

ANTI-PD-L1 ANTIBODIES IN COMBINATIONS WITH ONE OR MORE CHEMOTHERAPY AGENTS FOR TREATING ENDOMETRIAL CANCER

FIELD OF THE DISCLOSURE

[0001] The disclosure relates to methods, compositions, and combinations for the treatment of endometrial cancer. Specifically, the disclosure relates to methods of treating endometrial cancer in a subject in need thereof, comprising administering to the subject one or more chemotherapy agents, an anti-PD-L1 antibody or an antigen-binding fragment thereof, and optionally a PARP inhibitor. The disclosure also relates to combinations for use in the treatment of endometrial cancer comprising one or more chemotherapy agents, an anti-PD-L1 antibody or an antigen-binding fragment thereof, and a optionally PARP inhibitor.

BACKGROUND

[0002] Treatment of cancer commonly entails surgical resection followed by chemotherapy and radiotherapy. The standard treatment regimens show highly variable degrees of long-term success because of the ability of tumor cells to essentially escape by regenerating primary tumor growth and, often more importantly, seeding distant metastasis. Recent advances in the treatment of cancer and cancer-related diseases, disorders, and conditions comprise the use of combination therapy incorporating immunotherapy with more traditional chemotherapy and radiotherapy. Under most scenarios, immunotherapy is associated with less toxicity than traditional chemotherapy because it utilizes the patient's own immune system to identify and eliminate tumor cells.

[0003] Endometrial cancer is a disease in which malignant cancer cells form in the tissues of the endometrium, the lining of the uterus. Endometrial cancer is sometimes called uterine cancer. Endometrial cancer is one of the most common malignancies in the female genital tract with over 380,000 new cases worldwide in 2018 and an estimated 61,880 new cases diagnosed in the United States (US) in 2019. There is an increasing prevalence in developed countries and the highest incidences have been observed in the US, Canada, and Northern and Western Europe. From 2006 to 2015, the incidence rate increased by about 1% per year and from 2007 to 2016, the death rate increased by about 2% per year (American Cancer Society 2019). The main risk factor thought to be associated with the occurrence of endometrial cancer is exposure to excessive oestrogen levels associated with obesity, diabetes, use of tamoxifen, and reproductive factors (early menarche, late menopause, nulliparity). The growth of the aging population may also have a role in the increased incidence. Alternative

treatment options for recurrent endometrial cancer are limited and there is a high unmet need for new treatment.

SUMMARY

[0004] The disclosure relates to methods, compositions, and combinations for the treatment of endometrial cancer. Specifically, the disclosure relates to methods of treating endometrial cancer in a subject in need thereof, comprising administering to the subject one or more chemotherapy agents, an anti-PD-L1 antibody or an antigen-binding fragment thereof, and optionally a PARP inhibitor. The disclosure also relates to combinations for use in the treatment of endometrial cancer comprising one or more chemotherapy agents, an anti-PD-L1 antibody or an antigen-binding fragment thereof, and optionally a PARP inhibitor.

[0005] In one aspect, the disclosure provides a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and optionally a therapeutically effective amount of a PARP inhibitor.

[0006] In another aspect, the disclosure provides a combination for use in the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and optionally a therapeutically effective amount of a PARP inhibitor.

[0007] In another aspect, the disclosure provides use of a combination comprising: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and a therapeutically effective amount of a PARP inhibitor in the manufacture of a medicament for the treatment of endometrial cancer in a subject in need thereof.

[0008] In a further aspect, the disclosure provides use of a combination in the manufacture of a medicament for the treatment of ovarian cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-

L1 antibody or antigen-binding fragment thereof and optionally a therapeutically effective amount of a PARP inhibitor.

[0009] These and other features and advantages of the present disclosure will be more fully understood from the following detailed description taken together with the accompanying claims. It is noted that the scope of the claims is defined by the recitations therein and not by the specific discussion of features and advantages set forth in the present description.

BRIEF DESCRIPTION OF THE DRAWINGS

[0010] **FIGURE 1** illustrates the screening process. Abbreviations: ICF = informed consent form; MMR = mismatch repair. * Use of a freshly collected tumor sample is permitted provided the sample is taken as part of routine clinical practice ** Patients with unknown MMR status prior to randomization will be considered screen failures and will not be eligible. If the original MMR testing cannot be completed by the end of the 28-day screening period due to technical failure, patients must be re-screened to ensure adequate time for MMR re-testing. Sample must be shipped prior to signing the main informed consent and MMR results must be available prior to randomization. Submission and testing of new samples can only be performed if the original testing failed due to technical failure. Please refer to the laboratory manual for further details regarding re testing procedures.

[0011] **FIGURE 2** illustrates the study design diagram. During the chemotherapy phase, IV study treatments were administered on the same day and in the following order: 1. Durvalumab/placebo (1120 mg over 1 hour, or maximum 8 hours if there were infusion interruptions), 2. Paclitaxel 175 mg/m² by IV infusion over 3 hours), 3. Carboplatin (AUC 5 or AUC 6 by IV infusion over 1 hour, or in accordance with local practice). Maintenance therapy started 3–9 weeks after the last chemotherapy infusion.*Measurable disease per RECIST v1.1 following surgery or diagnostic biopsy (FIGO stage III) or with/without disease following surgery or diagnostic biopsy (FIGO stage IV) †Measurable or non-measurable disease using RECIST v1.1, where potential for cure by surgery alone or in combination is poor. ‡Prior adjuvant systemic anticancer treatment was permitted for recurrent disease of ≥12 months from last dose to subsequent relapse. bid, twice per day; EC, endometrial cancer; IV, intravenous; MMR, mismatch repair; PARP, poly(ADP-ribose) polymerase; q3w, every 3 weeks; q4w, every 4 weeks; R, randomized.

[0012] **FIGURE 3** illustrates the multiplicity control strategy. Alpha levels presented are 2-sided. *Overall 2.5% allocated using Lan-DeMets spending function approximating the

O'Brien-Fleming approach. H, hypothesis; PFS, progression-free survival; OS, overall survival.

[0013] FIGURE 4A-B illustrates Progression-Free Survival (A) and overall survival (B) in the intention-to-treat population as assessed by the investigator according to RECIST, Version 1.1. For the PFS analysis, the HRs and CIs were estimated from a Cox proportional hazards model stratified by MMR and disease status. For the OS analysis, the HRs and CIs were estimated from an unstratified Cox proportional hazards model. *P* values were calculated using a stratified log rank test. Tick marks indicate a censored observation. Patients without an event were censored at the latest evaluable RECIST assessment. CI, confidence interval; HR, hazard ratio; MMR, mismatch repair; NR, not reached; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

[0014] FIGURE 5A-B illustrates subgroup analysis of Progression-Free Survival in (A) doublet group and (B) triplet group. CI denotes confidence interval; ECOG Eastern Cooperative Oncology Group; FIGO International Federation of Gynecology and Obstetrics; G grade; HRRm, homologous recombination repair mutation; MMR mismatch repair; PD-L1 programmed cell death ligand-1; and RoW rest of world. Stratification factors (MMR status [proficient vs. deficient], disease status [newly diagnosed vs. recurrent], and geographic region [Asia vs. rest of world]) are per the randomization code.

[0015] FIGURE 6 illustrates enrolment, randomization and intervention.

[0016] FIGURE 7 illustrates Sensitivity Analysis of Progression-Free Survival as assessed by blinded independent central review.

[0017] FIGURE 8A-B illustrates Progression-Free Survival as assessed by the investigator According to RECIST Version 1.1, in (A) dMMR and (B) pMMR subgroups. CI denotes confidence interval; dMMR mismatch repair-deficient; pMMR mismatch repair-proficient; and RECIST Response Evaluation Criteria in Solid Tumors.

[0018] FIGURE 9 illustrates Overall Survival in the intent-to-treat population.

[0019] FIGURE 10A-B illustrates Progression-Free Survival as assessed by the investigator according to RECIST Version 1.1, in (A) PD-L1 positive and (B) PD-L1 negative subgroups. CI, confidence interval; dMMR, mismatch repair-deficient; HR, hazard ratio; MMR, mismatch repair; NR, not reached; PFS, progression-free survival; PD-L1,

programmed death ligand-1; pMMR, mismatch repair-proficient; RECIST, Response Evaluation Criteria in Solid Tumors.

[0020] **FIGURE 11** show summary of the DUO-E study design including patients and endpoints.

[0021] **FIGURE 12A-12B** shows patient characteristics data. Federation of Gynaecology and Obstetrics; HRR(m), homologous recombination repair (mutation); MMR, mismatch repair; NGS, next-generation sequencing; PD-L1, programmed death ligand 1; TAP, tumor area proportion.

[0022] **FIGURE 13A-13D** shows results of the intent to treat (ITT) population in (A) Progression Free Survival (PFS) and (B) Overall Survival (OS), (C) Objective Response Rate (ORR), and (D) Duration of Response (DoR).

[0023] **FIGURE 14A-14C** shows evaluation of secondary endpoints in the ITT population for (A) time to first subsequent therapy or death (TFST), (B) second progression-free survival (PFS2), and (C) time to first subsequent therapy or death (TFST), time to second subsequent therapy or death (TSST).

[0024] **FIGURE 15A-15B** show *post hoc* exploratory analyses for MMR subpopulations in Overall survival (OS) for (A) dMMR and (B) pMMR.

[0025] **FIGURE 16A-16F** show *post hoc* exploratory analyses for dMMR subpopulations (A) TFST, (B) PFS2, (C) TSST, (D) PFS by subgroup, (E) ORR, and (F) DoR.

[0026] **FIGURE 17A-17F** show *post hoc* exploratory analyses for pMMR subpopulations (A) TFST, (B) PFS2, (C) TSST, (D) PFS by subgroup (E) ORR, and (F) DoR.

[0027] **FIGURE 18A-18B** show MMR subpopulations for PFS, pre-specified exploratory analysis for (A) dMMR and (B) pMMR.

[0028] **FIGURE 19A-19B** shows additional results of the ITT population in (A) PFS and (B) OS.

[0029] **FIGURE 20A-20D** shows additional results of exploratory PFS analyses for (A) dMMR, (B) pMMR, (C) PD-L1-positive, and (D) PD-L1-negative subgroups.

DETAILED DESCRIPTION

[0030] The disclosure relates to methods, compositions, and combinations for the treatment of endometrial cancer. Specifically, the disclosure relates to methods of treating endometrial cancer in a subject in need thereof, comprising administering one or more

chemotherapy agents, an anti-PD-L1 antibody or an antigen-binding fragment thereof, and optionally a PARP inhibitor. The disclosure also relates to combinations for use in the treatment of endometrial cancer comprising one or more chemotherapy agents, an anti-PD-L1 antibody or an antigen-binding fragment thereof, and optionally a PARP inhibitor.

[0031] As utilized in accordance with the present disclosure, unless otherwise indicated or defined, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this disclosure belongs. The following references provide one of skill with a general definition of many of the terms used in this disclosure: Singleton *et al.*, Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger *et al.* (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

[0032] In this disclosure, "comprises," "comprising," "containing," and "having," and the like can have the meaning ascribed to them in U.S. patent law and can mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise have the meaning ascribed in U.S. patent law and are open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited are not changed by the presence of more than that which is recited, but excludes prior art aspects.

[0033] Unless specifically stated or obvious from context, the term "or," as used herein, is understood to be inclusive. Unless specifically stated or obvious from context, the terms "a," "an," and "the," as used herein, are understood to be singular or plural. Unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular.

[0034] Unless specifically stated or obvious from context, the term "about," as used herein, is understood as meaning within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. "About" can be understood as meaning within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

[0035] Any of the methods, compositions, or combinations provided herein can be combined with one or more of any of the other methods, compositions, or combinations provided herein.

[0036] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50.

[0037] The term "antibody," as used herein, refers to a protein that is capable of specifically binding to an antigen. Ordinary or conventional mammalian antibodies comprise a tetramer, which is typically composed of two identical pairs of polypeptide chains, each pair consisting of one "light" chain (typically having a molecular weight of about 25 kDa) and one "heavy" chain (typically having a molecular weight of about 50-70 kDa). The terms "heavy chain" and "light chain," as used herein, refer to any immunoglobulin polypeptide having sufficient variable domain sequence to confer specificity for a target antigen. The amino-terminal portion of each light and heavy chain typically includes a variable domain of about 100 to 110 or more amino acids that typically is responsible for antigen recognition. The carboxyl-terminal portion of each chain typically defines a constant domain responsible for effector function. Thus, in a naturally occurring antibody, a full-length heavy chain immunoglobulin polypeptide includes a variable domain (V_H) and three constant domains (C_{H1} , C_{H2} , and C_{H3}) and a hinge region between C_{H1} and C_{H2} , wherein the V_H domain is at the amino-terminus of the polypeptide and the C_{H3} domain is at the carboxyl-terminus, and a full-length light chain immunoglobulin polypeptide includes a variable domain (V_L) and a constant domain (C_L), wherein the V_L domain is at the amino-terminus of the polypeptide and the C_L domain is at the carboxyl-terminus.

[0038] Within full-length light and heavy chains, the variable and constant domains typically are joined by a "J" region of about 12 or more amino acids, with the heavy chain also including a "D" region of about 10 more amino acids. The variable regions of each light/heavy chain pair typically form an antigen-binding site. The variable domains of naturally occurring antibodies typically exhibit the same general structure of relatively conserved framework regions (FR) joined by three hypervariable regions, also called complementarity determining regions or CDRs. The CDRs from the two chains of each pair typically are aligned by the framework regions, which may enable binding to a specific epitope. From the amino-terminus to the carboxyl-terminus, both light and heavy chain variable domains typically comprise the domains FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4.

[0039] The term "antigen-binding fragment" refers to a portion of an intact antibody and/or refers to the antigenic determining variable domains of an intact antibody. It is known that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of antibody fragments include, but are not limited to, Fab, Fab', F(ab')₂, and Fv fragments, linear antibodies, single chain antibodies, diabodies, and multispecific antibodies formed from antibody fragments.

[0040] In one aspect, the disclosure provides a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and optionally a therapeutically effective amount of a PARP inhibitor.

[0041] In one embodiment the methods, compositions, and combinations comprise administering to the subject: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[0042] In some embodiments of the methods of the disclosure, step (b) occurs after completion of step (a).

[0043] In various embodiments of the first aspect, step (b) can exclude a therapeutically effective amount of a PARP inhibitor. In these embodiments, step (b) includes a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[0044] The number of treatment doses scheduled within each cycle depends on the chemotherapy agent. In some embodiments, each cycle may contain only 1 dose. In other embodiments, a cycle may contain more than 1 dose.

[0045] In some embodiments, provided herein is a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject an anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of from about 5 mg/kg to 25 mg/kg. In some embodiments, provided herein is a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject an anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of from about 10 mg/kg to 20 mg/kg.

[0046] In some embodiments, provided herein is a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject an anti-PD-L1 antibody or antigen-binding fragment thereof at a fixed dose of from about 800 mg to 1500 mg.

[0047] In some embodiments, provided herein is a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject an anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of about 15 mg/kg or 20mg/kg, or a fixed dose of about 1120 mg or 1500mg.

[0048] In non-limiting embodiments, an anti-PD-L1 antibody is administered using a fixed dose of 1120 mg or 1500 mg (based on an average body weight of 75 kg, this is equivalent to a weight based dose of 15 mg/kg or 20 mg/kg).

[0049] In some embodiments, provided herein is a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject a PARP inhibitor at a fixed dose of from about 100 mg to 300 mg.

[0050] In some embodiments, provided herein is a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject a PARP inhibitor at a fixed dose of 300 mg.

[0051] In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab. Durvalumab (MEDI4736, Imfinzi[®]) is a human monoclonal antibody directed against human PD-L1 that is capable of blocking the binding of PD-L1 to both the PD1 and CD80 receptors. Disclosure related to durvalumab can be found in U.S. Patent Nos. 8,779,108 and 9,493,565, which are incorporated herein by reference in their entirety.

[0052] Durvalumab and antigen-binding fragments thereof for use in the methods, compositions, and combinations provided herein comprises a heavy chain and a light chain or a heavy chain variable region and a light chain variable region. In some embodiments, durvalumab or antigen-binding fragment thereof for use in the methods, compositions, and combinations provided herein comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2. In some embodiments, durvalumab or antigen-binding fragment thereof for use in the methods, compositions, and combinations provided herein comprises a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises the Kabat-defined CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 3-5, and wherein the light chain variable region comprises the Kabat-defined CDR1, CDR2, and CDR3 sequences of SEQ ID NOs: 6-8. Those of ordinary skill in the art would easily be able to identify Chothia-defined, Abm-defined, or other CDR definitions known to

those of ordinary skill in the art. In some embodiments, durvalumab or antigen-binding fragment thereof for use in the methods, compositions, and combinations provided herein comprises the variable heavy chain and variable light chain CDR sequences of the 2.14H9OPT antibody as disclosed in U.S. Patent Nos. 8,779,108 and 9,493,565.

[0053] Durvalumab light chain (LC) variable region:

[0054] EIVLTQSPGTLSPGERATLSCRASQRVSSSYLAWYQQKPGQAPRLLIYD
ASSRATGIPDRFSGSGSGTDFTLTISRLEPEDFAVYYCQQYGSLPWTFGQGKVEIK
(SEQ ID NO: 1)

[0055] Durvalumab heavy chain (HC) variable region:

[0056] EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYWMSWVRQAPGKGLEWV
ANIKQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCAREGGWF
GELAFDYWGQGTLLTVSS (SEQ ID NO: 2)

[0057] Durvalumab heavy chain CDRs:

[0058] HC-CDR1: GFTFSRYWMS (SEQ ID NO: 3)

[0059] HC-CDR2: NIKQDGSEKYYVDSVKG (SEQ ID NO: 4)

[0060] HC-CDR3: EGGWFGELAFDY (SEQ ID NO: 5)

[0061] Durvalumab, light chain CDRs:

[0062] LC-CDR1: RASQRVSSSYLA (SEQ ID NO: 6)

[0063] LC-CDR2: DASSRAT (SEQ ID NO: 7)

[0064] LC-CDR3: QQYGSLPWT (SEQ ID NO: 8)

[0065] As used herein, the term "PARP inhibitor" means any agent that inhibits the activity of the poly (ADP-ribose) polymerase (PARP) enzyme in cells. PARP helps repair DNA when it becomes damaged. DNA damage may be caused by many things, including exposure to UV light, radiation, certain anticancer drugs, or other substances in the environment. In cancer treatment, blocking PARP may help keep cancer cells from repairing their damaged DNA, causing them to die. In some embodiments, the PARP inhibitor is Olaparib (Lynparza®). Disclosure related to olaparib can be found in European Patent Nos. 1 330 442 and 1 633 724, which are incorporated herein by reference in their entirety.

