ENGOT-ov43/BGOG

Leading group: BGOG

Clinical Trial Study: Randomized phase III first line study in ovarian cancer comparing paclitaxel carboplatinum, with paclitaxel/carboplatin and pembrolizumab and olaparib

First Submitted Date ICMJE	November 12, 2018
First Posted Date ICMJE	November 14, 2018
Last Update Posted Date	May 15, 2020
Actual Study Start Date ICMJE	December 18, 2018
Estimated Primary Completion Date	August 8,2025 (Final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE **(submitted: November 12, 2018)**	• Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as Assessed by the Investigator [Time Frame: Up to approximately 6 years] PFS is defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 based on Investigator assessment or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more lesions and the unequivocal progression of non-target lesions is also considered PD. The PFS per RECIST 1.1 as assessed by the Investigator will be presented. • Overall Survival (OS) [Time Frame: Up to approximately 6 years] OS is defined as the time from the date of randomization to death due to any cause. The OS will be presented.
Current Secondary Outcome Measures ICMJE **(submitted: May 19, 2019)**	• PFS Per RECIST 1.1 As Assessed by Blinded Independent Central Review [Time Frame: Up to approximately 6 years] PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent central review assessment or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also

demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more lesions and the unequivocal progression of non-target lesions is also considered PD. The PFS per RECIST 1.1 as assessed by blinded independent central review will be presented.

- PFS After Next-line Treatment (PFS2) Following Discontinuation of Study Treatment As Assessed by the Investigator [Time Frame: Up to approximately 78 months]

  PFS2 is defined as the time from randomization until PD on next-line treatment or death due to any cause, whichever occurs first. The PFS2 per Investigator assessment will be presented.

- Number of Participants Who Experience an Adverse Event (AE) [Time Frame: Up to approximately 73 months]

  An AE is any untoward medical occurrence in a participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment. The number of participants who experience an AE will be presented.

- Number of Participants Who Discontinue Study Treatment Due to an AE [Time Frame: Up to approximately 6 years]

  The number of participants who discontinue study treatment due to an AE will be presented.

- Change from Baseline in Global Health Status/Quality of Life (GHS/QoL) Score Using Questions from the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) [Time Frame: Baseline and End of Study Participation (Up to approximately 6 years)]

  Participants are asked to answer 2 questions from the EORTC QLQ-C30 about their GHS: "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?" Responses are based on a 7-point scale (1=Very poor; 7=Excellent), with a higher score indicating a better global health status. The change from baseline in GHS/QoL score of participants will be presented.

- Change from Baseline in Abdominal and Gastrointestinal (Abdominal/GI) Symptoms Score Using the EORTC Quality of Life Questionnaire-Ovarian Cancer (QLQ-OV28) Abdominal/GI Symptom Scale [Time Frame: Baseline and End of Study Participation (Up to approximately 6 years)]

  Participants are asked to answer 6 questions from the EORTC QoL Questionnaire-Ovarian Cancer (QLQ-OV28) abdominal/GI symptom scale about abdominal pain, bloated feeling in abdomen/stomach, changes in clothing fit, changes in bowel habit, flatulence and stomach fullness when eating. Responses are based on a 4-point scale (1=Not at all; 4=Very much), with a lower score indicating better abdominal/GI symptoms. The change from baseline in abdominal/GI symptom score of participants will be presented.

- Time to First Subsequent Anti-cancer Treatment (TFST) [Time Frame: Up to approximately 6 years]

	TFST is defined as the time from randomization to initiation of first subsequent anti-cancer treatment or death due to any cause, whichever occurs first. The TFST will be presented. • Time to Second Subsequent Anti-cancer Treatment (TSST) [Time Frame: Up to approximately 6 years] TSST is defined as the time from randomization to initiation of second subsequent anti-cancer treatment or death due to any cause, whichever occurs first. The TSST will be presented. • Time to Discontinuation of Study Treatment or Death (TDT) [Time Frame: Up to approximately 6 years] TDT is defined as the time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first. The TDT will be presented. • Pathological Complete Response (pCR) Rate [Time Frame: Up to approximately 30 months] pCR is defined as all surgical specimens collected during the interval debulking surgery are microscopically negative for malignancy. The pCR rate for all surgical specimens will be presented. • Time Without Symptom of Disease Progression or Toxicity of Treatment (TWiST) [Time Frame: Up to approximately 6 years] TWiST is defined as the time from randomization to disease progression or treatment-related toxicity, whichever occurs first. The TWiST will be presented.
Original Secondary Outcome Measures ICMJE **(submitted: November 12, 2018)**	• PFS Per RECIST 1.1 As Assessed by Blinded Independent Central Review [Time Frame: Up to approximately 6 years] PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on blinded independent central review assessment or death due to any cause, whichever occurs first. Per RECIST 1.1, PD is defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more lesions and the unequivocal progression of non-target lesions is also considered PD. The PFS per RECIST 1.1 as assessed by blinded independent central review will be presented. • PFS After Next-line Treatment (PFS2) Following Discontinuation of Study Treatment As Assessed by the Investigator [Time Frame: Up to approximately 78 months] PFS2 is defined as the time from randomization until PD on next-line treatment or death due to any cause, whichever occurs first. The PFS2 per Investigator assessment will be presented. • Number of Participants Who Experience an Adverse Event (AE) [Time Frame: Up to approximately 73 months] An AE is any untoward medical occurrence in a participant, temporally

