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Window of Opportunity Trial of Olaparib and Durvalumab (MEDI4736) before Standard Neoadjuvant Chemotherapy for Stage II/III Triple Negative or Low ER+ Breast Cancer

Sponsor: Seock-Ah Im, M.D & Ph.D, Seoul National University Hospital

PROTOCOL SYNOPSIS

Window of Opportunity Trial of Olaparib and Durvalumab before Standard Neoadjuvant Chemotherapy for Stage II/III Triple Negative or Low ER+ Breast Cancer

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Scientific Basis / Rationale:

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer and associated with higher expression of PDL-1 compared with other subtypes of breast cancer (Sabatier et al. 2015; Muenst et al 2015). Moreover, TNBC is the most common histological subtype observed in BRCA1 gene mutation carriers (Peshkin et al 2010). Olaparib increases genomic instability (O'Connor et al 2015) and it is plausible that increased mutations induced by olaparib could be associated with better response to immune checkpoint inhibitors such as durvalumab.

We propose a window-of-opportunity, serial biopsy trial of olaparib and durvalumab before standard neoadjuvant chemotherapy for locally advanced breast cancer.

1. Rationale #1

Mutation burden and response to Immune checkpoint inhibitors

Tumors with high nonsynonymous mutation burden were associated with improved outcome with immune checkpoint inhibitors (therapeutic antibodies to PD-1, PDL-1, or CTLA-4) in

NSCLC (Rizvi et al 2015) and melanoma (Snyder et al 2014). Moreover, colorectal cancer with mismatch repair deficiency was also associated with better outcome with PD-1 blocker, suggesting a relationship between high mutation burden and improved outcome (Le et al 2015). As olaparib increased the genomic instability by inhibiting PARP1, it is plausible that increased mutations induced by olaparib could be associated with better sensitivity to durvalumab.

2. Rationale #2

Immunoregulatory effects of PARP inhibitors

Beyond the function of PARP-1 as a DNA nick sensor and signaling molecule binding to single and double stranded DNA breaks, diverse roles of PARP in immunity, inflammation, and cell death are being investigated (Laudisi et al 2011, Rosado et al 2013). Indeed a PARP inhibitor was shown to increase peritoneal CD8 T cells and NK cells production of IFN-γ and TNF-α from the immune cells in a BRCA1-mutated ovarian cancer xenograft model (Huang et al 2015).

3. Rationale #3

Immunogenic cell death and local antigen release

Preclinical studies have shown that PARP inhibitors promote local antigen release, resulting in systemic antitumor response after tumor exposure to radiation or DNA-damaging agents or secondary to spontaneous or heritable defects in DNA (Kroemer et al 2013, Wu et al 2014).

Hypothesis:

Olaparib could increase genomic instability and sensitize triple negative breast cancer to durvalumab. The changes of tumor biology could be detected by serial biopsy of breast cancer before and after olaparib and durvalumab.

Objectives:

Primary Objectives:

The changes of tumor biology detected by serial biopsy of breast cancer before and after olaparib and durvalumab (exploratory serial biopsy study)

Secondary Objective(s):

1. Number of Participants with a Pathological Complete Response (ypT0/Tis, ypN0).
2. Response rate by RECIST v.1.1

3. Safety and toxicity of olaparib and durvalumab 4. Adverse events of special interest and immune-mediated adverse events (AESI/imAEs), which include diarrhoea/colitis, pneumonitis/ILD, hepatitis and increases in transaminases, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), dermatitis/rash and pruritus, nephritis and increases in serum creatinine, neuromuscular toxicity such as myasthenia gravis and Guillain-Barre, pancreatitis, other inflammatory responses that are rare with a potential immune-mediated aetiology (including myocarditis, pericarditis, and uveitis), infusion-related reactions and hypersensitivity/anaphylactic reactions.
Treatment Regimen: Study treatment Olaparib tablets (300mg BID) daily for 28 days (day 1 - day 28) Durvalumab (1500mg IV) on day 15Serial biopsy from breast (or lymph nodes) will be performed before olaparib (between day -28 and day 0), on day 14 (after olaparib before durvalumab), on day 29 (after olaparib and durvalumab) After the study treatment, the subject will receive standard neoadjuvant chemotherapy (Adriamycin/cyclophosphamide q 3 weeks for 4 cycles, followed by docetaxel q 3 weeks for 4 cycles) for approximately 6 months. All subjects are to receive definitive local-regional therapy (surgery ± radiotherapy) at the completion of neoadjuvant systemic therapy. Tumor specimen at the time of surgery will be collected from patients without pathologic complete response (if feasible).
Study Population: Newly diagnosed histologically confirmed stage II-III, ER, PR and HER2 negative breast cancer (TNBC, including low estrogen receptor (ER) tumors where ER is expressed in <10% in tumor cells)
Inclusion Criteria: • Nineteen years of age or older on the day of signing informed consent. • Willing and able to provide written informed consent for voluntary participation in the trial. • Has previously untreated, clinical stage II/III triple negative breast cancer (TNBC) or low estrogen receptor (ER) tumor where ER is expressed in ≤10% tumor cells) . • Willing to provide biopsies from the primary tumor or lymph nodes at screening to the central laboratory and agrees to have a core needle biopsy or incisional or excisional tumor biopsy after