[0066] As used herein, "chemotherapy" or "chemotherapy agents" can include any chemotherapeutic agents. In some embodiments, the chemotherapy agents comprise one or more platinum-based chemotherapeutic agents. In some embodiments, the one or more platinum-based chemotherapeutic agents comprise carboplatin, cisplatin, oxaliplatin, or combinations thereof. In some embodiments, the chemotherapy agents comprise one or more taxane-based chemotherapeutic agents. In some embodiments, the one or more taxane-based

chemotherapeutic agents comprise nab-paclitaxel, paclitaxel, docetaxel, cabazitaxel, abraxane, anthracycline (Pegylated Liposomal Doxorubicin), or combinations thereof. In some embodiments, the chemotherapy agents comprise one or more platinum-based chemotherapeutic agents in combination with one or more taxane-based chemotherapeutic agents. In various embodiments, the disclosure permits substitution of one or more chemotherapy agents for any other chemotherapy agent and at any time during administration. Substitution of chemotherapy agents may occur for any reason including, but not limited to, a reaction to, or development of hypersensitivity to one or more chemotherapy agents in the subject. In some embodiments, the chemotherapy agents comprise cisplatin and paclitaxel. In some embodiments, the patient is administered one or more doses of cisplatin, wherein the dose is about 25 mg/m². In some embodiments, the patient is administered one or more doses of cisplatin at a dose that produces an Area Under of Curve (AUC) of AUC5 or AUC6. In some embodiments, the patient is administered a dose of cisplatin from about 25 mg/m² to 100 mg/m². In some embodiments, the patient is administered one or more doses of paclitaxel, wherein the dose is about 175 mg/m². In various embodiments, the dose of the chemotherapy agent can be reduced.

[0067] In some embodiments, the number of doses of one or more chemotherapy agents is measured in cycles. The number of treatment doses scheduled within each cycle depends on the chemotherapy agent. In some embodiments, each cycle may contain only 1 dose. In one, non-limiting embodiment, the cycle may contain 1 dose administered on day 1 of the cycle. In other embodiments, a cycle may contain more than 1 dose. In one, non-limiting embodiment, the cycle may contain more than 1 dose given daily or weekly.

[0068] In some embodiments, the number of doses of the anti-PD-L1 antibody or antigen-binding fragment thereof, and/or the PARP inhibitor is measured in cycles. The number of treatment doses scheduled within each cycle depends on the antibody or inhibitor. In some embodiments, each cycle may contain only 1 dose. In one, non-limiting embodiment, the cycle may contain 1 dose administered on day 1 of the cycle. In other embodiments, a cycle may contain more than 1 dose. In one, non-limiting embodiment, the cycle may contain more than 1 dose given daily or weekly.

[0069] The term "subject" as used herein may be a human patient.

[0070] In some embodiments, the methods, compositions, and combinations disclosed herein are used for treating a subject with endometrial cancer, an endometrial tumor disorder, or uterine cancer.

[0071] The terms "treatment" or "treat," as used herein, refer to both therapeutic treatment and prophylactic or preventative measures. Those in need of treatment include subjects having cancer as well as those prone to having cancer or those in cancer is to be prevented. In some embodiments, the methods, compositions, and combinations disclosed herein can be used for the treatment of endometrial cancer. In other embodiments, those in need of treatment include subjects having a tumor as well as those prone to have a tumor or those in which a tumor is to be prevented. In certain embodiments, the methods, compositions, and combinations disclosed herein can be used for the treatment of tumors. In other embodiments, treatment of a tumor includes inhibiting tumor growth, promoting tumor reduction, or both inhibiting tumor growth and promoting tumor reduction.

[0072] In some embodiments, the methods, compositions, and combinations disclosed herein provide an increase in progression free survival (PFS) relative to placebo or standard of care or standard of care and durvalumab. In some embodiments, the methods, compositions, and combinations disclosed herein provide an increase in overall survival (OS) versus placebo or standard of care or standard of care and durvalumab.

[0073] Overall Survival (OS) relates to the time period beginning on the date of treatment until death due to any cause. OS may refer to overall survival within a period of time such as, for example, 2 months, 3 months, 4 months, 6 months, 8 months, 12 months, 18 months, 24 months, and the like. Such periods of time can be identified, for example, as "OS24" which refers to the number (%) of patients who are alive at 24 months after treatment onset per the Kaplan-Meier estimate of overall survival at 24 months. In some embodiments the overall survival is measured as compared to a patient who has only received durvalumab and chemotherapy or has only received chemotherapy. In other embodiments, the overall survival is measured as compared to a patient who has not received treatment.

[0074] Progression-Free Survival (PFS) relates to the time period beginning on the date of treatment until the date of objective disease progression (RECIST 1.1) or death (by any cause in the absence of progression). In some embodiments, the methods, compositions, and combinations of the disclosure provide for (statistically significant and/or clinically meaningful) increase in PFS. In some embodiments, the methods, compositions, and combinations of the disclosure provide for PFS of at least 9 months to at least about 24 months (*e.g.*, at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or more than 24 months, and up to about 5 years). In some embodiments the progression-free survival is measured as compared to a patient who has only received chemotherapy or chemotherapy (*e.g.*, platinum doublet chemotherapy) and durvalumab. In other

embodiments, the overall survival is measured as compared to a patient who has not received treatment. In various embodiments, the PFS benefit is irrespective of PD-L1 status (PD-L1 positive or PD-L1 negative).

[0075] The terms "administration" or "administering," as used herein, refer to providing, contacting, and/or delivering a compound or compounds by any appropriate route to achieve the desired effect. Administration may include, but is not limited to, oral, sublingual, parenteral (*e.g.*, intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, or intracranial injection), transdermal, topical, buccal, rectal, vaginal, nasal, ophthalmic, via inhalation, and implants.

[0076] In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents are administered intravenously. In some embodiments, the PARP inhibitor is administered orally.

[0077] Provided herein are methods, compositions, and combinations for treating endometrial cancer, an endometrial tumor, uterine cancer, or a uterine tumor in a subject in need thereof. The subject may be PARP inhibitor and immune-mediated therapy naïve. As used herein "endometrial cancer" refers to any cancer or tumor which originates in the endometrium, or uterine lining. Endometrial cancer can also be referred to as uterine cancer.

[0078] Endometrial cancer often displays symptoms of abnormal uterine bleeding, the majority (~75%) of patients are diagnosed at an early stage (Stage I or II), and these patients have a better prognosis with 5-year OS rate ranging from 74% to 91% (Creasman et al 2006, Siegel et al 2015). Standard therapy for these patients is surgery with or without radiotherapy. Systemic therapy is not frequently administered to these early stage patients. For patients diagnosed at a later stage or with advanced endometrial cancer, however, the prognosis is far worse. Although endometrial cancer shows a strong initial sensitivity to platinum doublet chemotherapy compared to many other solid tumors with a response rate of approximately 51%, most patients diagnosed at an advanced stage will show progression of their disease with median PFS of approximately 12 months (Miller et al 2012, Aghajanian et al 2018). Five-year OS rates also remain poor for these patients with advanced disease (57% to 66% for Stage III and 20% to 26% for Stage IV disease (Creasman et al 2006, Siegel et al 2015).

[0079] The severity of endometrial cancer is measured in stages. As used herein, "stages" refers to an international system used to assess how far the cancer has spread. In Stage I the cancer is confined to the uterus. In stage II the cancer has spread to the cervix. In stage III the cancer has spread to the vagina, ovaries, and/or lymph nodes. In stage IV the cancer has spread to the urinary bladder, rectum, or organs located far from the uterus, such as the lungs

or bones. Stage III and Stage IV are considered advanced endometrial cancer. The endometrial cancer referred to herein may be a selection from stage II, III, IV and recurrent cancer. In one embodiment, the endometrial cancer referred to herein is stage III, IV or recurrent cancer.

[0080] Endometrial cancer is a heterogeneous disease with various molecular patterns. Approximately 20% of endometrial cancer patients have MSI-H or deficient mismatch repair (dMMR) tumours. Mismatch repair is one of a cell's mechanisms for repairing damage to DNA that primarily results from single base pair insertions or deletions (called indels) when slippage occurs during DNA replication by DNA polymerases. This type of DNA polymerase error tends to occur at areas of short, repetitive DNA sequences, termed microsatellites. Therefore, deficient mismatch repair (dMMR) can be discovered by looking at the variation in the length of a microsatellite in normal tissue compared with its length in the same patient's tumor tissue. When a high rate of variation in microsatellite length exists across the genome, a tumor is said to have high levels of microsatellite instability (MSI-H), which reflects underlying deficiency in mismatch repair capability.

[0081] Deficient mismatch repair (dMMR) and its characteristic genetic signature, high levels of microsatellite instability (MSI-H) across the genome, define a unique biologic subset of cancers that are characterized by a high tumor mutational load and potential responsiveness to anti-programmed cell death 1 (PD-1)-based immune checkpoint inhibitor immunotherapy. dMMR may, for example, occur due to a mutation in one or a selection of (e.g., all of) the following MMR proteins: MLH1, PMS2, MSH2 and MSH6; and optionally a V600E mutated BRAF protein. MMR may be determined using the VENTANA MMR IHC panel. The VENTANA MMR IHC panel comprises the following primary antibodies VENTANA anti-MLH1 (M1), VENTANA anti-PMS2 (A16-4), VENTANA anti-MLH2 (G219-1129), VENTANA anti-MSH6 (SP93), and VENTANA anti-BRAF V600E (VE1).

[0082] In some embodiments, the methods, compositions, and combinations of the disclosure are used for treating a subject with endometrial cancer wherein the endometrial cancer tumor is deficient in mismatch repair (dMMR). In other embodiments, the methods, compositions, and combinations of the disclosure are used for treating a subject with endometrial cancer wherein the endometrial cancer tumor is not deficient in mismatch repair (MMR proficient, pMMR).

[0083] In some embodiments, the methods, compositions, and combinations of the disclosure comprise administering to a subject with deficient mismatch repair (dMMR) endometrial cancer: (a) a therapeutically effective amount of one or more chemotherapy

agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[0084] In some other embodiments, the methods, compositions, and combinations of the disclosure comprise administering to a subject with proficient mismatch repair (pMMR) endometrial cancer: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

[0085] In one embodiment, the endometrial cancer is naïve to first-line systemic anticancer treatment. In one embodiment, the endometrial cancer is naïve to PARP inhibitors and immune-mediated treatment.

[0086] In some embodiments, the methods, compositions, and combinations of the disclosure are used for treating a subject with endometrial cancer wherein the endometrial cancer tumor is PD-L1 positive (defined as tumor area positivity [TAP] $\geq 1\%$). In other embodiments, the methods, compositions, and combinations of the disclosure are used for treating a subject with endometrial cancer wherein the endometrial cancer tumor is PD-L1 negative.

[0087] Provided herein are methods of treating endometrial cancer in a subject in need thereof, comprising administering to the subject (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and a therapeutically effective amount of a PARP inhibitor. In some embodiments herein, step (b) can exclude a therapeutically effective amount of a PARP inhibitor. In these embodiments, step (b) includes a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[0088] In some embodiments, provided herein is a method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of about 10 mg/kg to 20 mg/kg (or a flat dose of about 800 mg to 1500 mg, such as 1120 mg or 1500 mg), and a PARP inhibitor at a dose of about 100 mg to 300 mg.

[0089] Also provided herein are combinations for the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises (a) a therapeutically effective

amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and a therapeutically effective amount of a PARP inhibitor. In some embodiments herein, the combination of (b) can exclude a therapeutically effective amount of a PARP inhibitor. In these embodiments, the combination of (b) includes a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[0090] In some embodiments, the combinations provided herein comprise an anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of about 10 mg/kg to 20 mg/kg (or a flat dose of about 800 mg to 1500 mg, such as 1120 mg or 1500mg), and a PARP inhibitor at a dose of about 100 mg to 300 mg.

[0091] The dose of the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor to be administered to the subject may vary depending, in part, upon the size (body weight, body surface, or organ size) and condition (the age and general health) of the subject.

[0092] In particular embodiments, the subject is administered one or more doses of the anti-PD-L1 antibody or antigen-binding fragment thereof, wherein the dose is about 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, 13 mg/kg, 14 mg/kg, or 15 mg/kg, 20 mg/kg, or 25 mg/kg. In some embodiments, the subject is administered one or more doses of the anti-PD-L1 antibody or antigen-binding fragment thereof wherein the dose is about 15 mg/kg or 20 mg/kg.

[0093] In particular embodiments, the subject is administered one or more flat doses of the anti-PD-L1 antibody or antigen-binding fragment thereof, wherein the dose is about 500 mg, 650 mg, 675 mg, 700 mg, 725 mg, 750 mg, 775 mg, 800 mg, 825 mg, 850 mg, 875 mg, 900 mg, 925 mg, 950 mg, 975 mg, 1000 mg, 1025 mg, 1050 mg, 1075 mg, 1100 mg, 1120 mg, 1125mg, 1150 mg, 1175 mg, 1180 mg, 1200 mg, 1225 mg, 1250 mg, 1275 mg, 1300 mg, 1325 mg, 1350 mg, 1375 mg, 1400 mg, 1450 mg, 1475 mg, 1500 mg, 1525 mg, 1550 mg, 1575 mg, 1600 mg, 1625 mg, 1650 mg, 1675 mg, 1700 mg, 1725 mg, 1750 mg, 1775 mg, 1800 mg, 1825 mg, 1850 mg, or 1875mg. In some embodiments, the subject is administered one or more flat doses of the anti-PD-L1 antibody or antigen-binding fragment thereof wherein the dose is about 1120 mg or 1500 mg.

[0094] In particular embodiments, the subject is administered one or more flat doses of the PARP inhibitor, wherein the dose is about 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 375 mg, 400 mg, 425 mg, 450 mg, 475

mg, 500 mg, 525 mg, 550 mg, 575 mg, or 600 mg. In some embodiments, the subject is administered one or more flat doses of the PARP inhibitor wherein the dose is 300 mg. In some embodiments, a dose of from 100 mg to 300 mg of the PARP inhibitor is administered twice daily. Thus, the PARP inhibitor may be administered at a daily dose of from 200 mg to 600 mg (2 x 100 mg to 300 mg). In other embodiments, the PARP inhibitor daily dose can be reduced.

[0095] In one particular non-limiting embodiment, step (a) comprises administration of 1120 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof.

[0096] In one particular non-limiting embodiment, step (b) comprises administration of 1500 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof; and 300 mg of the PARP inhibitor.

[0097] The terms "co-administered," "in combination," or "combination therapy," as used herein, refer to simultaneous or sequential administration of multiple compounds or agents. A first compound or agent may be administered before, concurrently with, or after administration of a second compound or agent; a third compound or agent may be administered before, concurrently with, or after administration of a first and/or second compound or agent; a fourth compound or agent may be administered before, concurrently with, or after administration of a first, second, and/or third compound or agent. The first compound or agent, the second compound or agent, the third compound or agent, and the fourth compound or agent may be simultaneously or sequentially administered on the same day, or may be sequentially administered within 1 day, 2 days, 3 days, 4 days, 5 days, 6 days, 1 week, 2 weeks, 3 weeks, or 1 month of each other. In some embodiments, compounds or agents are co-administered during the period in which each of the compounds or agents are exerting at least some physiological effect and/or has remaining efficacy. In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents in step (a) are administered to the subject simultaneously, separately, and/or sequentially (e.g., separately, and sequentially). In some embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor in step (b) are administered to the subject simultaneously, separately, and/or sequentially (e.g., separately, and sequentially).

[0098] In particular embodiments, an initial step (step (a)) of the methods disclosed herein or an initial component of the combinations disclosed herein comprise a therapeutically effective amount of one or more chemotherapy agents, and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof administered

over a two week treatment period, over a three week treatment period, over a four week treatment period, over a five week treatment period, over a six week treatment period, over an eight week treatment period, over a twelve week treatment period, over a fourteen week treatment period, over a sixteen week treatment period, over an eighteen week treatment period, over a twenty-four week treatment period, or over a one-year or more treatment period. In particular embodiments, an initial step (step (a)) of the methods disclosed herein or an initial component of the combinations disclosed herein comprise a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof administered over a nine, ten or twelve to eighteen-week treatment period. In one non-limiting embodiment, step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every three weeks for eighteen weeks.

[0099] In certain embodiments, a subsequent step (step (b)) of the methods disclosed herein or a subsequent component of the combinations disclosed herein comprise a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and optionally a therapeutically effective amount of a PARP inhibitor administered over a two week treatment period, over a three week treatment period, over a four week treatment period, over a five week treatment period, over a six week treatment period, over an eight week treatment period, over a twelve week treatment period, over a fourteen week treatment period, over a sixteen week treatment period, over an eighteen week treatment period, over a twenty-four week treatment period, over a six month treatment period, over an eight month treatment period, over a twelve month treatment period, over a fourteen month treatment period, over a fifteen month treatment period, over a sixteen month treatment period, over a eighteen month treatment period, over a twenty month treatment period, over a twenty four month treatment period or more. In certain embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof and the optional PARP inhibitor is administered over a one month to twenty-four month or more treatment period. In certain embodiments, the anti-PD-L1 antibody or antigen-binding fragment thereof and PARP inhibitor is administered over a twenty-four month treatment period. In certain embodiments, step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks or up until disease progression.

[00100] In particular embodiments of (a) of the methods, compositions, and combinations of the disclosure, a therapeutically effective amount of one or more chemotherapy agents is administered about every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, every eight weeks, every ten weeks, or every twelve weeks; and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered about every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, every eight weeks, every ten weeks, or every twelve weeks.

[00101] In one particular embodiment of (a) a therapeutically effective amount of one or more chemotherapy agents, and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every three weeks.

[00102] In another particular embodiment of (a) a therapeutically effective amount of one or more chemotherapy agents, and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every three weeks for a minimum of three cycles and a maximum of eight cycles. In one, non-limiting embodiment of (a) a therapeutically effective amount of one or more chemotherapy agents, and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every three weeks for six cycles. In another particular embodiment of (a), a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every three weeks for nine, ten or twelve to eighteen weeks.

[00103] In particular embodiments of (b) of the methods, compositions, and combinations of the disclosure, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered about every week, every two weeks, every three weeks, every four weeks, every five weeks, every six weeks, every seven weeks, every eight weeks, every ten weeks, or every twelve weeks, and a therapeutically effective amount of a PARP inhibitor is administered once, twice or thrice daily.

[00104] In one particular embodiment of (b), a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every four weeks.

[00105] In one particular embodiment of (b), a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every four weeks; and a therapeutically effective amount of a PARP inhibitor is administered twice daily.

[00106] In another particular embodiment of (b), a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every four weeks

for at least 12 weeks, or 3 months, and up to twenty-four months, and a therapeutically effective amount of a PARP inhibitor is administered twice daily for at least 12 weeks, or 3 months, and up to twenty-four months.

[00107] In another particular embodiment of (b), a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof is administered every four weeks for at least 12 weeks, or 3 months, and up to twenty-four months.

[00108] In particular embodiments, a therapeutically effective amount of one or more chemotherapy agents is administered for a minimum of three cycles and a maximum of eight cycles. In one, non-limiting embodiment, a therapeutically effective amount of one or more chemotherapy agents is administered for six cycles. In particular embodiments, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof (*e.g.*, durvalumab) is administered for a total of up to about 24 months for a total of up to 35 cycles. In particular embodiments, a therapeutically effective amount of a PARP inhibitor (*e.g.*, olaparib) is administered for a total of up to 24 months.

[00109] In particular embodiments, provided herein are methods, compositions, and combinations for the treatment of endometrial cancer in a subject in need thereof, wherein (a) a therapeutically effective amount of one or more chemotherapy agents is administered every three weeks for nine, ten, or twelve to eighteen weeks, and an anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of 1120 mg every three weeks for nine, ten, or twelve to eighteen weeks; and (b) an anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of 1500 mg every four weeks, preferably for a total of twenty-four months, and a PARP inhibitor is administered at a dose of 300 mg twice daily, preferably for a total of twenty-four months.