associated with the use of study treatment, whether or not considered related to the study treatment. The number of participants who experience an AE will be presented.

- Number of Participants Who Discontinue Study Treatment Due to an AE [Time Frame: Up to approximately 6 years]

  The number of participants who discontinue study treatment due to an AE will be presented.

- Change from Baseline in Global Health Status/Quality of Life (GHS/QoL) Score Using Questions from the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) [Time Frame: Baseline and End of Study Participation (Up to approximately 6 years)]

  Participants are asked to answer 2 questions from the EORTC QLQ-C30 about their GHS: "How would you rate your overall health during the past week?" and "How would you rate your overall quality of life during the past week?" Responses are based on a 7-point scale (1=Very poor; 7=Excellent), with a higher score indicating a better global health status. The change from baseline in GHS/QoL score of participants will be presented.

- Change from Baseline in Abdominal and Gastrointestinal (Abdominal/GI) Symptoms Score Using the EORTC Quality of Life Questionnaire-Ovarian Cancer (QLQ-OV28) Abdominal/GI Symptom Scale [Time Frame: Baseline and End of Study Participation (Up to approximately 6 years)]

  Participants are asked to answer 6 questions from the EORTC QoL Questionnaire-Ovarian Cancer (QLQ-OV28) abdominal/GI symptom scale about abdominal pain, bloated feeling in abdomen/stomach, changes in clothing fit, changes in bowel habit, flatulence and stomach fullness when eating. Responses are based on a 4-point scale (1=Not at all; 4=Very much), with a lower score indicating better abdominal/GI symptoms. The change from baseline in abdominal/GI symptom score of participants will be presented.

- Time to First Subsequent Anti-cancer Treatment (TFST) [Time Frame: Up to approximately 6 years]

  TFST is defined as the time from randomization to initiation of first subsequent anti-cancer treatment or death due to any cause, whichever occurs first. The TFST will be presented.

- Time to Second Subsequent Anti-cancer Treatment (TSST) [Time Frame: Up to approximately 6 years]

  TSST is defined as the time from randomization to initiation of second subsequent anti-cancer treatment or death due to any cause, whichever occurs first. The TSST will be presented.

- Time to Discontinuation of Study Treatment or Death (TDT) [Time Frame: Up to approximately 6 years]

  TDT is defined as the time from the date of randomization to discontinuation of study treatment or death due to any cause, whichever occurs first. The TDT will be presented.

	• Pathological Complete Response (pCR) Rate [Time Frame: Up to approximately 30 months] pCR is defined as no evidence of neoplastic cells in all surgical specimens collected during the interval debulking surgery. The pCR rate will be presented. • Time Without Symptom of Disease Progression or Toxicity of Treatment (TWiST) [Time Frame: Up to approximately 6 years] TWiST is defined as the time from randomization to disease progression or treatment-related toxicity, whichever occurs first. The TWiST will be presented.
Descriptive Information	
Brief Title ICMJE	Study of Chemotherapy With Pembrolizumab (MK-3475) Followed by Maintenance With Olaparib (MK-7339) for the First-Line Treatment of Women With BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (MK-7339-001/KEYLYNK-001/ENGOT-ov43)
Official Title ICMJE	A Randomized Phase 3, Double-Blind Study of Chemotherapy With or Without Pembrolizumab Followed by Maintenance With Olaparib or Placebo for the First-Line Treatment of BRCA Non-mutated Advanced Epithelial Ovarian Cancer (EOC) (KEYLYNK-001/ENGOT-ov43)
Brief Summary	The purpose of this study is to assess the efficacy and safety of treatment with carboplatin/paclitaxel PLUS pembrolizumab (MK-3475) and maintenance olaparib (MK-7339) in women with epithelial ovarian cancer (EOC), fallopian tube cancer, or primary peritoneal cancer. The primary study hypotheses are that the combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab and maintenance olaparib is superior to carboplatin/paclitaxel alone with respect to Progression Free Survival (PFS) per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) and/or Overall Survival (OS), and that the combination of pembrolizumab plus carboplatin/paclitaxel followed by continued pembrolizumab is superior to carboplatin/paclitaxel alone with respect to PFS per RECIST 1.1 and/or OS.
Detailed Description	Following a lead-in period during which all participants receive a single 3-week cycle of carboplatin/paclitaxel, participants will be randomly assigned in to one of three treatment arms: Pembrolizumab+Olaparib, Pembrolizumab+Placebo for Olaparib, or Placebo for Pembrolizumab+Placebo for Olaparib. At Investigator's discretion and prior to participant randomization, one of the following carboplatin/paclitaxel regimens is to be selected: 1. up to 5 cycles of carboplatin Area Under the Curve (AUC)5 or AUC6 AND paclitaxel 175 mg/m^2 on Day 1 of each 3-week cycle