[00110] In particular embodiments, provided herein are methods, compositions, and combinations for the treatment of endometrial cancer in a subject in need thereof, wherein (a) paclitaxel at a dose of 175 mg/m² and carboplatin at a dose of AUC5 or AUC6 are administered intravenously every three weeks for nine, ten, or twelve to eighteen weeks, and durvalumab is administered intravenously at a dose of 1120 mg every three weeks for nine, ten, or twelve to eighteen weeks; and followed by (b) durvalumab is administered intravenously at a dose of 1500 mg every four weeks, preferably for a total of twenty-four months, and olaparib is administered orally at a dose of 300 mg twice daily, preferably for a total of twenty-four months.

[00111] In particular embodiments, provided herein are methods, compositions, and combinations for the treatment of endometrial cancer in a subject in need thereof, wherein

step (a) comprises administration of three to eight doses of the anti-PD-L1 antibody or antigen-binding fragment thereof, and three to eight cycles of the one or more chemotherapy agents. In one, non-limiting embodiment provided herein are methods, compositions, and combinations for the treatment of endometrial cancer in a subject in need thereof, wherein step (a) comprises administration of six doses of the anti-PD-L1 antibody or antigen-binding fragment thereof, and six cycles of the one or more chemotherapy agents.

[00112] In particular embodiments, provided herein are methods, compositions, and combinations for the treatment of endometrial cancer in a subject in need thereof, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks, or 3 months, and up to 24 months and optionally twice daily doses of the PARP inhibitor for at least 12 weeks, or 3 months, and up to 24 months.

[00113] In certain embodiments of the disclosed methods, compositions, and/or combinations, step/combination (a) is administered prior to step/combination (b). In another embodiment, step/combination (b) is not administered until after completion of step/combination (a).

[00114] The terms "pharmaceutical composition" or "therapeutic composition," as used herein, refer to a compound or composition capable of inducing a desired therapeutic effect when properly administered to a subject. In some embodiments, the disclosure provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one antibody of the disclosure.

[00115] The terms "pharmaceutically acceptable carrier" or "physiologically acceptable carrier," as used herein, refer to one or more formulation materials suitable for accomplishing or enhancing the delivery of one or more antibodies of the disclosure.

[00116] When used for *in vivo* administration, the formulations of the disclosure should be sterile. The formulations of the disclosure may be sterilized by various sterilization methods, including, for example, sterile filtration or radiation. In one embodiment, the formulation is filter sterilized with a presterilized 0.22-micron filter. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice as described in "Remington: The Science & Practice of Pharmacy," 21st ed., Lippincott Williams & Wilkins, (2005).

[00117] In some embodiments, antibodies can be formulated for particular routes of administration, such as oral, nasal, pulmonary, topical (including buccal and sublingual), rectal, vaginal, and/or parenteral administration. The terms "parenteral administration" and "administered parenterally," as used herein, refer to modes of administration other than

enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, epidural and intrasternal injection, and infusion. Formulations of the disclosure that are suitable for topical or transdermal administration include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The antibodies and other actives may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required (*see, e.g.*, U.S. Patent Nos. 7,378,110; 7,258,873; and 7,135,180; U.S. Patent Application Publication Nos. 2004/0042972 and 2004/0042971).

[00118] The formulations can be presented in unit dosage form and can be prepared by any method known in the art of pharmacy. Actual dosage levels of the active ingredients in the formulation of the present disclosure may be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular subject, composition, and mode of administration, without being toxic to the subject (*e.g.*, "a therapeutically effective amount"). Dosages can also be administered via continuous infusion (such as through a pump). The administered dose may also depend on the route of administration. For example, subcutaneous administration may require a higher dosage than intravenous administration.

[00119] Without limiting the disclosure, a number of embodiments of the disclosure are described herein for purpose of illustration.

[00120] Embodiment 1. A method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

[00121] Embodiment 2. A method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[00122] Embodiment 3. The method of either embodiment 1 or 2, wherein step (b) occurs after completion of step (a).

- [00123] Embodiment 4. The method according any one of embodiments 1-3, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab.
- [00124] Embodiment 5. The method according to any one of embodiments 1 to 4, wherein the PARP inhibitor is olaparib.
- [00125] Embodiment 6. The method according to any one of claims 1 to 5, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of from 800 mg to 1500 mg.
- [00126] Embodiment 7. The method according to embodiment 6, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of 1120 mg and/or 1500mg.
- [00127] Embodiment 8. The method according to any one of embodiments 1 to 7, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of from 10 mg/kg to 20 mg/kg.
- [00128] Embodiment 9. The method according to embodiment 8, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg and/or 20 mg/kg.
- [00129] Embodiment 10. The method according to any one of embodiments 1 to 9, wherein the PARP inhibitor is administered at a dose of 100 mg to 300 mg.
- [00130] Embodiment 11. The method according to embodiment 10, wherein the PARP inhibitor is administered at a dose of 300 mg.
- [00131] Embodiment 12. The method according to any one of embodiments 1 to 11, wherein the one or more chemotherapy agents is paclitaxel and/or carboplatin.
- [00132] Embodiment 13. The method according to any one of embodiments 1 to 12, wherein the paclitaxel is administered at a dose of 175 mg/m².
- [00133] Embodiment 14. The method according to embodiment 12 or embodiment 13, wherein the carboplatin is administered at a dose that produces an Area Under of Curve (AUC) of AUC₅ or AUC₆.
- [00134] Embodiment 15. The method according to any one of embodiments 1 to 14, wherein step (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents every two to four weeks.
- [00135] Embodiment 16. The method according to embodiment 15, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every two to four weeks for nine to eighteen weeks.

[00136] Embodiment 17. The method according to any one of embodiments 1 to 15, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every three weeks.

[00137] Embodiment 18. The method according to embodiment 17, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every three weeks for twelve to eighteen weeks.

[00138] Embodiment 19. The method according to embodiment 17, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every three weeks for eighteen weeks.

[00139] Embodiment 20. The method according to any one of embodiments 1 to 19, wherein step (a) comprises administration of four to six doses of the anti-PD-L1 antibody or antigen-binding fragment thereof and four to six cycles of the one or more chemotherapy agents.

[00140] Embodiment 21. The method according to any one of embodiments 1 to 20, wherein step (a) comprises administration of 1120 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof.

[00141] Embodiment 22. The method according to embodiment 21, wherein step (a) comprises administration of 1120 mg of durvalumab.

[00142] Embodiment 23. The method according to embodiment 22, wherein step (a) comprises administration of 1120 mg of durvalumab every 3 weeks.

[00143] Embodiment 24. The method according to any one of embodiments 21 to 23, wherein step (a) further comprises administration of: 175 mg/m² of paclitaxel; AUC 5 or AUC 6 of carboplatin; and/or 25 mg/m² of cisplatin.

[00144] Embodiment 25. The method according to any one of embodiments 1 to 24, wherein step (b) comprises: administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every two to four weeks; and administration of a dose of the PARP inhibitor twice daily.

[00145] Embodiment 26. The method according to any one of embodiments 1 to 25, wherein step (b) comprises: administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks; and administration of a dose of the PARP inhibitor twice daily.

[00146] Embodiment 27. The method according to any one of embodiments 1 to 26, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks.

[00147] Embodiment 28. The method according to embodiment 27, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months and twice daily doses of the PARP inhibitor for up to 24 months.

[00148] Embodiment 29. The method according to any one of embodiments 1 to 28, wherein step (b) comprises administration of: 1500 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof; and 300 mg of the PARP inhibitor.

[00149] Embodiment 30. The method according to embodiment 29, wherein step (b) comprises administration of: 1500 mg of durvalumab; and 300 mg olaparib.

[00150] Embodiment 31. The method according to embodiment 30, wherein step (b) comprises administration of: 1500 mg of durvalumab every 4 weeks; and 300 mg olaparib twice a day.

[00151] Embodiment 32. The method according to any one of embodiments 2 to 24, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every two to four weeks.

[00152] Embodiment 33. The method according to any one of embodiments 2 to 24, or 32, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks.

[00153] Embodiment 34. The method according to any one of embodiments 2 to 24, or 32-33 wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks.

[00154] Embodiment 35. The method according to embodiment 34, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months.

[00155] Embodiment 36. The method according to any one of embodiments 2 to 24 or 32-35, wherein step (b) comprises administration of 1500 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof.

[00156] Embodiment 37. The method according to embodiment 36, wherein step (b) comprises administration of 1500 mg of durvalumab.

- [00157] Embodiment 38. The method according to embodiment 37, wherein step (b) comprises administration of 1500 mg of durvalumab every 4 weeks.
- [00158] Embodiment 39. The method according to any one of embodiments 1 to 38, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents are administered intravenously.
- [00159] Embodiment 40. The method according to any one of embodiments 1 to 39, wherein the PARP inhibitor is administered orally.
- [00160] Embodiment 41. The method according to any one of embodiments 1 to 40, wherein the antigen-binding fragment thereof, the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents in step (a) are administered to the subject simultaneously, separately, and/or sequentially.
- [00161] Embodiment 42. The method according to any one of embodiments 1 to 42, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor in step (b) are administered to the subject simultaneously, separately, and/or sequentially.
- [00162] Embodiment 43. The method according to any one of embodiments 1 to 42, wherein the endometrial cancer is advanced endometrial cancer.
- [00163] Embodiment 44. The method according to any one of embodiments 1 to 43, wherein the endometrial cancer is an endometrial cancer tumor lacking mismatch repair (MMR-deficient (dMMR)).
- [00164] Embodiment 45. The method according to embodiment 44, comprising administering to the subject with deficient mismatch repair (dMMR) endometrial cancer: (a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.
- [00165] Embodiment 46. The method according to any one of embodiments 1 to 43, wherein the endometrial cancer is an endometrial cancer tumor that is MMR proficient (pMMR).
- [00166] Embodiment 47. The method according to embodiment 46, comprising administering to the subject with proficient mismatch repair (pMMR) endometrial cancer: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a

therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

[00167] Embodiment 48. The method according to any one of embodiments 1 to 47, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 positive.

[00168] Embodiment 49. The method according to any one of embodiments 1 to 47, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 negative.

[00169] Embodiment 50. The method according to any one of embodiments 1 to 49, wherein the treatment produces an increase in progression free survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

[00170] Embodiment 51. The method according to embodiment 50, wherein the treatment produces an increase in progression free survival for at least 4 months.

[00171] Embodiment 52. The method according to any one of embodiments 1 to 51, wherein the treatment produces an increase in overall survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

[00172] Embodiment 53. The method according to embodiment 52, wherein the treatment produces an increase in overall survival for at least 4 months.

[00173] Embodiment 54. A combination for use in the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and a therapeutically effective amount of a PARP inhibitor.

[00174] Embodiment 55. A combination for use in the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[00175] Embodiment 56. The combination for use according to either embodiment 54 or embodiment 55, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab.

[00176] Embodiment 57. The combination for use according to any one of embodiments 54 to 56, wherein the PARP inhibitor is olaparib.

[00177] Embodiment 58. The combination for use according to any one of embodiments 54 to 57, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 800 mg to 1500 mg.

[00178] Embodiment 59. The combination for use according to embodiment 58, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 1120 mg and/or 1500 mg.

[00179] Embodiment 60. The combination for use according to any one of embodiments 54 to 59, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 10 mg/kg to 20 mg/kg.

[00180] Embodiment 61. The combination for use according to embodiment 60, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 15 mg/kg and/or 20 mg/kg.

[00181] Embodiment 62. The combination for use according to any one of embodiments 54 to 61, wherein the dose of PARP inhibitor is from 100 mg to 300 mg.

[00182] Embodiment 63. The combination for use according to embodiment 62, wherein the dose of PARP inhibitor is 300 mg.

[00183] Embodiment 64. The combination for use according to any one of embodiments 54 to 63, wherein the one or more chemotherapy agents is paclitaxel and/or carboplatin.

[00184] Embodiment 65. The combination for use according to embodiment 64, wherein the dose of paclitaxel is 175 mg/m².

[00185] Embodiment 66. The combination for use according to embodiment 64 or embodiment 65, wherein the dose of carboplatin produces an Area Under of Curve (AUC) of AUC₅ or AUC₆.

[00186] Embodiment 67. The combination for use according to any one of embodiments 54 to 66, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents every two to four weeks.

[00187] Embodiment 68. The combination for use according to embodiment 67, wherein administration is every two to four weeks for nine to twenty-four weeks.

[00188] Embodiment 69. The combination for use according to embodiment 67 or embodiment 68, wherein administration is every three weeks or every four weeks.

[00189] Embodiment 70. The combination for use according to embodiment 69, wherein administration is every three weeks for twelve to eighteen weeks.

[00190] Embodiment 71. The combination for use according to embodiment 70, wherein administration is every three weeks for eighteen weeks.

[00191] Embodiment 72. The combination for use according to any one of embodiments 54 to 71, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof for three to six doses, and the one or more chemotherapy agents for four to six doses.

[00192] Embodiment 73. The combination for use according to any one of embodiments 54 to 72, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1120 mg.

[00193] Embodiment 74. The combination for use according to embodiment 73, wherein the durvalumab is administered at a dose of 1120 mg.

[00194] Embodiment 75. The combination for use according to embodiment 73 or embodiment 74, wherein the durvalumab is administered at a dose of 1120 mg every 3 weeks.

[00195] Embodiment 76. The combination for use according to any one of embodiments 73 to 75, wherein (a) further comprises: 175 mg/m² of paclitaxel; AUC 5 or AUC 6 of carboplatin; and/or 25 mg/m² of cisplatin.

[00196] Embodiment 77. The combination for use according to any one of embodiments 54 to 76, wherein (b) comprises: the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks; and the PARP inhibitor administered twice daily.

[00197] Embodiment 78. The combination for use according to any one of embodiments 54 to 77, wherein (b) comprises: the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks; and the PARP inhibitor administered twice daily.

[00198] Embodiment 79. The combination for use according to any one of embodiments 54 to 78, wherein (b) comprises administration of: the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg; and the PARP inhibitor at a dose of 300 mg.

[00199] Embodiment 80. The combination for use according to embodiment 77, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks.

[00200] Embodiment 81. The combination for use according to embodiment 79, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months and twice daily doses of the PARP inhibitor for up to 24 months.

[00201] Embodiment 82. The combination for use according to embodiment 79, wherein (b) comprises administration of: durvalumab at a dose of 1500 mg; and olaparib at a dose of 300 mg.

[00202] Embodiment 83. The combination for use according to any one of embodiments 79 to 81, wherein (b) comprises administration of: durvalumab at a dose of 1500 mg every 3 weeks; and olaparib at a dose of 300 mg twice a day.

[00203] Embodiment 84. The combination for use according to any one of embodiments 55 to 76, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks.

[00204] Embodiment 85. The combination for use according to any one of embodiments 55 to 76, or 84, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks.

[00205] Embodiment 86. The combination for use according to any one of embodiments 55 to 76, or 84-85, wherein (b) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg.

[00206] Embodiment 87. The combination for use according to embodiment 85, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12.

[00207] Embodiment 88. The combination for use according to embodiment 87, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months.

[00208] Embodiment 89. The combination for use according to embodiment 86, wherein (b) comprises administration of durvalumab at a dose of 1500 mg.

[00209] Embodiment 90. The combination for use according to any one of embodiments 84 to 89, wherein (b) comprises administration of durvalumab at a dose of 1500 mg every 3 weeks.

[00210] Embodiment 91. The combination for use according to any one of embodiments 54 to 90, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents are administered intravenously.

[00211] Embodiment 92. The combination for use according to any one of embodiments 54 to 91, wherein the PARP inhibitor is administered orally.

[00212] Embodiment 93. The combination for use according to any one of embodiments 54 to 92, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one

or more chemotherapy agents in (a) are administered to the subject simultaneously, separately, and/or sequentially.

[00213] Embodiment 94. The combination for use according to any one of embodiments 54 to 93, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor in (b) are administered to the subject simultaneously, separately, and/or sequentially.

[00214] Embodiment 95. The combination for use according to any one of embodiments 54 to 94, wherein the endometrial cancer is advanced endometrial cancer.

[00215] Embodiment 96. The combination for use according to any one of embodiments 54 to 95, wherein the endometrial cancer is an endometrial cancer tumor lacking mismatch repair (dMMR).

[00216] Embodiment 97. The combination for use according to embodiment 96 in the treatment of deficient mismatch repair (dMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[00217] Embodiment 98. The combination for use according to any one of embodiments 54 to 95, wherein the endometrial cancer is an endometrial cancer tumor that is MMR proficient (pMMR).

[00218] Embodiment 99. The combination for use according to embodiment 98 in the treatment of proficient mismatch repair (pMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

[00219] Embodiment 100. The combination for use according to any one of embodiments 54 to 99, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 positive.

[00220] Embodiment 101. The combination for use according to any one of embodiments 54 to 99, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 negative.

[00221] Embodiment 102. The combination for use according to any one of embodiments 54 to 101, wherein treatment with the combination produces an increase in progression free survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

[00222] Embodiment 103. The combination for use according to embodiment 102, wherein the treatment produces an increase in progression free survival for at least 4 months.

[00223] Embodiment 104. The combination for use according to any one of embodiments 54 to 101, wherein treatment with the combination produces an increase in overall survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

[00224] Embodiment 105. The combination for use according to embodiment 104, wherein the treatment produces an increase in overall survival for at least 4 months.

[00225] Embodiment 106. Use of a combination in the manufacture of a medicament for the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and a therapeutically effective amount of a PARP inhibitor.

[00226] Embodiment 107. Use of a combination in the manufacture of a medicament for the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[00227] Embodiment 108. The use according to embodiment 106 or embodiment 107, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab.

[00228] Embodiment 109. The use according to any one of embodiments 106 to 108, wherein the PARP inhibitor is olaparib.

[00229] Embodiment 110. The use according to any one of embodiments 106 to 109, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 800 mg to 1500 mg.

[00230] Embodiment 111. The use according to embodiment 110, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 1120 mg and/or 1500 mg.

- [00231] Embodiment 112. The use according to any one of embodiments 106 to 111, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 10 mg/kg to 20 mg/kg.
- [00232] Embodiment 113. The use according to embodiment 112, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 15 mg/kg and/or 20 mg/kg.
- [00233] Embodiment 114. The use according to any one of embodiments 106 to 113, wherein the dose of PARP inhibitor is from 100 mg to 300 mg.
- [00234] Embodiment 115. The use according to embodiment 114, wherein the dose of PARP inhibitor is 300 mg.
- [00235] Embodiment 116. The use according to any one of embodiments 114 to 115, wherein the one or more chemotherapy agents is paclitaxel and/or carboplatin.
- [00236] Embodiment 117. The use according to embodiment 116, wherein the dose of paclitaxel is 175 mg/m².
- [00237] Embodiment 118. The use according to embodiment 116 or embodiment 117, wherein the dose of carboplatin produces an Area Under of Curve (AUC) of AUC5 or AUC6.
- [00238] Embodiment 119. The use according to any one of embodiments 106 to 118, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents every two to four weeks.
- [00239] Embodiment 120. The use according to embodiment 119, wherein administration is every two to four weeks for nine to twenty-four weeks.
- [00240] Embodiment 121. The use according to embodiment 119 or embodiment 120, wherein administration is every three weeks or every four weeks.
- [00241] Embodiment 122. The use according to embodiment 121, wherein administration is every three weeks for twelve to eighteen weeks.
- [00242] Embodiment 123. The use according to embodiment 122, wherein administration is every three weeks for eighteen weeks.
- [00243] Embodiment 124. The use according to any one of embodiments 106 to 123, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof for three to six doses, and the one or more chemotherapy agents for four to six doses.
- [00244] Embodiment 125. The use according to any one of embodiments 106 to 124, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1120 mg.
- [00245] Embodiment 126. The use according to embodiment 125, wherein the durvalumab is administered at a dose of 1120 mg.

- [00246] Embodiment 127. The use according to embodiment 125 or embodiment 126, wherein the durvalumab is administered at a dose of 1120 mg every 3 weeks.
- [00247] Embodiment 128. The use according to any one of embodiments 125 to 127, wherein (a) further comprises: 175 mg/m² of paclitaxel; AUC 5 or AUC 6 of carboplatin; and/or 25 mg/m² of cisplatin.
- [00248] Embodiment 129. The use according to any one of embodiments 106 to 128, wherein (b) comprises: the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks; and the PARP inhibitor administered twice daily.
- [00249] Embodiment 130. The use according to any one of embodiments 106 to 129, wherein (b) comprises: the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks; and the PARP inhibitor administered twice daily.
- [00250] Embodiment 131. The use according to any one of embodiments 106 to 130, wherein (b) comprises administration of: the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg; and the PARP inhibitor at a dose of 300 mg.
- [00251] Embodiment 132. The use according to embodiment 131, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks.
- [00252] Embodiment 133. The use according to embodiment 131, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months and twice daily doses of the PARP inhibitor for up to 24 months.
- [00253] Embodiment 134. The use according to embodiment 131, wherein (b) comprises administration of: durvalumab at a dose of 1500 mg; and olaparib at a dose of 300 mg.
- [00254] Embodiment 135. The use according to any one of embodiments 131 to 134, wherein (b) comprises administration of: durvalumab at a dose of 1500 mg every 3 weeks; and olaparib at a dose of 300 mg twice a day.
- [00255] Embodiment 136. The use according to any one of embodiments 107 to 128, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks.
- [00256] Embodiment 137. The use according to any one of embodiments 107 to 128, or 136, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks.

[00257] Embodiment 138. The use according to any one of embodiments 106 to 128 or 136 to 137 wherein (b) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg.

[00258] Embodiment 139. The use according to embodiment 137, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks.

[00259] Embodiment 140. The use according to embodiment 137, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months.

[00260] Embodiment 141. The use according to embodiment 137, wherein (b) comprises administration of durvalumab at a dose of 1500 mg.

[00261] Embodiment 142. The use according to any one of embodiments 137 to 141, wherein (b) comprises administration of durvalumab at a dose of 1500 mg every 3 weeks.

[00262] Embodiment 143. The use according to any one of embodiments 106 to 142, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents are administered intravenously.

[00263] Embodiment 144. The use according to any one of embodiments 106 to 143, wherein the PARP inhibitor is administered orally.

[00264] Embodiment 145. The use according to any one of embodiments 106 to 144, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents in (a) are administered to the subject simultaneously, separately, and/or sequentially.

[00265] Embodiment 146. The use according to any one of embodiments 106 to 145, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor in (b) are administered to the subject simultaneously, separately, and/or sequentially.

[00266] Embodiment 147. The use according to any one of embodiments 106 to 146, wherein the endometrial cancer is advanced endometrial cancer.

[00267] Embodiment 148. The use according to any one of embodiments 106 to 147, wherein the endometrial cancer is an endometrial cancer tumor lacking mismatch repair (dMMR).

[00268] Embodiment 149. The use according to embodiment 148 in the manufacture of a medicament for the treatment of deficient mismatch repair (dMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective

amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

[00269] Embodiment 150. The use according to any one of embodiments 106 to 147, the endometrial cancer is an endometrial cancer tumor that is MMR proficient (pMMR).

[00270] Embodiment 151. The use according to embodiment 150 the manufacture of a medicament for the treatment of proficient mismatch repair (pMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises: (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

[00271] Embodiment 152. The use according to any one of embodiments 106 to 151, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 positive.

[00272] Embodiment 153. The use according to any one of embodiments 106 to 151, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 negative.

[00273] Embodiment 154. The use according to any one of embodiments 106 to 153, wherein treatment with the combination produces an increase in progression free survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

[00274] Embodiment 155. The use according to embodiment 154, wherein the treatment produces an increase in progression free survival for at least 4 months.

[00275] Embodiment 156. The use according to any one of embodiments 106 to 153, wherein treatment with the combination produces an increase in overall survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

[00276] Embodiment 157. The use according to embodiment 156, wherein the treatment produces an increase in overall survival for at least 4 months.

EXAMPLES

[00277] The Examples that follow are illustrative of specific embodiments of the disclosure, and various uses thereof. They are set forth for explanatory purposes only and should not be construed as limiting the scope of the disclosure in any way.

Example 1: Durvalumab with or without Olaparib as Maintenance Therapy after First Line Treatment of Advanced and Recurrent Endometrial Cancer (DUO-E)

[00278] A phase III study assessed the efficacy and safety of durvalumab in combination with platinum-based chemotherapy (paclitaxel + carboplatin) followed by maintenance durvalumab with or without olaparib for patients with newly diagnosed advanced or recurrent endometrial cancer.

[00279] *Overall design*

[00280] This is a randomized, double-blind, placebo controlled, multicenter Phase III study to evaluate the efficacy, safety, and patient reported outcomes of durvalumab in combination with platinum based chemotherapy (carboplatin and paclitaxel) followed by maintenance durvalumab with or without olaparib in patients with advanced or recurrent endometrial cancer compared to platinum-based chemotherapy. AstraZeneca considers that the endometrial cancer patient population involved in this study falls under the advanced cancer, limited life expectancy definition outlined in ICH S9 guideline "Non-clinical Evaluation For Anticancer Pharmaceuticals" and meets the requirements outlined in the guideline. The primary endpoint of this study will be progression free survival (using investigator assessment of scans according to RECIST 1.1). Secondary endpoints will include OS, PFS2, ORR, DoR, TFST, TSST, and TDT. For an overview of the study design see **Figure 2**.

[00281] The study will include 3 arms:

Table 1 Study treatments

	Arm A	Arm B	Arm C
Chemotherapy phase treatment	carboplatin/paclitaxel chemotherapy + durvalumab placebo Q3W	carboplatin/paclitaxel chemotherapy + durvalumab 1120 mg Q3W	carboplatin/paclitaxel chemotherapy + durvalumab 1120 mg Q3W
Maintenance phase treatment	durvalumab placebo Q4W + olaparib placebo tablets twice daily	durvalumab 1500 mg Q4W + olaparib placebo tablets twice daily	durvalumab 1500 mg Q4W + olaparib 300 mg tablets twice daily
Route of administration	IV durvalumab placebo / oral olaparib placebo	IV durvalumab / oral olaparib placebo	IV durvalumab / oral olaparib
Duration of study treatment	Until objective disease progression (PD)	Until objective disease progression (PD)	Until objective disease progression (PD)

Abbreviations: IV = intravenous; Q3W = every 3 weeks; Q4W = every 4 weeks.

[00282] Patients will be stratified according to MMR expression status (proficient versus deficient), disease status (recurrent versus newly diagnosed) and geographic region (Asia versus rest of the world [RoW]). Patients will provide a tumor sample at screening to determine MMR status for stratification.

[00283] As part of the global recruitment, approximately 699 patients will be randomized in a 1:1:1 ratio to the study treatments specified below (N=233 patients per arm). If necessary, enrolment in China will continue after global enrolment is closed (i.e., last subject randomized from a non-China site) to allow inclusion of a China cohort consisting of approximately 129 patients randomized in a 1:1:1 ratio from sites in China. Any patient from China randomized before the global recruitment is closed will be included in the global population.

[00284] Arm A (control): Platinum-based chemotherapy (paclitaxel and carboplatin) with durvalumab placebo (IV) during the chemotherapy phase. Patients who achieve and maintain disease control (i.e., complete response [CR], partial response [PR], or stable disease [SD]) during the chemotherapy phase will receive durvalumab placebo (IV) and olaparib placebo (tablets) in the maintenance phase.

[00285] Arm C (durvalumab+olaparib): Platinum-based chemotherapy (paclitaxel and carboplatin) with durvalumab (IV) during the chemotherapy phase. Patients who achieve and maintain disease control (i.e., CR, PR, or SD) during the chemotherapy phase will receive durvalumab (IV) with olaparib (tablets) in the maintenance phase.

[00286] Patients should be randomized and begin treatment on Day 1. The randomization scheme will be stratified according to:

[00287] Tumor tissue's mismatch repair (MMR) status: Patients with MMR deficient tumors versus those with proficient tumors. Tumor MMR status will be determined prior to randomization based on evaluation of MMR status in tumor cells from a formalin fixed, paraffin embedded (FFPE) tumor tissue sample, using the Ventana immunohistochemistry (IHC) MMR panel.

[00288] Disease status: Patients with recurrent disease versus those newly diagnosed. This study will enroll patients with newly diagnosed Stage III/ IV and recurrent endometrial cancer. Generally, recurrent disease shows a lower response rate to treatment and poorer prognosis compared to newly diagnosed cancer. Furthermore, patients with recurrent cancer may have unresolved toxicity from previous anti-cancer treatment and more comorbidities due to longer duration of disease which make them frailer than newly diagnosed patients. Due to these differences, the randomization will incorporate disease status as a stratification factor.

[00289] Stratification by MMR status. Defects in Mismatch Repair, known as MMR loss/deficiency is observed across various tumour types. In advanced endometrial cancer, approximately 15% of patients have an MMR-deficiency. Multiple institutions in the US have initiated testing all patients with a histologically-confirmed diagnosis of endometrial cancer (universal tumour testing) for MMR or MSI. MMR-deficiency can be detected by IHC staining, typically for the loss of expression of any of the 4 most common MMR proteins: MutL homologue 1 (MLH1), MutS protein homologue 2 (MSH2), MutS protein homologue 6 (MSH6), and PMS1 protein homologue 2 (PMS2). Loss of expression by IHC of any MMR protein suggests the possibility of a germline mutation in the corresponding MMR gene. Patients with such pathogenic germline MMR mutations suffer from Lynch Syndrome. The NCCN guidelines recommend screening for MMR-deficiency in all patients with endometrial cancers to identify individuals at risk for Lynch Syndrome. As highlighted in previous section, preliminary data suggest that agents targeting the PD-1 pathway leads to remarkable clinical responses in patients with endometrial cancers that are MMR-deficient tumours and, to a lesser extent, with MMR-proficient tumours, therefore providing the rationale to stratify based on MMR status.

[00290] *Treatments and treatment duration*

[00291] Patients should receive platinum based chemotherapy and durvalumab/placebo for the first 6 cycles (minimum of 4 cycles). Patients without evidence of PD (per RECIST 1.1) will receive durvalumab/placebo and olaparib/placebo during the maintenance phase.

[00292] Arm A (control): Patients will receive platinum-based chemotherapy (paclitaxel and carboplatin) every 3 weeks (Q3W) for a maximum of 6 cycles with durvalumab placebo (intravenous [IV]) Q3W during the chemotherapy phase. Following completion of the chemotherapy phase, patients without objective disease progression will receive durvalumab placebo (IV) every 4 weeks (Q4W) and olaparib placebo (tablets) twice daily (bd) in the maintenance phase until disease progression.

[00293] Arm B (durvalumab+placebo): Patients will receive platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W during the chemotherapy phase. Following completion of the chemotherapy phase, patients without objective disease progression will receive 1500 mg durvalumab (IV) Q4W and olaparib placebo (tablets) bd in the maintenance phase until disease progression.

[00294] Arm C (durvalumab+olaparib): Patients will receive platinum-based chemotherapy (paclitaxel and carboplatin) Q3W for a maximum of 6 cycles with 1120 mg durvalumab (IV) Q3W during the chemotherapy phase. Following completion of

chemotherapy, patients without objective disease progression will receive 1500 mg durvalumab (IV) Q4W and 300 mg olaparib (tablets) bd orally in the maintenance phase until disease progression.

[00295] Patients should continue to receive study treatment until radiological disease progression per RECIST 1.1 as assessed by the investigator (refer to Appendix G), unless there is unacceptable toxicity, withdrawal of consent, or confirmed another discontinuation criterion is met. The general study design is summarized in **Figure 2**.

[00296] *Objectives and Endpoints*

[00297] Objectives and associated endpoints are presented in **Table 2**.

Table 2 Study objectives and endpoints

Primary Objective	Endpoint/Variable
To demonstrate the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) by assessment of progression-free survival (PFS), in patients with newly diagnosed advanced or recurrent endometrial cancer	PFS (per RECIST 1.1 as assessed by investigator), defined as the time from randomisation until the date of objective disease progression or death (by any cause in the absence of progression). This will be assessed via determining the efficacy of: • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance in combination with olaparib versus SoC platinum-based chemotherapy. • Durvalumab in combination with platinum-based chemotherapy and continued as maintenance versus SoC platinum-based chemotherapy.

Table 2 Study objectives and endpoints

Secondary Objectives	Endpoint/Variable
To determine the efficacy of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients by assessment of: PFS2, OS, ORR, DoR, TFST, TSST, and TDT	PFS2: Second progression-free survival is defined as the time from randomisation to the earliest of progression event subsequent to first subsequent therapy (assessed by the investigator per local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression), or death due to any cause. OS: Overall survival is defined as the time from the date of randomisation until death due to any cause. ORR: Objective response rate is the proportion of patients with measurable disease at baseline who have complete response (CR) or partial response (PR), as determined by the investigator at local site. DoR: Duration of response is time from the date of first documented response until date of documented progression or death in the absence of disease progression. TFST: Time to first subsequent therapy or death is time from randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment or death due to any cause. TSST: Time to second subsequent therapy or death is time from randomisation to the earlier of start date of the second subsequent anti-cancer therapy after discontinuation of first subsequent treatment or death due to any cause. TDT: Time to study treatment discontinuation or death is time from randomisation to the earlier of the date of study treatment discontinuation or death.
To characterise the PK and immunogenicity of durvalumab and durvalumab in combination with olaparib	Serum concentrations of durvalumab Anti-drug antibodies (ADA) to durvalumab
To determine effects on symptoms, functioning and overall health-related quality of life (HRQoL) of durvalumab in combination with platinum-based chemotherapy (paclitaxel and carboplatin) followed by maintenance durvalumab (Arm B) or durvalumab with olaparib (Arm C) when compared to platinum-based chemotherapy alone (Arm A) in newly diagnosed advanced or recurrent endometrial cancer patients	Change from baseline in: - Physical functioning score of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-C30) - Role functioning score of the EORTC QLQ-C30 - Global health status/quality of life (QoL) score of the EORTC QLQ-C30 - All other functioning and symptom subscale scores of the EORTC QLQ-C30 (excluding the financial subscale) Time to deterioration in: - Physical functioning score of the EORTC QLQ-C30 - Role functioning score of the EORTC QLQ-C30 - Back/pelvic pain of the EORTC QLQ-EN24 - Gastrointestinal (GI) symptoms of the EORTC QLQ-EN24 - Urological symptoms of the EORTC QLQ-EN24

Table 2 Study objectives and endpoints

^a These endpoints may be reported separately to the clinical study report.

[00298] *Efficacy assessments and analysis*

[00299] *CT and MRI scans tumor assessments (RECIST 1.1)*

[00300] Efficacy assessments will be derived (by AstraZeneca) using RECIST 1.1 assessments based on investigator evaluation. Details of RECIST 1.1 (Eisenhauer et al 2009) are provided in Appendix G. The methods of assessment are CT or MRI scans of chest, abdomen and pelvis. The use of positron emission tomography (PET) scans is described in Appendix G. The same methods for assessment of tumor burden must be used at baseline and at each subsequent follow-up assessment. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

[00301] Radiological examinations performed in the conduct of this study should be retained at sites as source data. Anonymized copies of the scans will be collected from all patients and will be sent to an AstraZeneca appointed CRO; scans will undergo BICR assessment.

[00302] All treatment decisions will be based on site assessment of scans. After the primary PFS analysis, central review of scans will no longer be required, and investigators will be notified when copies of the scans are no longer required to be shared with the CRO conducting the central review. However, sites should continue RECIST 1.1 tumor assessments until radiological progression and should record the RECIST assessments in the eCRF.

[00303] It is important to follow the assessment schedule as closely as possible; timing of scans is relative to the date of randomization, irrespective of any dosing delays. If scans are performed outside of the scheduled visit windows and the patient has not progressed, every attempt should be made to perform the subsequent scans at their scheduled time points. Patients will be evaluated until objective radiological disease progression by RECIST 1.1, and then followed for second progression and survival, regardless of whether study treatment is discontinued or delayed and/or protocol violations have occurred, unless patients withdraw consent.

[00304] *Tumor evaluation*

[00305] RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS times and ORR. The RECIST 1.1 guidelines that define measurable, non-measurable, target lesions (TLs) and non-target lesions (NTLs) and the objective tumor

response criteria are presented in Appendix G. Categorization of overall response will be based on the assessments of TLs, NTLs and new lesions.

[00306] For patients with TL at baseline, progression will be calculated in comparison to when the tumor burden was at a minimum (i.e., smallest sum of diameters previously recorded on study, nadir). Tumor response (CR, PR, SD) will be calculated in comparison to the baseline tumor measurements obtained before randomization.

[00307] For patients with no evidence of disease (NED) at baseline (i.e., TL and NTL are not applicable [NA]), following a complete resection after surgery, RECIST 1.1 outcomes at follow-up are NED or PD. Progression is defined by the detection of new lesions on follow up radiological assessments (RECIST 1.1).

[00308] For patients with non-measurable disease only at baseline, categorization of objective tumor response assessment will be based on the RECIST 1.1 criteria of response: CR, PD and Non CR/Non PD.

[00309] In the absence of clinical progression or if the investigator is in doubt as to whether progression has occurred, particularly with response to NTLs or the appearance of a new lesion, it is advisable to continue randomized treatment and on treatment assessments until the next scheduled scan, or sooner if clinically indicated, and reassess the patient's status with a new scan. If the repeat scan confirms progression, then the date of the initial scan should be declared as the date of progression.

[00310] To achieve 'unequivocal progression' on the basis of NTLs, there must be an overall level of substantial worsening in NTLs such that, even in presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more NTLs is usually not sufficient to qualify for unequivocal progression status.

[00311] *Central reading of scans*

[00312] An independent review will be conducted of all scans used in the assessment of tumors according to RECIST 1.1. All imaging assessments including unscheduled visit scans will be collected on an ongoing basis and sent to an AstraZeneca appointed CRO for central analysis. Results of this independent review will not be communicated to investigators, and the management of patients will be based solely upon the results of the RECIST 1.1 assessment conducted by the investigator.

[00313] *Subgroup analyses*

[00314] Subgroup analyses will be conducted comparing PFS (per RECIST 1.1 using investigator assessments) in the durvalumab+placebo arm versus control and in the

durvalumab+olaparib arm versus control to assess consistency of treatment effect across potential or expected prognostic factors including the following subgroups of the FAS (but not limited to):

- MMR status (proficient versus deficient)
- Disease status (recurrent versus newly diagnosed)
- Region (Asia versus RoW).