	2. up to 5 cycles of carboplatin AUC5 or AUC6 on Day 1 of each 3-week cycle AND paclitaxel 80 mg/m^2 on Days 1, 8 and 15 of each 3-week cycle; or 3. up to 5 cycles of carboplatin AUC2 or AUC2.7 AND paclitaxel 60 mg/m^2 on Days 1, 8 and 15 of each 3-week cycle.
Study Type ICMJE	Interventional
Study Phase ICMJE	Phase 3
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment
Condition ICMJE	• Ovarian Cancer • Fallopian Tube Cancer • Peritoneal Neoplasms
Intervention ICMJE	• Biological: Pembrolizumab IV infusion Other Names: ○ MK-3475 ○ KEYTRUDA® • Drug: Placebo for pembrolizumab IV infusion Other Name: normal saline or dextrose • Drug: Carboplatin IV infusion Other Name: PARAPLATIN® • Drug: Paclitaxel IV infusion Other Name: TAXOL® • Drug: Olaparib Oral tablet Other Names: ○ MK-7339 ○ LYNPARZA® • Drug: Placebo for olaparib

	Oral tablet • Biological: Bevacizumab IV infusion Other Name: AVASTIN®
Study Arms ICMJE	• Experimental: Pembrolizumab+Olaparib Participants receive carboplatin/paclitaxel via intravenous (IV) infusion for five 3-week cycles PLUS pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles PLUS olaparib 300 mg via oral tablet twice each day (BID), starting with Cycle 7. Participants may also receive bevacizumab via IV infusion on Day 1 of each 3-week cycle. Interventions: ○ Biological: Pembrolizumab ○ Drug: Carboplatin ○ Drug: Paclitaxel ○ Drug: Olaparib ○ Biological: Bevacizumab • Experimental: Pembrolizumab+Placebo for Olaparib Participants receive carboplatin/paclitaxel via IV infusion for five 3-week cycles starting in Cycle 1 PLUS pembrolizumab 200 mg via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles PLUS placebo for olaparib via oral tablet BID, starting with Cycle 7. Participants may also receive bevacizumab via IV infusion on Day 1 of each 3-week cycle. Interventions: ○ Biological: Pembrolizumab ○ Drug: Carboplatin ○ Drug: Paclitaxel ○ Drug: Placebo for olaparib ○ Biological: Bevacizumab • Active Comparator: Placebo for Pembrolizumab+Placebo for Olaparib Participants receive carboplatin/paclitaxel via IV infusion for five 3-week cycles PLUS placebo for pembrolizumab (normal saline or dextrose) via IV infusion on Day 1 of each 3-week cycle for up to 35 cycles PLUS placebo for olaparib via oral tablet BID, starting with Cycle 7. Participants may also receive bevacizumab via IV infusion on Day 1 of each 3-week cycle. Interventions: ○ Drug: Placebo for pembrolizumab ○ Drug: Carboplatin ○ Drug: Paclitaxel ○ Drug: Placebo for olaparib ○ Biological: Bevacizumab
Recruitment Information	
Recruitment Status ICMJE	Recruiting
Estimated Enrollment ICMJE **(submitted: Novemb**	1086