[00315] Other baseline variables, including biomarkers, may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms.

[00316] No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of PFS.

[00317] *Overall survival*

[00318] OS will be analyzed using a stratified log rank tests, using the same methodology as described for the primary PFS endpoint. The same stratification factors will be used as the primary PFS analysis. If the number of deaths is too small for a meaningful analysis (less than 5 deaths per stratum), a pre-specified strategy to account for such a situation will be applied. Further details will be documented in the SAP. The effect of durvalumab+placebo versus control will be estimated by the HR together with its corresponding CI and p value. This will be repeated for the comparison of durvalumab+olaparib versus control.

[00319] A KM plot of OS will be presented by treatment arm for each comparison (durvalumab+placebo versus control and durvalumab+olaparib versus control).

[00320] Summaries of the number and percentage of patients who have died, those still in survival follow-up, those lost to follow-up, and those who have withdrawn consent will be provided along with the median OS for each treatment.

[00321] *Dosage and Study Treatment*

[00322] Study treatment is defined as any investigational product(s) and non-investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to chemotherapy, durvalumab/placebo and olaparib/placebo. Study treatments are summarized in **Table 1**.

[00323] Patients should receive platinum based chemotherapy and durvalumab/placebo for the first 6 cycles (minimum of 4 cycles). Patients without evidence of PD (per RECIST 1.1) will receive durvalumab/placebo and olaparib/placebo during the maintenance phase.

[00324] During the chemotherapy phase, the intravenous study treatments should ideally be administered on the same day and in the following order:

[00325] Durvalumab/placebo: Durvalumab dose of 1120 mg (Q3W) should be administered over 1 hour, however if there are interruptions during infusion, the total infusion time should not exceed 8 hours at room temperature.

[00326] Paclitaxel: 175 mg/m² by IV infusion over 3 hours.

[00327] Carboplatin: AUC5 or AUC6 by IV infusion over 1 hour (or in accordance with local practice).

[00328] *Durvalumab*

[00329] M For ease of use and convenience to investigators and patients, durvalumab will be administered Q3W in the chemotherapy phase to align with the treatment interval of the platinum-based chemotherapy, and will use a fixed dose of 1120 mg (based on an average body weight of 75 kg, this is equivalent to a weight based dose of 15 mg/kg Q3W).

[00330] A population PK analysis has indicated that body weight has a minor impact on the PK of durvalumab and subsequent modelling demonstrated that body-weight-based and fixed dosing regimens yield similar median steady state PK concentrations. Based on a median body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is currently being administered in numerous clinical studies across multiple tumor types. Durvalumab 1500 mg Q4W dosing was convincingly supported by the National Cancer Institute (NCI) Study ESR 14-10366 (hereafter referred to as the “NCI study”; Lee et al 2017). This dosing regimen is equivalent to a fixed dose of 1120 mg Q3W and was chosen for the maintenance phase of this study, to align with other studies.

[00331] The 2 durvalumab dosing schedules used in this study (1120 mg Q3W in the chemotherapy phase and 1500 mg Q4W in the maintenance phase) are equivalent to administering 10 mg/kg Q2W as recommended in the label.

[00332] Please note, if a patient’s weight falls to 30 kg or below (≤ 30 kg) during the maintenance phase, then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between Investigator and Study Physician, until the weight improves to above 30 kg (> 30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W.

[00333] *Olaparib*

[00334] Olaparib will be administered at the dose approved for use in ovarian and breast cancer, i.e. 300 mg bd. Dose reductions will be permitted, according to the Prescribing Information.

[00335] *Durvalumab and olaparib combination*

[00336] Durvalumab and olaparib have been administered in combination in a range of indications, including ovarian, breast, SCLC and gastric cancers (MEDIOLA; NCT02734004). The safety and tolerability of olaparib 300 mg bid in combination with durvalumab 1500 mg Q4W is convincingly supported by the NCI study (Lee et al 2017).

Table 3 Investigational study treatments

	Olaparib	Durvalumab
Study treatment name:	olaparib/placebo	durvalumab/placebo
Dosage formulation:	300 mg olaparib/placebo (2 × 150 mg olaparib/placebo tablets) bd 100 mg olaparib/placebo tablet available if dose reductions are required	1120 mg durvalumab/placebo Q3W for a maximum of 6 cycles, followed by 1500 mg durvalumab/placebo Q4W 500 mg vial containing a 50 mg/mL solution for IV infusion after dilution
Route of administration:	Oral	IV
Dosing instructions:	Two × 150 mg olaparib/placebo tablets should be taken twice daily at the same times each day, approximately 12 hours apart with one glass of water. The tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food. If vomiting occurs shortly after the study treatment tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (eg. as a result of forgetting to take the tablets or vomiting), the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.	Durvalumab/placebo should be administered prior to dosing with chemotherapy. The dose of durvalumab/placebo for administration must be prepared by the investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab/placebo vial to the start of administration should not exceed: • 24 hours at 2°C to 8°C (36°F to 46°F) • 4 hours at room temperature A dose of 1120 mg/placebo (chemotherapy phase) or 1500 mg/placebo (maintenance phase) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 22.4 mL (chemotherapy phase) or 30.0 mL (maintenance phase) of durvalumab/placebo (ie, 1120 mg or 1500 mg of durvalumab, respectively) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag. If a patient's weight falls to ≤ 30 kg during the maintenance phase, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter.

Table 3 **Investigational study treatments**

	Olaparib	Durvalumab
		Standard infusion time is 1 hour, however if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature. Do not co-administer other drugs through the same infusion line. The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab/placebo do not contain preservatives, and any unused portion must be discarded.
Packaging and labelling	Study treatment will be provided in HDPE bottles with child-resistant closures. Each bottle will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.	Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% w/v polysorbate 80; it has a pH of 6.0 and a density of 1.054 g/mL. The placebo contains 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% w/v polysorbate 80; it has a pH of 6.0. The nominal fill volume for durvalumab and placebo is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure. Each vial will be labelled in accordance with GMP Annex 13 and per country regulatory requirement.
Provider	AstraZeneca	AstraZeneca

Abbreviations: bd = twice daily; GMP = Good Manufacturing Practice; HDPE = high-density polyethylene; IP = investigational product; IV = intravenous; IWRS = interactive web response system; Q3W = every 3 weeks; Q4W = every 4 weeks; w/v = weight/volume.

[00337] *Chemotherapy agents*

[00338] The chemotherapy agents (paclitaxel and carboplatin) will either be locally sourced or, under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drug, which will be labelled in the local language in accordance with regulatory guidelines. In the EU, carboplatin and paclitaxel are considered auxiliary medicinal products according to EU clinical trials guidance (EU Guidance 2017).

[00339] Chemotherapy is a “non-investigational drug” as it is a recommended SoC in international guidelines. Chemotherapy will be administered in accordance with the

recommendation of this treatment combination in international guidelines (NCCN Uterine Neoplasms 2019).

[00340] Platinum-based chemotherapy should continue for a maximum of 6 cycles. If required due to toxicity, 4 cycles of platinum based chemotherapy may be given as a minimum. Chemotherapy dosing will be as follows:

- Carboplatin (AUC5 or AUC6) Q3W (Note: Dose reduction to AUC5 may be considered for patients who had prior pelvic radiotherapy)
- Paclitaxel 175 mg/m² Q3W.

[00341] Each chemotherapy agent will be administered in accordance with local guidelines and premedication may be provided.

[00342] For carboplatin dosing recommendations please refer to NCCN guidelines https://www.nccn.org/professionals/OrderTemplates/PDF/appendix_B.pdf. As per NCCN guidance, to avoid overestimation of CrCL and subsequent overestimation of carboplatin dose, in patients with low serum creatinine, the creatinine clearance should be estimated using a minimum value of 0.7 mg/dL (equivalent to 62 µmol/L). The Calvert Formula should be used to calculate the dose of carboplatin as shown:

[00343] Carboplatin dose (mg) = target AUC × (GFR + 25)

[00344] NOTE: It is recommended that the GFR used in the Calvert formula should not exceed 125 mL/min. For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance.

[00345] Maximum carboplatin dose (mg) = target AUC (mg/mL × min) × 150 mL/min

[00346] The maximum recommended doses of carboplatin are:

- AUC6 = 900 mg
- AUC5 = 750 mg

[00347] If chemotherapy is permanently discontinued early (prior to completing 4 cycles) as a result of toxicities or disease progression, all study treatments will be discontinued, and the patient will not enter the maintenance phase. A study treatment discontinuation visit will be conducted, and follow-up will continue unless the patient withdraws consent to continue in the study.

[00348] Patients who develop a hypersensitivity reaction to carboplatin should be managed according to standard clinical practice. Patients may be retreated as per local clinical guidance including increased hypersensitivity prophylaxis or using desensitizing protocols. If hypersensitivity prevents further administration of carboplatin, substitution with cisplatin

may be considered for patients, provided this aligns with standard clinical practice at the site and only where the chemotherapy is locally sourced. Substitution with cisplatin should be discussed with the AstraZeneca study physician before implementing.

[00349] Patients who develop a hypersensitivity reaction to paclitaxel should be managed according to standard clinical practice. Patients may be retreated as per local clinical guidance depending on the severity of the reaction. In cases of recurrent hypersensitivity reaction, despite adequate premedication, preventing further dosing of paclitaxel, the investigator may consider omitting paclitaxel from the chemotherapy regimen or substituting with another taxane (nab-paclitaxel or docetaxel) provided this aligns with standard clinical practice at the site and only where the chemotherapy is locally sourced.

[00350] Patients who develop chemotherapy induced peripheral neuropathy should be managed according to standard clinical practice. Dose of chemotherapy may be reduced as per local clinical guidance. If permanent discontinuation of paclitaxel is required due to persistent significant peripheral neuropathy, substitution with docetaxel may be considered for patients, provided this aligns with standard clinical practice at the site, and only where the chemotherapy is locally sourced.

Example 2: Durvalumab plus Olaparib for Newly Diagnosed Advanced or Recurrent Endometrial Cancer

METHODS

[00351] *Trial Design and Patients*

[00352] DUO-E was a randomized, double-blind, placebo-controlled multicenter Phase III trial conducted in 22 countries. Eligible patients were aged ≥ 18 years with newly diagnosed advanced (International Federation of Gynecology and Obstetrics [FIGO] stage III/IV) or recurrent endometrial cancer of epithelial histology (excluding sarcomas) and were naïve to first-line systemic anticancer treatment. For patients with recurrent disease, prior chemotherapy was allowed if it was administered in the adjuvant setting and there was ≥ 12 months between the last chemotherapy dose and subsequent relapse. DNA MMR status was determined prior to randomization (see Supplementary Appendix). Patients also had Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1. Full inclusion and exclusion criteria are provided in the Supplementary Appendix.

[00353] *Randomization and Study Treatment*

[00354] Patients were randomized 1:1:1 to three treatment arms (**Figure 2**) using an interactive voice/web response system, stratified by MMR expression status (proficient vs.

deficient), disease status (newly diagnosed vs. recurrent), and geographic region (Asia vs. rest of world). Patients with unknown MMR status prior to randomization were ineligible.

[00355] Patients entered a chemotherapy phase, followed by a maintenance phase that continued until radiologic disease progression (Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1, investigator-assessed), unacceptable toxicity, withdrawal of consent, or other discontinuation criteria were met. Only patients without objective disease progression during the chemotherapy phase who met other eligibility requirements (see Full Eligibility Criteria below) were permitted to start maintenance therapy.

[00356] Patients received platinum-based chemotherapy (carboplatin at an area under the curve of 5 or 6 and paclitaxel 175 mg per square meter) plus placebo intravenously every 3 weeks for six cycles, followed by maintenance placebo intravenously every 4 weeks plus placebo tablets twice daily; platinum-based chemotherapy plus durvalumab 1120 mg intravenously every 3 weeks for six cycles, followed by maintenance durvalumab 1500 mg intravenously every 4 weeks plus placebo tablets twice daily; or platinum-based chemotherapy plus durvalumab 1120 mg intravenously every 3 weeks for six cycles, followed by maintenance durvalumab 1500 mg intravenously every 4 weeks plus olaparib 300 mg tablets twice daily.

[00357] *Determination of DNA mismatch repair (MMR) status*

[00358] DNA MMR status was determined prior to randomization via central testing of MMR status in tumor cells from a formalin-fixed, paraffin-embedded (FFPE) tumor tissue sample, using the Ventana MMR IHC panel (Roche Diagnostics, Rotkreuz, Switzerland).

[00359] In compliance with local regulations, a FFPE tumor tissue sample from a tumor lesion that was not previously irradiated was provided for each patient. The FFPE tumor tissue sample could be from either the locoregional or a metastatic site and be any of the following:

- A tumor sample obtained from the cytoreductive surgery (in patients who have already undergone such surgery)
- A biopsy sample obtained at diagnosis (if a sample from cytoreductive surgery is not available)
- A newly collected tumor sample (if the sample is taken as part of routine clinical practice).

[00360] *Determination of Programmed Death Ligand-1 (PD-L1) Status*

[00361] Pre-treatment tumor tissue samples were centrally tested post randomization using the VENTANA PD-L1 (SP263) immunohistochemical assay (Roche Diagnostics). PD-L1 expression was determined using a combined tumor cell and tumor-associated immune cell positivity scoring method. The tumor area positivity (TAP) score was calculated as the proportion of tumor area occupied by tumor cells and immune cells with PD-L1 staining at any intensity. A sample was considered PD-L1 positive if a TAP score $\geq 1\%$ and PD-L1 negative if a TAP score $<1\%$.

[00362] *Determination of Homologous Recombination Repair Mutation (HRRm) Status*

[00363] Pre-treatment baseline tumor tissue samples were used for homologous recombination repair mutation (HRRm) testing post randomization. HRRm status was assessed centrally using the Foundation One CDx NGS assay (Foundation Medicine, Inc., Cambridge, MA). A sample was considered positive if a deleterious or suspected deleterious HRRm was detected in any one of the following prespecified genes associated with HRR: ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L. Negative HRRm status (non-HRRm) was defined as a sample with no pathogenic mutations in any of the prespecified genes associated with HRR. Unknown HRRm status included patients recruited in China where HRR testing was not performed and patients who withdrew consent or due to sample unavailability.

[00364] *Eligibility for maintenance phase*

[00365] Patients received a maximum of 6 cycles of chemotherapy and must have received a minimum of 4 cycles of platinum-based chemotherapy to continue into the maintenance phase of the study.

[00366] Following completion of chemotherapy, the durvalumab/placebo dosing schedule changed to 1500 mg every 4 weeks. Patients also received maintenance olaparib/placebo following completion of chemotherapy (maintenance therapy commenced a minimum of 3 weeks and a maximum of 9 weeks after the last day of chemotherapy infusion).

[00367] Subgroup analysis: Prespecified subgroup analyses evaluated progression-free survival in the doublet group vs. the control group, triplet group vs. the control group, and the triplet group vs. the doublet group, according to the following factors: MMR status (proficient vs deficient), HRRm status (HRRm v non-HRRm v unknown), PD-L1 status (PD-L1 positive, PD-L1 negative, unknown), disease status (recurrent vs newly diagnosed), region (Asia vs rest of world), age (<65 vs ≥ 65 years), race (white vs black/African American vs Asian vs other), histology (endometrioid vs serous vs others), ECOG performance status (0 vs 1), and FIGO stage at initial diagnosis in newly diagnosed patients (III vs IV).

[00368] Efficacy data were summarized and analyzed in the intent-to-treat population (all randomized patients) and safety data were summarized in the safety analysis set (all randomized patients who received at least one dose of investigational treatment, i.e. durvalumab/placebo or olaparib/placebo); for the maintenance phase, safety data were summarized in patients from the safety analysis set who entered the maintenance phase and received at least one dose of olaparib/placebo.

[00369] The primary progression-free survival analysis for each comparison was performed separately using a stratified log-rank test for generation of p-values, with hazard ratio and confidence intervals (CIs) estimated using a stratified Cox proportional hazards model. Kaplan-Meier (KM) plots were presented by treatment arm and were utilized to estimate median survival times and the proportion of patients alive and progression free at 6 monthly intervals from randomization. Analyses of secondary time-to-event endpoints used a similar method.

RESULTS

[00370] *Patients*

[00371] From June 2, 2020 through April 20, 2022, 718 patients were randomized: 241, 238, and 239 to the control, doublet, and triplet groups, respectively. Of those randomized, 236 patients (97.9%) in the control group, 235 (98.7%) in the doublet group, and 238 (99.6%) in the triplet group received any study treatment, and 169 (70.1%), 183 (76.9%) and 192 (80.3%), respectively, started the maintenance phase and received olaparib/placebo (**Figure 6**).

[00372] Patient baseline characteristics were generally balanced across treatment arms (**Table 4**) and were representative of patients with newly diagnosed advanced or recurrent endometrial cancer (**Table 5**). The stratification factors were balanced across treatment arms: 80% of patients in each arm had MMR-proficient (pMMR) tumors, approximately 28% were from Asia, and approximately 47% had newly-diagnosed disease.

Table 4. Patient Baseline Characteristics.

Characteristic	Durvalumab+Olaparib Arm (N = 239)	Durvalumab Arm (N = 238)	Control Arm (N = 241)
Median (range) age, years	63 (27-86)	64 (22-84)	64 (31-85)
Geographic region, ^a no. (%)			
Asia ^b	67 (28.0)	68 (28.6)	68 (28.2)

Non-Asia	172 (72.0)	170 (71.4)	173 (71.8)
Race, no. (%)			
White	133 (55.6)	136 (57.1)	143 (59.3)
Asian	70 (29.3)	72 (30.3)	73 (30.3)
Black/African American	14 (5.9)	11 (4.6)	10 (4.1)
American Indian or Alaska Native	6 (2.5)	6 (2.5)	0
Native Hawaiian or other Pacific Islander	1 (0.4)	0	2 (0.8)
Other	12 (5.0)	8 (3.4)	10 (4.1)
Not reported	3 (1.3)	5 (2.1)	3 (1.2)
Ethnicity, no. (%)			
Not Hispanic or Latino	206 (86.2)	208 (87.4)	218 (90.5)
Hispanic or Latino	32 (13.4)	28 (11.8)	20 (9.3)
Missing	1 (0.4)	2 (0.8)	3 (1.2)
ECOG Performance Status, no. (%)			
0	166 (69.5)	156 (65.5)	156 (64.7)
1	73 (30.5)	81 (34.0)	85 (35.3)
Disease status, no. (%)			
Recurrent ^a	125 (52.3)	125 (52.5)	126 (52.3)
Newly diagnosed ^a	114 (47.7)	113 (47.5)	115 (47.7)
FIGO stage in newly diagnosed patients ^c			
I	1 (0.9)	0	0
II	0	0	1 (0.4)
III	12 (5.0)	17 (7.1)	12 (5.0)
IV	99 (41.4)	96 (40.3)	101 (41.9)
Histology type, ^d no. (%)			
Endometrioid	152 (63.6)	141 (59.2)	139 (57.7)
Serous	42 (17.6)	58 (24.4)	54 (22.4)
Carcinosarcoma	18 (7.5)	12 (5.0)	21 (8.7)
Mixed, epithelial	9 (3.8)	9 (3.8)	11 (4.6)
Clear cell	8 (3.3)	4 (1.7)	7 (2.9)
Undifferentiated	5 (2.1)	4 (1.7)	3 (1.2)
Mucinous	0	1 (0.4)	0
Other	5 (2.1)	9 (3.8)	6 (2.5)
MMR status, ^{ae} no. (%)			
Proficient	191 (79.9)	192 (80.7)	192 (79.7)
Deficient	48 (20.1)	46 (19.3)	49 (20.3)
HRRm status, ^f no. (%)			
HRRm	39 (16.3)	26 (10.9)	32 (13.3)
Non-HRRm	141 (59.0)	138 (58.0)	132 (54.8)

Unknown	59 (24.7)	74 (31.1)	77 (32.0)
PD-L1 expression, ^g no. (%)			
Positive	150 (62.8)	170 (71.4)	163 (67.6)
Negative	82 (34.3)	61 (25.6)	75 (31.1)
Unknown	7 (2.9)	7 (2.9)	3 (1.2)
Previous chemotherapy			
Yes	54 (22.6)	51 (21.4)	51 (21.2)
No	185 (77.4)	187 (78.6)	190 (78.8)
Prior surgery, no. (%)			
Yes	207 (86.6)	205 (86.1)	202 (83.8)
No	32 (13.4)	33 (13.9)	39 (16.2)
Previous radiotherapy, no. (%)			
Yes ^h	85 (35.6)	73 (30.7)	71 (29.5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRRm, homologous recombination repair mutation; MMR, mismatch repair; PD-L1, programmed death ligand-1; TAP, tumor area positivity.