er 12, 2018)	
Original Estimated Enrollment ICMJE	*Same as current*
Estimated Study Completion Date ICMJE	August 8, 2025
Estimated Primary Completion Date	August 8, 2025 (Final data collection date for primary outcome measure)
Eligibility Criteria ICMJE	Inclusion Criteria: Has histologically confirmed International Federation of Gynecology and Obstetrics (FIGO) Stage III or Stage IV EOC (high-grade predominantly serous, endometrioid, carcinosarcoma, mixed mullerian with high-grade serous component, clear cell, or low-grade serous OC), primary peritoneal cancer, or fallopian tube cancer Has just completed primary debulking surgery or is eligible for primary or interval debulking surgery Is a candidate for carboplatin and paclitaxel chemotherapy, to be administered in the adjuvant or neoadjuvant setting Candidates for neoadjuvant chemotherapy, has a cancer antigen 125 (CA-125) (kilounits/L):carcinoembryonic antigen (CEA; ng/mL) ratio greater than or equal to 25 Is able to provide a newly obtained core or excisional biopsy of a tumor lesion for prospective testing of BRCA1/2 and Programmed Cell Death-Ligand 1 (PD-L1) tumor markers status prior to randomization Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 7 days prior to initiating chemotherapy in the lead-in period and within 7 days prior to randomization Is not pregnant, not breastfeeding, and 1 of the following conditions applies: a.) Not a woman of childbearing potential (WOCBP) OR b.) A WOCBP who agrees to follow contraceptive guidance during the treatment period and for at least 120 days following the last dose of pembrolizumab (or pembrolizumab placebo) and olaparib (or olaparib placebo) and at least 210 days following the last dose of chemotherapy or bevacizumab (if administered) Has adequate organ function Exclusion Criteria: Has mucinous, germ cell, or borderline tumor of the ovary Has a known or suspected deleterious mutation (germline or somatic) in either BRCA1 or BRCA2 Has a history of non-infectious pneumonitis that required treatment with steroids or currently has pneumonitis Has either myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) or has features suggestive of MDS/AML Has a known additional malignancy that is progressing or has required active treatment in the last 3 years Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. ductal carcinoma in situ, cervical

	carcinoma in situ) that has undergone potentially curative therapy are not excluded. Has ongoing Grade 3 or Grade 4 toxicity, excluding alopecia, following chemotherapy administered during the lead-in period Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (dosing >10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to randomization Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs) Note: Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed. Has a known history of active tuberculosis (TB; Bacillus Tuberculosis) Has an active infection requiring systemic therapy Has received colony-stimulating factors (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 4 weeks prior to receiving chemotherapy during the lead-in period Is considered to be of poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection Has had surgery to treat borderline tumors, early stage EOC, or fallopian tube cancer <6 months prior to screening Has a known history of human immunodeficiency virus (HIV) infection Has a known history of hepatitis B virus (HBV) or known active hepatitis C virus (HCV) infection Is either unable to swallow orally administered medication or has a gastrointestinal (GI) disorder affecting absorption (e.g. gastrectomy, partial bowel obstruction, malabsorption) Has uncontrolled hypertension, defined as defined as systolic >140 mm Hg or diastolic >90 mm Hg documented by 2 blood pressure readings taken at least 1 hour apart. Note: This applies to participants who will receive bevacizumab. Use of antihypertensive medications to control blood pressure is allowed. Has current, clinically relevant bowel obstruction (including sub-occlusive disease), abdominal fistula or GI perforation, related to underlying EOC (for participants receiving bevacizumab) Has a history of hemorrhage, hemoptysis or active GI bleeding within 6 months prior to randomization (for participants receiving bevacizumab) Is a WOCBP who has a positive urine pregnancy test within 72 hours before the first dose of chemotherapy in the lead-in period and within 72 hours prior to randomization, is pregnant or breastfeeding, or is expecting to conceive children within the projected duration of the study, starting with screening through 120 days following the last dose of pembrolizumab (or pembrolizumab placebo) and olaparib (or olaparib placebo) and at least 210 days following the last dose of chemotherapy or bevacizumab (if administered)

	Has received prior treatment for advanced or metastatic OC, including radiation or systemic anti-cancer therapy (e.g. chemotherapy, hormonal therapy, immunotherapy, investigational therapy) Has received prior therapy with an anti-Programmed Cell Death-1 (anti-PD-1), anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. cytotoxic T lymphocyte antigen-4 [CTLA-4], OX 40, CD137) Has received prior therapy with either olaparib or any other poly(adenosine-ribose) polymerase (PARP) inhibitor Has intraperitoneal chemotherapy planned or has been administered as first-line therapy Has received a live vaccine within 30 days prior to the first dose of study treatment Has severe hypersensitivity (≥Grade 3) to pembrolizumab, olaparib, carboplatin, paclitaxel or bevacizumab (if using) and/or any of their excipients Is currently receiving either strong (e.g. itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of cytochrome P450 (CYP)3A4 that cannot be discontinued for the duration of the study Is currently receiving either strong (e.g. phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, and St John's Wort) or moderate (e.g. bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study Has received whole blood transfusions in the last 120 days prior to randomization Is currently participating or has participated in a study of an investigational agent or has used an investigational device within 4 weeks of the first dose of study treatment Has resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions or participant has congenital long QT syndrome Has had an allogenic tissue/solid organ transplant, has received previous allogenic bone-marrow transplant, or has received double umbilical cord transplantation Either has had major surgery within 2 weeks of randomization or has not recovered from any effects of any major surgery
Sex/Gender ICMJE	Sexes Eligible for Study: Female
Ages ICMJE	18 Years and older (Adult, Older Adult)