^aStratification factors (MMR status [proficient *v* deficient], disease status [newly diagnosed *v* recurrent], and geographic region [Asia *v* non-Asia]) are per the randomization code.

^bIncludes China, Hong Kong, India, Japan, Republic of Korea, Singapore. Two patients in India were stratified in error to the Asia subgroup.

^cFIGO stage was determined by electronic case report form. Reported as a percentage of the total number of patients in each arm.

^dPathology-related disease characteristics were collected at the time of primary diagnosis of disease under investigation.

^eMMR status was evaluated using the Ventana MMR RxDx panel (Roche Diagnostics, Rotkreuz, Switzerland).

^fHRRm status was evaluated using the Foundation One CDx NGS assay (Foundation Medicine, Inc., Cambridge, MA). A positive HRRm status (HRRm) was defined as a sample with a pathogenic mutation in any of the following pre-specified genes: *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, *RAD54L*. A negative HRRm status (non-HRRm) was defined as a sample with no pathogenic mutations in any of the pre-specified genes. Unknown HRRm status included patients recruited in China where HRR testing was not performed and patients who withdrew consent or due to sample unavailability.

^gPD-L1 expression was assessed using the Ventana SP263 immunohistochemical assay (Roche Diagnostics). PD-L1 positive was defined as TAP $\geq$ 1%. PD-L1 negative was defined as TAP < 1%. Unknown included patients who withdrew consent or due to sample unavailability.

^hOnly 'yes' reported.

Table 5. Representativeness of Study Participants.

Category	DUO-E Study Population
Disease under investigation	Newly diagnosed advanced or recurrent endometrial cancer
Special considerations related to:	
Sex and gender	Endometrial cancer affects women
Age	Prevalence increases with age. The peak ages of diagnosis are between ages 55 and 64 years (median 62 years). Endometrial cancer primarily affects postmenopausal women.

Category	DUO-E Study Population
Race or ethnic group	The incidence of endometrial cancer is rising disproportionately among minority racial and ethnic groups.
Geography	Like many cancers, the incidence of endometrial cancer varies across the world. The epidemiological diversity in different regions can be attributed to environmental risk factors.
Overall representativeness of this trial	The DUO-E study population is generally representative of the global, real-world population of women with newly diagnosed advanced or recurrent endometrial cancer. DUO-E study sites were located in Europe, North and South America, and Asia Pacific, and the study population includes approximately 30% of Asian ethnicity. An unmet need would be to confirm whether the findings from DUO-E are applicable to other regions and/or ethnic groups not represented in this trial.

[00373] *Efficacy*

[00374] The primary analysis of investigator-assessed progression-free survival was performed after 438 of 718 patients in the intent-to-treat population had disease progression or death (data maturity, 61%) (data cut-off, April 12, 2023). The median duration of follow-up in censored patients was 12.6 months (range, 0.0 to 31.6) in the control group, 15.4 months (range, 0.0 to 29.1) in the doublet group, and 15.4 months (range, 0.0 to 31.7) in the triplet group.

[00375] In the intent-to-treat population, the durvalumab arm had a statistically significant 29% lower risk of disease progression or death versus control (HR, 0.71; 95% CI, 0.57 to 0.89; $P = .003$; median PFS 10.2 v 9.6 months) (**Figure 4A**; **Table 7**). The durvalumab+olaparib arm had a statistically significant 45% lower risk of disease progression or death versus control (HR, 0.55; 95% CI, 0.43 to 0.69; $P < .001$; median PFS 15.1 v 9.6 months) (**Figure 4A**; **Table 7**). The PFS Kaplan-Meier curves overlap until approximately 6 months, after which time there is a clear and sustained separation that favors both investigational treatment arms compared with control (**Figure 4A**). This delayed separation was expected due to the known delayed treatment effect for durvalumab, as well as the fact that olaparib maintenance therapy only started after completion of chemotherapy. The delay in separation of the curves suggested non-proportionality ($P = .018$ and $P = .03$ for the durvalumab v control and durvalumab+olaparib v control comparisons, respectively). In the presence of non-proportional hazards, the overall PFS HR is to be interpreted as an average estimate of the observed benefit. Rates at specific timepoints and the median PFS values are shown in **Table 7**.

[00376] In an exploratory analysis of investigator-assessed progression-free survival in the triplet vs. doublet groups, the hazard ratio for disease progression or death was 0.78 (95% CI, 0.61 to 0.99; $P=0.045$).

[00377] A sensitivity analysis of progression-free survival by blinded independent central review assessment was consistent with the results by investigator assessment in both the doublet vs. control (hazard ratio 0.74; 95% CI 0.58 to 0.94) and triplet vs. control (hazard ratio 0.55; 95% CI 0.42 to 0.70) comparisons (**Figure 6**).

[00378] In a predefined, exploratory analysis of investigator-assessed PFS in the durvalumab+olaparib versus durvalumab arms, the HR was 0.78 (95% CI, 0.61 to 0.99; median PFS 15.1 v 10.2 months) (**Table 7**).

[00379] Exploratory analyses of progression-free survival in predefined subgroups demonstrated a consistent treatment effect, with all observed hazard ratio point estimates favoring the doublet group vs. control, and the triplet group vs. control (**Figure 5A-B**). A global interaction test showed a potentially quantitatively different treatment effect by MMR status and region for the doublet vs. control comparison (**Table 6**). Analyses by MMR status are reported in **Table 7** and **Figure 8**.

[00380] The first interim analysis of OS was conducted at the time of the primary PFS analysis, at which point 199 (28%) deaths had occurred in the intent-to-treat population. The median (range) duration of follow-up in patients censored for OS was 18.6 months (0.5-32.9) in the control arm, 18.4 months (2.1-33.0) in the durvalumab arm, and 18.7 months (1.1-33.4) in the durvalumab+olaparib arm. The HRs for both comparisons favored the investigational arms; however, neither comparison reached statistical significance at this first interim analysis of OS (durvalumab v control: HR, 0.77, 95% CI, 0.56 to 1.07; $P = .120$; durvalumab+olaparib v control: HR, 0.59, 95% CI, 0.42 to 0.83; $P = .003$, **Figure 4B**).

In prespecified exploratory subgroup analyses of PFS, all observed HR point estimates favored the durvalumab and durvalumab+olaparib arms versus control (**Figures 5A-B**). In the dMMR subgroup, the HRs for PFS were 0.42 (95% CI, 0.22 to 0.80, median PFS not reached [NR] v 7.0 months) for durvalumab versus control and 0.41 (95% CI, 0.21 to 0.75, median PFS 31.8 v 7.0 months) for durvalumab+olaparib versus control (**Table 7** and **Figure 8A**). In the pMMR subgroup, the HRs for PFS were 0.77 (95% CI, 0.60 to 0.97, median PFS 9.9 v 9.7 months) for durvalumab versus control and 0.57 (95% CI, 0.44 to 0.73, 15.0 v 9.7 months) for durvalumab+olaparib versus control (**Table 7** and **Figure 8B**). Comparison of durvalumab+olaparib versus durvalumab by MMR status is reported in **Table 7**. In subgroup analyses by PD-L1 status, in the PD-L1 positive subgroup (defined as tumor area positivity

[TAP] $\geq 1\%$), the HRs for PFS were 0.63 (95% CI, 0.48 to 0.83), median PFS 11.3 versus 9.5 months for durvalumab versus control and 0.42 (95% CI, 0.31 to 0.57), median PFS 20.8 versus 9.5 months for durvalumab+olaparib versus control (**Figure 10A**). In the PD-L1 negative subgroup (TAP < 1%), the HRs for PFS were 0.89 (95% CI, 0.59 to 1.34), median PFS 9.7 versus 9.9 for durvalumab versus control, and 0.80 (95% CI, 0.55 to 1.16), median PFS 10.1 versus 9.9 for durvalumab+olaparib versus control (**Figure 10B**). Details of the duration of study treatment are provided in **Table 8**.

Table 6. Interaction test for Progression-free Survival based on Investigator Assessment (RECIST, Version 1.1).

Interaction test	Degrees of freedom	P-value	If significant, quantitative or qualitative
Doublet vs. Control group			
Global test	10	0.036	NA
MMR status	1		Quantitative
Region	1		Quantitative
Triplet vs. Control group			
Global test	10	0.133	NA
Triplet vs. Doublet group		0.625	NA
Global test	10		

MMR denotes mismatch repair; NA not applicable; and RECIST Response Evaluation Criteria in Solid Tumors.

Table 7. PFS in the ITT Population and by MMR and PD-L1 Subgroup Status

Subgroup	Durvalumab+Olaparib Arm	Durvalumab Arm	Control Arm
ITT	n = 239	n = 238	n = 241
Progression events or death, no. (%)	126 (52.7)	139 (58.4)	173 (71.8)
Median PFS (95% CI), months ^b	15.1 (12.6 to 20.7)	10.2 (9.7 to 14.7)	9.6 (9.0 to 9.9)
Hazard ratio (95% CI) v control arm ^c	0.55 (0.43 to 0.69); <i>P</i> = .003	0.71 (0.57 to 0.89); <i>P</i> < .001	
Hazard ratio (95% CI) v durvalumab arm ^c	0.78 (0.61 to 0.99)		
6-month PFS rate, % (95% CI) ^b	83.9 (78.6 to 88.0)	83.8 (78.4 to 88.0)	82.5 (76.9 to 86.8)
12-month PFS rate, % (95% CI) ^b	61.5 (54.9 to 67.4)	48.5 (41.8 to 54.9)	41.1 (34.6 to 47.5)
18-month PFS rate, % (95% CI) ^b	46.3 (39.2 to 53.0)	37.8 (31.0 to 44.5)	21.7 (16.0 to 27.9)
dMMR	n = 48	n = 46	n = 49
Progression events or death, no. (%)	18 (37.5)	15 (32.6)	25 (51.0)
Median PFS (95% CI), months ^b	31.8 (12.4 to NR)	NR (NR to NR)	7.0 (6.7 to 14.8)
Hazard ratio (95% CI) v control arm ^d	0.41 (0.21 to 0.75)	0.42 (0.22 to 0.80)	
Hazard ratio (95% CI) v durvalumab arm ^d	0.97 (0.49 to 1.98)		
6-month PFS rate, % (95% CI) ^b	87.2 (73.8 to 94.1)	90.6 (76.9 to 96.4)	73.1 (56.6 to 84.2)
12-month PFS rate, % (95% CI) ^b	70.0 (54.7 to 81.0)	67.9 (51.1 to 80.0)	43.3 (27.3 to 58.3)
18-month PFS rate, % (95% CI) ^b	62.7 (46.9 to 75.0)	67.9 (51.1 to 80.0)	31.7 (16.7 to 47.9)
pMMR	n = 191	n = 192	n = 192
Progression events or death, no. (%)	108 (56.5)	124 (64.6)	148 (77.1)
Median PFS (95% CI), months ^b	15.0 (12.4 to 18.0)	9.9 (9.4 to 12.5)	9.7 (9.2 to 10.1)

Subgroup	Durvalumab+Olaparib Arm	Durvalumab Arm	Control Arm
Hazard ratio (95% CI) v control arm ^d	0.57 (0.44 to 0.73)	0.77 (0.60 to 0.97)	
Hazard ratio (95% CI) v durvalumab arm ^d	0.76 (0.59 to 0.99)		
6-month PFS rate, % (95% CI) ^b	83.1 (77.0 to 87.7)	82.4 (76.1 to 87.1)	84.4 (78.4 to 88.9)
12-month PFS rate, % (95% CI) ^b	59.4 (52.0 to 66.0)	44.4 (37.1 to 51.4)	40.8 (33.6 to 47.8)
18-month PFS rate, % (95% CI) ^b	42.0 (34.1 to 49.6)	31.3 (24.2 to 38.6)	20.0 (14.1 to 26.7)
PD-L1 positive	n = 150	n = 170	n = 163
Progression events or death, no. (%)	68 (45.3)	97 (57.1)	114 (69.9)
Median PFS (95% CI), months ^b	20.8 (15.1 to NR)	11.3 (9.7 to 15.4)	9.5 (7.9 to 9.9)
Hazard ratio (95% CI) v control arm ^d	0.42 (0.31 to 0.57)	0.63 (0.48 to 0.83)	
Hazard ratio (95% CI) v durvalumab arm ^d	0.67 (0.49 to 0.91)		
PD-L1 negative	n = 82	n = 61	n = 75
Progression events or death, no. (%)	55 (67.1)	38 (62.3)	57 (76.0)
Median PFS (95% CI), months ^b	10.1 (9.5 to 15.0)	9.7 (7.0 to 14.7)	9.9 (7.6 to 12.5)
Hazard ratio (95% CI) v control arm ^d	0.80 (0.55 to 1.16)	0.89 (0.59 to 1.34)	
Hazard ratio (95% CI) v durvalumab arm ^d	0.93 (0.61 to 1.41)		

Abbreviations: CI, confidence interval; dMMR, mismatch repair deficient; NR, not reached; PFS, progression-free survival; MMR, mismatch repair; pMMR, mismatch repair proficient; PD-L1, programmed death ligand-1.

^aMMR status is per the randomization code.

^bCalculated using the Kaplan-Meier technique. CI for median PFS was derived based on Brookmeyer-Crowley method.

^cThe hazard ratio and CI were estimated from a Cox proportional hazards model stratified by MMR and disease status. A hazard ratio less than 1 favored the treatment arm of interest over the comparator arm.

^dThe hazard ratio and CI were estimated from an unstratified Cox proportional hazards model. A hazard ratio less than 1 favored the treatment arm of interest over the comparator arm.

Table 8. Summary of Study Treatment Duration.

	Triplet (N=238)	Doublet (N=235)	Control (N=236)	Triplet (N=192)	Doublet (N=183)	Control (N=169)
Median (range) treatment duration for durvalumab/placebo, months	50.0 (0.7 to 140.3)	41.1 (0.9 to 130.3)	35.3 (0.7 to 141.3)	39.5 (0.0 to 122.3)	31.6 (0.0 to 114.0)	24.0 (3.0 to 123.6)
Median (range) treatment duration for olaparib/placebo, months	-	-	-	38.1 (0.3 to 122.6)	32.4 (0.9 to 113.3)	24.0 (-0.3 to 124.3)
Median (range) number of cycles of carboplatin	6.0 (1 to 6)	6.0 (1 to 6)	6.0 (1 to 6)	-	-	-
Median (range) number of cycles of paclitaxel	6.0 (1 to 7)	6.0 (1 to 6)	6.0 (1 to 7)	-	-	-

[00381] The phase 3 DUO-E trial demonstrated that durvalumab in combination with first-line carboplatin and paclitaxel followed by maintenance durvalumab with or without olaparib resulted in significantly lower risk of disease progression or death than standard chemotherapy (45% risk reduction with olaparib and 29% without olaparib) for patients with newly diagnosed advanced or recurrent endometrial cancer. These data confirm the clinical benefit of integrating immunotherapy with or without a PARP inhibitor into first-line chemotherapy for patients with newly diagnosed advanced or recurrent endometrial cancer and are the first data to demonstrate that the addition of a PARP inhibitor confers further benefit in this setting.

[00382] In prespecified exploratory subgroup analyses of PFS, all observed HR point estimates favored the durvalumab and durvalumab+olaparib arms versus control. Analyses by MMR status showed that in the dMMR subgroup, similar clinically meaningful benefit was observed in the durvalumab arm versus control (HR, 0.42; 95% CI, 0.22 to 0.80) and in the durvalumab+olaparib arm versus control (HR, 0.41; 95% CI, 0.21 to 0.75). In the pMMR subgroup, clinically meaningful benefit was observed in the durvalumab arm versus control (HR, 0.77; 95% CI, 0.60 to 0.97) and the addition of maintenance olaparib to durvalumab suggested further benefit (HR v control, 0.57; 95% CI, 0.44 to 0.73). Prespecified, exploratory analysis of the durvalumab+olaparib versus durvalumab arms suggested the contribution of olaparib was in the pMMR subgroup (HR in pMMR subgroup, 0.76, 95% CI, 0.59 to 0.99; HR in dMMR subgroup, 0.97, 95% CI, 0.49 to 1.98).). Analyses by PD-L1 status indicated benefit was observed for both the PD-L1 positive subgroup, which demonstrated a clinically meaningful improvement in PFS (HR, 0.63 [95% CI, 0.48 to 0.83] for the durvalumab arm v control and HR 0.42 [95% CI, 0.31 to 0.57] for the durvalumab+olaparib arm v control), and for the PD-L1 negative subgroup, with a smaller magnitude of improvement (HR 0.89 [95% CI, 0.59 to 1.34] and 0.80 [95% CI, 0.55 to 1.16] for durvalumab and durvalumab+olaparib arms v control, respectively).

[00383] In DUO-E, results in the doublet group showed a clinical benefit for combination therapy with an immune checkpoint inhibitor and standard chemotherapy for newly diagnosed advanced or recurrent endometrial cancer.

[00384] Progression-free survival sensitivity analyses were consistent with the main analysis. The first interim analysis of overall survival favored the investigational arms, in support of the primary endpoints.

[00385] The safety profiles of the experimental groups were generally consistent with the known profiles of each individual component of the regimen. The delivery of standard of care treatment was not compromised by the delivery of any other treatment, and frequency of discontinuations of chemotherapy was similar across arms.

[00386] For adverse events of special or potential interest related to durvalumab, events were consistent with the known safety profile of durvalumab in combination with chemotherapy, which are mainly driven by chemotherapy. For adverse events of special interest related to olaparib, events of myelodysplastic syndrome and acute myeloid leukemia were low and consistent with the known safety profile of olaparib.

[00387] The addition of durvalumab to standard first-line platinum-based chemotherapy followed by maintenance durvalumab with or without olaparib significantly improved progression-free survival outcomes for patients with first-line advanced or recurrent endometrial cancer, confirming the clinical benefit of integrating immunotherapy with or without a PARP inhibitor into first-line chemotherapy in this setting. The addition of olaparib to maintenance durvalumab further enhanced clinical benefit. The safety profiles of the experimental groups were generally consistent with the known profiles of each individual component of the regimen.

[00388] Olaparib (Lynparza) in combination with durvalumab is indicated for the maintenance treatment of adult patients with primary advanced or recurrent endometrial cancer that is mismatch repair proficient (pMMR) whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel.

[00389] Predefined, exploratory subgroup analyses demonstrates an improvement in PFS with the addition of maintenance olaparib to the combination of durvalumab plus chemotherapy may improve outcomes in the pMMR and PD-L1 positive patient populations. While there was a higher rate of grade 3 or higher AEs in the durvalumab+olaparib arm, the safety profiles of each arm were generally consistent with the known profiles of individual components of the regimen.

Example 3: Durvalumab + carboplatin/paclitaxel (CP) followed by durvalumab ± olaparib as a first-line (1L) treatment for endometrial cancer (EC): progression-free survival (PFS) by clinical factors in DUO-E

METHODS

[00390] Patients (pts) with newly diagnosed stage III/IV or recurrent EC were randomized 1:1:1 to CP (CP + durvalumab placebo [pbo] followed by durvalumab pbo + olaparib pbo), CP+D (CP + durvalumab followed by durvalumab + olaparib pbo), or CP+D+O (CP + durvalumab followed by durvalumab + olaparib). Post hoc exploratory PFS subgroup analyses by key clinical factors, age (<65 v ≥65 years); BMI (<25 v ≥25); ECOG PS (0 v 1); and prior chemotherapy, surgery, and radiotherapy (yes v no) in the ITT and mismatch repair populations are reported.

RESULTS

[00391] At primary data cut-off (12 Apr 2023), PFS subgroup analyses by age, BMI, ECOG PS, and prior treatment generally showed benefit for CP+D±O v CP in the ITT population (**Table 9**). PFS subgroup analyses showed consistent PFS benefit for CP+D v CP in dMMR pts (HRs <1.00 in all subgroups). In pMMR pts, CP+D generally showed benefit v CP, with addition of olaparib consistently enhancing PFS (HRs <1.00 for CP+D+O v CP in all subgroups).

[00392] The DUO-E ITT population derived PFS benefit with CP+D±O v CP across a range of key clinical factors explored in these analyses. In dMMR pts, a consistent PFS benefit was observed across key clinical factors for CP+D v CP. pMMR pts derived benefit from CP+D v CP across a range of key clinical factors, with addition of olaparib consistently enhancing PFS within each subgroup category. These DUO-E subgroup analyses support prior PFS analyses of the ITT and dMMR populations (benefit for CP+D v CP), and with enhanced benefit in pMMR pts with the addition of olaparib.

Table 9.

N	CP 241	CP+D 238	CP+D+O 239
	e/n	e/n HR v CP (95% CI)	e/n HR v CP (95% CI)
BMI*			
<25	59/78	54/84 0.76 (0.53–1.11)	46/80 0.59 (0.40–0.87)
≥25†	112/161	84/152 0.64 (0.48–0.85)	79/158 0.50 (0.37–0.66)
Prior chemotherapy			
Y	43/51	38/51 1.15 (0.74–1.79)	36/54 0.55 (0.35–0.86)
N	130/190	101/187 0.61 (0.47–0.79)	90/185 0.52 (0.39–0.68)
Prior surgery			
Y	145/202	116/205 0.68 (0.53–0.87)	103/207 0.53 (0.41–0.68)
N	28/39	23/33 0.70 (0.40–1.24)	23/32 0.52 (0.29–0.92)
Prior radiotherapy			
Y	52/71	45/73 0.81 (0.54–1.21)	55/85 0.72 (0.49–1.05)
N	121/170	94/165 0.63 (0.48–0.83)	71/154 0.44 (0.32–0.59)
N	CP 241	CP+D 238	CP+D+O 239
	e/n	e/n HR v CP (95% CI)	e/n HR v CP (95% CI)
BMI*			
<25	59/78	54/84 0.76 (0.53–1.11)	46/80 0.59 (0.40–0.87)
≥25†	112/161	84/152 0.64 (0.48–0.85)	79/158 0.50 (0.37–0.66)
Prior chemotherapy			
Y	43/51	38/51 1.15 (0.74–1.79)	36/54 0.55 (0.35–0.86)
N	130/190	101/187 0.61 (0.47–0.79)	90/185 0.52 (0.39–0.68)
Prior surgery			
Y	145/202	116/205 0.68 (0.53–0.87)	103/207 0.53 (0.41–0.68)
N	28/39	23/33 0.70 (0.40–1.24)	23/32 0.52 (0.29–0.92)
Prior radiotherapy			
Y	52/71	45/73 0.81 (0.54–1.21)	55/85 0.72 (0.49–1.05)
N	121/170	94/165 0.63 (0.48–0.83)	71/154 0.44 (0.32–0.59)

*Data missing in 2 pts in both CP and CP+D, 1 pt in CP+D+O; †Overweight/obesity.

e, events; n, patients; N, no; Y, yes

Example 4: First-line (1L) durvalumab + carboplatin/paclitaxel (CP) followed by durvalumab ± olaparib for endometrial cancer (EC) (DUO-E): Objective response rate (ORR), duration of response (DoR) and time to treatment discontinuation or death (TDT) by mismatch repair (MMR) status

METHODS

[00393] Pts with newly diagnosed FIGO Stage III (measurable disease [RECIST 1.1] before randomization) or IV or recurrent EC and naïve to systemic 1L treatment were randomized 1:1:1 to CP + durvalumab placebo (pbo; 6 cycles) followed by durvalumab pbo + olaparib pbo (CP arm); CP + durvalumab (1120 mg IV q3w) followed by durvalumab (1500 mg IV q4w) + olaparib pbo (CP+D arm); or CP + durvalumab followed by durvalumab + olaparib (300 mg

tablets bid; CP+D+O arm). ORR, DoR and TDT were assessed in ITT and MMR populations (exploratory).

RESULTS

[00394] At primary data cutoff (12 Apr 2023), overall, ORRs with CP+D and CP+D+O were improved v CP (62 and 64 v 55%); median (m)DoR and mTDT were longer for CP+D v CP (mDoR: 13.1 [95% CI 6.0–NR] v 7.7 [5.1–13.5] months [mo]; mTDT: 9.9 [8.8–11.2] v 8.8 [7.6–9.7] mo) and further increased with CP+D+O (mDoR: 21.3 [8.1–29.9] mo; mTDT: 15.1 [12.5–18.6] mo; **Table 10**). In MMR deficient (dMMR) pts, CP+D and CP+D+O v CP improved ORRs (71 and 73 v 40%), mDoR (NR and 29.9 [95% CI 9.7–29.9] v 10.5 [4.6–NR] mo) and mTDT (21.2 [9.3–NR] and 20.6 [13.4–NR] v 6.7 [5.1–7.9] mo). In pMMR pts, ORRs were similar across arms but mDoR and mTDT were longer with CP+D v CP (mDoR: 10.6 [95% CI 5.6–NR] v 7.6 [5.1–13.1] mo; mTDT: 9.6 [8.1–10.6] v 9.3 [8.0–9.9] mo) and further extended with CP+D+O (mDoR: 18.7 [8.0–NR] mo; mTDT: 13.4 [10.6–15.6] mo).

[00395] CP + durvalumab followed by durvalumab ± olaparib improved ORR, DoR and TDT v CP (ITT population). In dMMR pts, CP+D consistently improved ORR, DoR and TDT v CP. In pMMR pts, CP+D improved mDoR v CP and adding olaparib further extended mDoR and mTDT v CP+D.

Example 5: Interim Analysis of DUO-E Results

[00396] An updated DUO-E study design including endpoints and patients are shown in **Figure 11**. †Six cycles of carboplatin at an area under the concentration–time curve of 5 or 6 mg/mL/min and paclitaxel 175 mg/m². bid, twice daily; CP, carboplatin/paclitaxel; D, durvalumab; DCO1, data cut-off 1; FIGO, International Federation of Gynaecology and Obstetrics; IV, intravenously; O, olaparib; q3(4)w, every 3(4) weeks; R, randomization; RECIST, Response Evaluation Criteria in Solid Tumors. **Figure 12** shows patient characteristics data. Federation of Gynaecology and Obstetrics; HRR(m), homologous recombination repair (mutation); MMR, mismatch repair; NGS, next-generation sequencing; PD-L1, programmed death ligand 1; TAP, tumor area proportion. Percentages may not total 100% because of rounding. Data on ethnicity was missing for 6 patients; 1 newly diagnosed patient was FIGO Stage I and 1 was FIGO Stage II; 1 patient in the CP+D arm had an ECOG PS of 2. Stratification factors (MMR status [proficient vs deficient], disease status [newly diagnosed vs recurrent], and

geographic region [Asia vs non-Asia]) are in accordance with the randomization code. Two patients with ‘unknown’ MMR status, as determined by the central laboratory, were randomized as ‘deficient’ by the interactive voice response system based on local testing. ‘Asia’ included China, Hong Kong, India, Japan, Singapore and Republic of Korea; †MMR status evaluated using the Ventana MMR immunohistochemistry panel; ‡PD-L1 expression evaluated using Ventana SP263 assay; §HRRm status evaluated using the Foundation One CDx NGS assay and includes deleterious or suspected deleterious mutations in ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L. HRRm status unknown includes patients recruited in China, where HRR testing was not performed, and patients with samples that were unavailable for testing. ECOG PS, Eastern Cooperative Oncology Group performance status;

[00397] The results of the ITT population are shown in **Figure 13**. The *best objective response was determined based on data obtained until starting of any subsequent cancer therapy and up to and including RECIST progression or the last RECIST assessment in the absence of progression. Calculated based on the number of patients with measurable disease at baseline; †Odds of a response (complete or partial). Odds ratio >1 favors CP+D or CP+D+O arm; ‡Time from randomization to onset of response; §DoR is the time from the first confirmed complete/partial response until the date of progression or the date of censoring for PFS. Rates of patients remaining in response were estimated by the Kaplan–Meier method. IQR, interquartile range; NR, not reached. The secondary endpoint in the ITT population are shown in **Figure 14**. TFST, PFS2 and TSST rates were estimated by the Kaplan–Meier method. *HRs were estimated from a Cox proportional hazards model stratified by MMR and disease status variables. CIs were calculated using a profile likelihood approach.

[00398] *Post hoc* exploratory analyses for MMR subpopulations are shown in **Figure 15**. For the dMMR subpopulation, median duration of follow-up for OS was 18.4 (CP), 19.1 (CP+D) and 19.9 months (CP+D+O) in censored patients; for the pMMR subpopulation, median duration of follow-up was 18.6 (CP), 18.2 (CP+D) and 18.4 months (CP+D+O) in censored patients. MMR status was evaluated using the Ventana MMR immunohistochemistry panel. OS rates were

estimated by the Kaplan–Meier method. *HRs and CIs were estimated from an unstratified Cox proportional hazards model.

[00399] **Figure 16** show *post hoc* exploratory analyses for dMMR subpopulations. MMR status was evaluated using the Ventana MMR immunohistochemistry panel. TFST, PFS2 and TSST rates were estimated by the Kaplan–Meier method. *HRs and CIs were estimated from an unstratified Cox proportional hazards model. Stratification factors (disease status, MMR status, and geographic region) are per the randomization code. HRRm status was evaluated using the Foundation One CDx NGS assay and includes deleterious or suspected deleterious mutations in ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L. HRRm status unknown includes patients recruited in China, where HRR testing was not performed, and patients with samples that were unavailable for testing. PD-L1 status in baseline tumor tissue was determined centrally using Ventana SP263 assay. Expression was assessed using a TAP score, calculated based on the proportion of the tumor area populated by tumor cells or immune cells with membranous PD-L1 staining. FIGO stage determined at the time of initial diagnosis of endometrial cancer under investigation. G, grade; NC, not calculated. Best objective response was determined based on data obtained until starting of any subsequent cancer therapy and up to and including RECIST progression or the last RECIST assessment in the absence of progression. Calculated based on the number of patients with measurable disease at baseline; †Odds of a response (complete or partial). Odds ratio >1 favors CP+D or CP+D+O arm; ‡Time from randomization to onset of response; §DoR is the time from the first confirmed complete/partial response until the date of progression or the date of censoring for PFS. Rates of patients remaining in response were estimated by the Kaplan–Meier method.

[00400] **Figure 17** shows *post hoc* exploratory analyses for pMMR subpopulations. MMR status was evaluated using the Ventana MMR immunohistochemistry panel. TFST, PFS2 and TSST rates were estimated by the Kaplan–Meier method. *HRs and CIs were estimated from an unstratified Cox proportional hazards model. Stratification factors (disease status, MMR status, and geographic region) are per the randomization code. HRRm status was evaluated using the Foundation One CDx NGS assay and includes deleterious or suspected deleterious mutations in ATM, BRCA1, BRCA2, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L. HRRm status unknown includes patients recruited

in China, where HRR testing was not performed, and patients with samples that were unavailable for testing. PD-L1 status in baseline tumor tissue was determined centrally using Ventana SP263 assay. Expression was assessed using a TAP score, calculated based on the proportion of the tumor area populated by tumor cells or immune cells with membranous PD-L1 staining. FIGO stage determined at the time of initial diagnosis of endometrial cancer under investigation. Best objective response was determined based on data obtained until starting of any subsequent cancer therapy and up to and including RECIST progression or the last RECIST assessment in the absence of progression. Calculated based on the number of patients with measurable disease at baseline; †Odds of a response (complete or partial). Odds ratio >1 favors CP+D or CP+D+O arm; ‡Time from randomization to onset of response; §DoR is the time from the first confirmed complete/partial response until the date of progression or the date of censoring for PFS. Rates of patients remaining in response were estimated by the Kaplan–Meier method.

[00401] For the MMR subpopulations, the results are shown in **Figure 18**. MMR status evaluated using the Ventana immunohistochemistry MMR panel. PFS rates were estimated by the Kaplan–Meier method. *CI for median PFS was derived based on the Brookmeyer–Crowley method; †HRs and CIs were estimated from an unstratified Cox proportional hazards model. CI, confidence interval; CP, carboplatin/paclitaxel; D, durvalumab; DCO, data cut-off; dMMR, MMR deficient; HR, hazard ratio; ITT, intent to treat; NR, not reached; O, olaparib; PFS, progression-free survival; pMMR, MMR proficient.

[00402] Finally, **Figures 19-20** show additional results of the ITT population and exploratory PFS analyses.

	ITT			dMMR			pMMR		
	CP n=241	CP+D n=238	CP+D+O n=239	CP n=49	CP+D n=46	CP+D+O n=48	CP n=192	CP+D n=192	CP+D+O n=191
mTDT, mo (95% CI)	8.8 (7.6–9.7)	9.9 (8.8–11.2)	15.1 (12.5–18.6)	6.7 (5.1–7.9)	21.2 (9.3–NR)	20.6 (13.4–NR)	9.3 (8.0–9.9)	9.6 (8.1–10.6)	13.4 (10.6–15.6)
Pts with measurable disease at baseline, n	198	202	184	42	42	37	156	160	147
Objective response, n (%) [*]	109 (55)	125 (62)	117 (64)	17 (40)	30 (71)	27 (73)	92 (59)	95 (59)	90 (61)
mDoR, mo (IQR)	7.7 (5.1–13.5)	13.1 (6.0–NR)	21.3 (8.1–29.9)	10.5 (4.6–NR)	NR (22.0–NR)	29.9 (9.7–29.9)	7.6 (5.1–13.1)	10.6 (5.6–NR)	18.7 (8.0–NR)

^{*}In pts with measurable disease at baseline. CI, confidence interval; IQR, interquartile range; ITT, intent to treat; NR, not reached

REFERENCES:

1. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019;394(10212):1929-1939. (In eng). DOI: 10.1016/s0140-6736(19)32222-6.
2. Johnson ML, Cho BC, Luft A, et al. Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study. *Journal of Clinical Oncology* 2023;41(6):1213-1227. DOI: 10.1200/jco.22.00975.
3. Oh DY, Lee KH, Lee DW, et al. Gemcitabine and cisplatin plus durvalumab with or without tremelimumab in chemotherapy-naïve patients with advanced biliary tract cancer: an open-label, single-centre, phase 2 study. *Lancet Gastroenterol Hepatol* 2022;7(6):522-532. DOI: 10.1016/S2468-1253(22)00043-7.
1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022;72(1):7-33. (In eng). DOI: 10.3322/caac.21708.
2. NCCN. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Uterine neoplasms. Version 1.2023. Plymouth Meeting, PA: National Comprehensive Cancer Network, 2022.
3. Aghajanian C, Filiaci V, Dizon DS, et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. *Gynecol Oncol* 2018;150(2):274-281. DOI: 10.1016/j.ygyno.2018.05.018.
4. Miller D, Filiaci V, Fleming G, et al. Late-Breaking Abstract 1: Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2012;125(3):771. DOI: 10.1016/j.ygyno.2012.03.034.
5. Pectasides D, Xiros N, Papaxoinis G, et al. Carboplatin and paclitaxel in advanced or metastatic endometrial cancer. *Gynecol Oncol* 2008;109(2):250-4. DOI: 10.1016/j.ygyno.2008.01.028.
6. André T, Berton-Rigaud D, Curigliano G, et al. 549P Progression-free survival (PFS) and overall survival (OS) in patients (pts) with mismatch repair deficient (dMMR) solid tumors treated with dostarlimab in the GARNET study. *Ann Oncol* 2022;33:S799-800; abstract. DOI: 10.1016/j.annonc.2022.07.677.

7. Antill Y, Kok PS, Robledo K, et al. Clinical activity of durvalumab for patients with advanced mismatch repair-deficient and repair-proficient endometrial cancer. A nonrandomized phase 2 clinical trial. *J Immunother Cancer* 2021;9(6):e002255. DOI: 10.1136/jitc-2020-002255.
8. Marabelle A, Le DT, Ascierto PA, et al. Efficacy of pembrolizumab in patients with noncolorectal high microsatellite instability/mismatch repair-deficient cancer: results from the Phase II KEYNOTE-158 study. *J Clin Oncol* 2020;38(1):1-10. DOI: 10.1200/JCO.19.02105.
9. Makker V, Colombo N, Casado Herráez A, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. *New England Journal of Medicine* 2022;386(5):437-448. DOI: 10.1056/NEJMoa2108330.
10. Mirza MR, Chase DM, Slomovitz BM, et al. Dostarlimab for primary advanced or recurrent endometrial cancer. *N Engl J Med* 2023;388:2145-2158. DOI: 10.1056/NEJMoa2216334.
11. Eskander RN, Sill MW, Beffa L, et al. Pembrolizumab plus chemotherapy in advanced endometrial cancer. *N Engl J Med* 2023;388(23):2159-2170. DOI: 10.1056/NEJMoa2302312.
12. Stewart RA, Pilié PG, Yap TA. Development of PARP and Immune-Checkpoint Inhibitor Combinations. *Cancer Research* 2018;78(24):6717-6725. DOI: 10.1158/0008-5472.Can-18-2652.
13. Li A, Yi M, Qin S, Chu Q, Luo S, Wu K. Prospects for combining immune checkpoint blockade with PARP inhibition. *J Hematol Oncol* 2019;12(1):98. DOI: 10.1186/s13045-019-0784-8.
14. Wanderley CWS, Correa TS, Scaranti M, Cunha FQ, Barroso-Sousa R. Targeting PARP1 to Enhance Anticancer Checkpoint Immunotherapy Response: Rationale and Clinical Implications. *Front Immunol* 2022;13:816642. DOI: 10.3389/fimmu.2022.816642.
15. Lee EK, Konstantinopoulos PA. Combined PARP and Immune Checkpoint Inhibition in Ovarian Cancer. *Trends Cancer* 2019;5(9):524-528. DOI: 10.1016/j.trecan.2019.06.004.
16. AstraZeneca. Global Policy: bioethics.
(www.astrazeneca.com/content/dam/az/PDF/2019/Bioethics%20Policy%20final.pdf).

WHAT IS CLAIMED IS:

Claim 1. A method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject:

(a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

Claim 2. A method of treating endometrial cancer in a subject in need thereof, comprising administering to the subject:

(a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 3. The method of either claim 1 or 2, wherein step (b) occurs after completion of step (a).

Claim 4. The method according any one of claims 1-3, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab.

Claim 5. The method according to any one of claims 1 to 4, wherein the PARP inhibitor is olaparib.

Claim 6. The method according to any one of claims 1 to 5, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of from 800 mg to 1500 mg.

Claim 7. The method according to claim 6, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of 1120 mg and/or 1500mg.

Claim 8. The method according to any one of claims 1 to 7, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of from 10 mg/kg to 20 mg/kg.

Claim 9. The method according to claim 8, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is administered at a dose of 15 mg/kg and/or 20 mg/kg.

Claim 10. The method according to any one of claims 1 to 9, wherein the PARP inhibitor is administered at a dose of 100 mg to 300 mg.

Claim 11. The method according to claim 10, wherein the PARP inhibitor is administered at a dose of 300 mg.

Claim 12. The method according to any one of claims 1 to 11, wherein the one or more chemotherapy agents is paclitaxel and/or carboplatin.

Claim 13. The method according to any one of claims 1 to 12, wherein the paclitaxel is administered at a dose of 175 mg/m².

Claim 14. The method according to claim 12 or claim 13, wherein the carboplatin is administered at a dose that produces an Area Under of Curve (AUC) of AUC5 or AUC6.

Claim 15. The method according to any one of claims 1 to 14, wherein step (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents every two to four weeks.

Claim 16. The method according to claim 15, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every two to four weeks for nine to eighteen weeks.

Claim 17. The method according to any one of claims 1 to 15, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every three weeks.

Claim 18. The method according to claim 17, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every three weeks for twelve to eighteen weeks.

Claim 19. The method according to claim 17, wherein step (a) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof and a cycle of the one or more chemotherapy agents every three weeks for eighteen weeks.

Claim 20. The method according to any one of claims 1 to 19, wherein step (a) comprises administration of four to six doses of the anti-PD-L1 antibody or antigen-binding fragment thereof and four to six cycles of the one or more chemotherapy agents.

Claim 21. The method according to any one of claims 1 to 20, wherein step (a) comprises administration of 1120 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 22. The method according to claim 21, wherein step (a) comprises administration of 1120 mg of durvalumab.

Claim 23. The method according to claim 22, wherein step (a) comprises administration of 1120 mg of durvalumab every 3 weeks.

Claim 24. The method according to any one of claims 21 to 23, wherein step (a) further comprises administration of:

175 mg/m² of paclitaxel;
AUC 5 or AUC 6 of carboplatin; and/or
25 mg/m² of cisplatin.

Claim 25. The method according to any one of claims 1 to 24, wherein step (b) comprises:
administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof
every two to four weeks; and administration of a dose of the PARP inhibitor twice daily.

Claim 26. The method according to any one of claims 1 to 25, wherein step (b) comprises:
administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof
every four weeks; and administration of a dose of the PARP inhibitor twice daily.

Claim 27. The method according to any one of claims 1 to 26, wherein step (b) comprises
administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every
four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12
weeks.

Claim 28. The method according to claim 27, wherein step (b) comprises administration of
a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up
to 24 months and twice daily doses of the PARP inhibitor for up to 24 months.

Claim 29. The method according to any one of claims 1 to 28, wherein step (b) comprises
administration of:
1500 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof; and
300 mg of the PARP inhibitor.

Claim 30. The method according to claim 29, wherein step (b) comprises administration of:
1500 mg of durvalumab; and
300 mg olaparib.

Claim 31. The method according to claim 30, wherein step (b) comprises administration of:

1500 mg of durvalumab every 4 weeks; and
300 mg olaparib twice a day.

Claim 32. The method according to any one of claims 2 to 24, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every two to four weeks.

Claim 33. The method according to any one of claims 2 to 24, or 32, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks.

Claim 34. The method according to any one of claims 2 to 24, or 32-33 wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks.

Claim 35. The method according to claim 34, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months.

Claim 36. The method according to any one of claims 2 to 24 or 32-35, wherein step (b) comprises administration of 1500 mg of the anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 37. The method according to claim 36, wherein step (b) comprises administration of 1500 mg of durvalumab.

Claim 38. The method according to claim 37, wherein step (b) comprises administration of 1500 mg of durvalumab every 4 weeks.

Claim 39. The method according to any one of claims 1 to 38, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents are administered intravenously.

Claim 40. The method according to any one of claims 1 to 39, wherein the PARP inhibitor is administered orally.

Claim 41. The method according to any one of claims 1 to 40, wherein the antigen-binding fragment thereof, the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents in step (a) are administered to the subject simultaneously, separately, and/or sequentially.

Claim 42. The method according to any one of claims 1 to 42, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor in step (b) are administered to the subject simultaneously, separately, and/or sequentially.

Claim 43. The method according to any one of claims 1 to 42, wherein the endometrial cancer is advanced endometrial cancer.

Claim 44. The method according to any one of claims 1 to 43, wherein the endometrial cancer is an endometrial cancer tumor lacking mismatch repair (MMR-deficient (dMMR)).

Claim 45. The method according to claim 44, comprising administering to the subject with deficient mismatch repair (dMMR) endometrial cancer:

(a) a therapeutically effective amount of one or more chemotherapy agents and a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 46. The method according to any one of claims 1 to 43, wherein the endometrial cancer is an endometrial cancer tumor that is MMR proficient (pMMR).

Claim 47. The method according to claim 46, comprising administering to the subject with proficient mismatch repair (pMMR) endometrial cancer:

(a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

Claim 48. The method according to any one of claims 1 to 47, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 positive.

Claim 49. The method according to any one of claims 1 to 47, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 negative.

Claim 50. The method according to any one of claims 1 to 49, wherein the treatment produces an increase in progression free survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

Claim 51. The method according to claim 50, wherein the treatment produces an increase in progression free survival for at least 4 months.

Claim 52. The method according to any one of claims 1 to 51, wherein the treatment produces an increase in overall survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

Claim 53. The method according to claim 52, wherein the treatment produces an increase in overall survival for at least 4 months.

Claim 54. A combination for use in the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises:

- (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and
- (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and a therapeutically effective amount of a PARP inhibitor.

Claim 55. A combination for use in the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises:

- (a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and
- (b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 56. The combination for use according to either claim 54 or claim 55, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab.

Claim 57. The combination for use according to any one of claims 54 to 56, wherein the PARP inhibitor is olaparib.

Claim 58. The combination for use according to any one of claims 54 to 57, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 800 mg to 1500 mg.

Claim 59. The combination for use according to claim 58, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 1120 mg and/or 1500 mg.

Claim 60. The combination for use according to any one of claims 54 to 59, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 10 mg/kg to 20 mg/kg.

Claim 61. The combination for use according to claim 60, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 15 mg/kg and/or 20 mg/kg.

Claim 62. The combination for use according to any one of claims 54 to 61, wherein the dose of PARP inhibitor is from 100 mg to 300 mg.

Claim 63. The combination for use according to claim 62, wherein the dose of PARP inhibitor is 300 mg.

Claim 64. The combination for use according to any one of claims 54 to 63, wherein the one or more chemotherapy agents is paclitaxel and/or carboplatin.

Claim 65. The combination for use according to claim 64, wherein the dose of paclitaxel is 175 mg/m².

Claim 66. The combination for use according to claim 64 or claim 65, wherein the dose of carboplatin produces an Area Under of Curve (AUC) of AUC5 or AUC6.

Claim 67. The combination for use according to any one of claims 54 to 66, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents every two to four weeks.

Claim 68. The combination for use according to claim 67, wherein administration is every two to four weeks for nine to twenty-four weeks.

Claim 69. The combination for use according to claim 67 or claim 68, wherein administration is every three weeks or every four weeks.

Claim 70. The combination for use according to claim 69, wherein administration is every three weeks for twelve to eighteen weeks.

Claim 71. The combination for use according to claim 70, wherein administration is every three weeks for eighteen weeks.

Claim 72. The combination for use according to any one of claims 54 to 71, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof for three to six doses, and the one or more chemotherapy agents for four to six doses.

Claim 73. The combination for use according to any one of claims 54 to 72, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1120 mg.

Claim 74. The combination for use according to claim 73, wherein the durvalumab is administered at a dose of 1120 mg.

Claim 75. The combination for use according to claim 73 or claim 74, wherein the durvalumab is administered at a dose of 1120 mg every 3 weeks.

Claim 76. The combination for use according to any one of claims 73 to 75, wherein (a) further comprises:

175 mg/m² of paclitaxel;
AUC 5 or AUC 6 of carboplatin; and/or
25 mg/m² of cisplatin.

Claim 77. The combination for use according to any one of claims 54 to 76, wherein (b) comprises:

the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks; and
the PARP inhibitor administered twice daily.

Claim 78. The combination for use according to any one of claims 54 to 77, wherein (b) comprises:

the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks; and

the PARP inhibitor administered twice daily.

Claim 79. The combination for use according to any one of claims 54 to 78, wherein (b) comprises administration of:

the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg; and
the PARP inhibitor at a dose of 300 mg.

Claim 80. The combination for use according to claim 77, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks.

Claim 81. The combination for use according to claim 79, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months and twice daily doses of the PARP inhibitor for up to 24 months.

Claim 8271. The combination for use according to claim 79, wherein (b) comprises administration of:

durvalumab at a dose of 1500 mg; and
olaparib at a dose of 300 mg.

Claim 83. The combination for use according to any one of claims 79 to 81, wherein (b) comprises administration of:

durvalumab at a dose of 1500 mg every 3 weeks; and
olaparib at a dose of 300 mg twice a day.

Claim 84. The combination for use according to any one of claims 55 to 76, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks.

Claim 85. The combination for use according to any one of claims 55 to 76, or 84, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks.

Claim 86. The combination for use according to any one of claims 55 to 76, or 84-85, wherein (b) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg.

Claim 87. The combination for use according to claim 85, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12.

Claim 88. The combination for use according to claim 87, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months.

Claim 89. The combination for use according to claim 86, wherein (b) comprises administration of durvalumab at a dose of 1500 mg.

Claim 90. The combination for use according to any one of claims 84 to 89, wherein (b) comprises administration of durvalumab at a dose of 1500 mg every 3 weeks.

Claim 91. The combination for use according to any one of claims 54 to 90, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents are administered intravenously.

Claim 92. The combination for use according to any one of claims 54 to 91, wherein the PARP inhibitor is administered orally.

Claim 93. The combination for use according to any one of claims 54 to 92, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents in (a) are administered to the subject simultaneously, separately, and/or sequentially.

Claim 94. The combination for use according to any one of claims 54 to 93, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor in (b) are administered to the subject simultaneously, separately, and/or sequentially.

Claim 95. The combination for use according to any one of claims 54 to 94, wherein the endometrial cancer is advanced endometrial cancer.

Claim 96. The combination for use according to any one of claims 54 to 95, wherein the endometrial cancer is an endometrial cancer tumor lacking mismatch repair (dMMR).

Claim 97. The combination for use according to claim 96 in the treatment of deficient mismatch repair (dMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises:

(a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 98. The combination for use according to any one of claims 54 to 95, wherein the endometrial cancer is an endometrial cancer tumor that is MMR proficient (pMMR).

Claim 99. The combination for use according to claim 98 in the treatment of proficient mismatch repair (pMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises:

(a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

Claim 100. The combination for use according to any one of claims 54 to 99, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 positive.

Claim 101. The combination for use according to any one of claims 54 to 99, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 negative.

Claim 102. The combination for use according to any one of claims 54 to 101, wherein treatment with the combination produces an increase in progression free survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

Claim 103. The combination for use according to claim 102, wherein the treatment produces an increase in progression free survival for at least 4 months.

Claim 104. The combination for use according to any one of claims 54 to 101, wherein treatment with the combination produces an increase in overall survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

Claim 105. The combination for use according to claim 104, wherein the treatment produces an increase in overall survival for at least 4 months.

Claim 106. Use of a combination in the manufacture of a medicament for the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises:

(a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof, and a therapeutically effective amount of a PARP inhibitor.

Claim 107. Use of a combination in the manufacture of a medicament for the treatment of endometrial cancer in a subject in need thereof, wherein the combination comprises:

(a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 108. The use according to claim 106 or claim 107, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof is durvalumab.

Claim 109. The use according to any one of claims 106 to 108, wherein the PARP inhibitor is olaparib.

Claim 110. The use according to any one of claims 106 to 109, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 800 mg to 1500 mg.

Claim 111. The use according to claim 110, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 1120 mg and/or 1500 mg.

Claim 112. The use according to any one of claims 106 to 111, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is from 10 mg/kg to 20 mg/kg.

Claim 113. The use according to claim 112, wherein the dose of anti-PD-L1 antibody or antigen-binding fragment thereof is 15 mg/kg and/or 20 mg/kg.

Claim 114. The use according to any one of claims 106 to 113, wherein the dose of PARP inhibitor is from 100 mg to 300 mg.

- Claim 115. The use according to claim 114, wherein the dose of PARP inhibitor is 300 mg.
- Claim 116. The use according to any one of claims 114 to 115, wherein the one or more chemotherapy agents is paclitaxel and/or carboplatin.
- Claim 117. The use according to claim 116, wherein the dose of paclitaxel is 175 mg/m².
- Claim 118. The use according to claim 116 or claim 117, wherein the dose of carboplatin produces an Area Under of Curve (AUC) of AUC5 or AUC6.
- Claim 119. The use according to any one of claims 106 to 118, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents every two to four weeks.
- Claim 120. The use according to claim 119, wherein administration is every two to four weeks for nine to twenty-four weeks.
- Claim 121. The use according to claim 119 or claim 120, wherein administration is every three weeks or every four weeks.
- Claim 122. The use according to claim 121, wherein administration is every three weeks for twelve to eighteen weeks.
- Claim 123. The use according to claim 122, wherein administration is every three weeks for eighteen weeks.
- Claim 124. The use according to any one of claims 106 to 123, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof for three to six doses, and the one or more chemotherapy agents for four to six doses.

Claim 125. The use according to any one of claims 106 to 124, wherein (a) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1120 mg.

Claim 126. The use according to claim 125, wherein the durvalumab is administered at a dose of 1120 mg.

Claim 127. The use according to claim 125 or claim 126, wherein the durvalumab is administered at a dose of 1120 mg every 3 weeks.

Claim 128. The use according to any one of claims 125 to 127, wherein (a) further comprises:
175 mg/m² of paclitaxel;
AUC 5 or AUC 6 of carboplatin; and/or
25 mg/m² of cisplatin.

Claim 129. The use according to any one of claims 106 to 128, wherein (b) comprises:
the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks; and
the PARP inhibitor administered twice daily.

Claim 130. The use according to any one of claims 106 to 129, wherein (b) comprises:
the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks; and
the PARP inhibitor administered twice daily.

Claim 131. The use according to any one of claims 106 to 130, wherein (b) comprises administration of:
the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg; and
the PARP inhibitor at a dose of 300 mg.

Claim 132. The use according to claim 131, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks.

Claim 133. The use according to claim 131, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months and twice daily doses of the PARP inhibitor for up to 24 months.

Claim 134. The use according to claim 131, wherein (b) comprises administration of:
durvalumab at a dose of 1500 mg; and
olaparib at a dose of 300 mg.

Claim 135. The use according to any one of claims 131 to 134, wherein (b) comprises administration of:
durvalumab at a dose of 1500 mg every 3 weeks; and
olaparib at a dose of 300 mg twice a day.

Claim 136. The use according to any one of claims 107 to 128, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every two to four weeks.

Claim 137. The use according to any one of claims 107 to 128, or 136, wherein (b) comprises the anti-PD-L1 antibody or antigen-binding fragment thereof administered every four weeks.

Claim 138. The use according to any one of claims 106 to 128 or 136 to 137 wherein (b) comprises administration of the anti-PD-L1 antibody or antigen-binding fragment thereof at a dose of 1500 mg.

Claim 139. The use according to claim 137, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for at least 12 weeks and twice daily doses of the PARP inhibitor for at least 12 weeks.

Claim 140. The use according to claim 137, wherein step (b) comprises administration of a dose of the anti-PD-L1 antibody or antigen-binding fragment thereof every four weeks for up to 24 months.

Claim 141. The use according to claim 137, wherein (b) comprises administration of durvalumab at a dose of 1500 mg.

Claim 142. The use according to any one of claims 137 to 141, wherein (b) comprises administration of durvalumab at a dose of 1500 mg every 3 weeks.

Claim 143. The use according to any one of claims 106 to 142, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents are administered intravenously.

Claim 144. The use according to any one of claims 106 to 143, wherein the PARP inhibitor is administered orally.

Claim 145. The use according to any one of claims 106 to 144, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the one or more chemotherapy agents in (a) are administered to the subject simultaneously, separately, and/or sequentially.

Claim 146. The use according to any one of claims 106 to 145, wherein the anti-PD-L1 antibody or antigen-binding fragment thereof, and the PARP inhibitor in (b) are administered to the subject simultaneously, separately, and/or sequentially.

Claim 147. The use according to any one of claims 106 to 146, wherein the endometrial cancer is advanced endometrial cancer.

Claim 148. The use according to any one of claims 106 to 147, wherein the endometrial cancer is an endometrial cancer tumor lacking mismatch repair (dMMR).

Claim 149. The use according to claim 148 in the manufacture of a medicament for the treatment of deficient mismatch repair (dMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises:

(a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof.

Claim 150. The use according to any one of claims 106 to 147, the endometrial cancer is an endometrial cancer tumor that is MMR proficient (pMMR).

Claim 151. The use according to claim 150 the manufacture of a medicament for the treatment of proficient mismatch repair (pMMR) endometrial cancer in a subject in need thereof, wherein the combination comprises:

(a) a therapeutically effective amount of one or more chemotherapy agents, a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof; and

(b) a therapeutically effective amount of an anti-PD-L1 antibody or antigen-binding fragment thereof and a therapeutically effective amount of a PARP inhibitor.

Claim 152. The use according to any one of claims 106 to 151, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 positive.

Claim 153. The use according to any one of claims 106 to 151, wherein the endometrial cancer is an endometrial cancer tumor that is PD-L1 negative.

Claim 154. The use according to any one of claims 106 to 153, wherein treatment with the combination produces an increase in progression free survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

Claim 155. The use according to claim 154, wherein the treatment produces an increase in progression free survival for at least 4 months.

Claim 156. The use according to any one of claims 106 to 153, wherein treatment with the combination produces an increase in overall survival in the subject compared to a patient who has only received durvalumab and chemotherapy.

Claim 157. The use according to claim 156, wherein the treatment produces an increase in overall survival for at least 4 months.