14 days and 28 days of olaparib treatment (before and after durvalumab treatment) if tumor biopsy is feasible as judged by the investigator.

- Has Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥60 years old and no menses for >1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry and agree to use contraception if they or their partner are of reproductive potential.
- Has adequate organ function.
  - Hemoglobin ≥ 10.0 g/dL
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (> 1500 per mm^3)
  - Platelet count ≥ 100 x 10^9/L (>100,000 per mm^3)
  - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
  - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional ULN unless due to Gilbert's syndrome
  - INR/PT/APTT each ≤ 1.5 x ULN
  - TSH within normal limits
  - Serum creatinine < 1.5 x ULN or serum creatinine CL > 51 mL/min by the Cockcroft-Gault formula (Cockroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance
- Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

Exclusion Criteria:

- Underweighted populations - ≤30kg
- Has evidence of metastatic breast cancer, inflammatory breast cancer, or concurrent bilateral invasive breast cancer where ER is expressed in >10% tumor cells. (Note) Patients with bilateral invasive breast cancers can be enrolled if both tumors are TNBCs, including low estrogen receptor (ER) tumor where ER is expressed in ≤10% tumor cells.
- Has another malignancy within the last 3 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and thyroid cancer that has undergone potentially curative surgery, or in situ cervical cancer.

  (Note) These patients should be consulted to the principal investigator for a case-by-case decision before enrollment.
- Has received prior chemotherapy, targeted therapy, radiation therapy, immunotherapy that targets immune checkpoints, co-stimulatory or co-inhibitory pathways for T cell receptors within the past 12 months.
- Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab

- Is currently participating and receiving study therapy, or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study drug.
- Has received a live vaccine within 30 days of the first dose of durvalumab. Note: Patients, if enrolled, should not receive live vaccine up to 30 days after the last dose of IP.
- Has an active autoimmune disease or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]) that has required systemic treatment in past 2 years. The followings are exceptions to this criterion:
  - Patients with vitiligo or alopecia
  - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment.
  - Any chronic skin condition that does not require systemic therapy
  - Patients without active disease in the last 3 years may be included but only after consultation with the principal investigator.
  - Patients with celiac disease controlled by diet alone may be included but only after consultation with the principal investigator.
- Has a diagnosis of immunodeficiency
- Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
  - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
  - Systemic corticosteroid at physiologic dose not to exceed 10 mg/day of prednisone or its equivalent
  - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)
- Has a known history of Human Immunodeficiency Virus (HIV).
- Active infection, including tuberculosis (clinical evaluation *that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice*), hepatitis B, hepatitis C, or human immunodeficiency virus (HIV, positive HIV 1 or 2 antibodies). Active hepatitis B virus (HBV) infection is defined by a positive HBV surface antigen (HBsAg) and positive titer for HBV DNA.result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core IgG antibody and the absence of HBsAg, deoxyribonucleic acid [DNA] negative) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA)..
- Has evidence of active, non-infectious pneumonitis.

- Has history of pneumonitis requiring treatment with steroids or history of interstitial lung disease.
- Has an active infection requiring systemic therapy.
- Has significant cardiovascular disease, such as: History of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months; Congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF NYHA class III or IV
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
- Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study drug.
- Has a known hypersensitivity to the components of the study drug or its analogs.
- Concurrent use of any medications or substances that are strong ihibitors of cytochrome P450 (CYP) 3A (CYP3A), such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir, or strong inducers of CYP3A4. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.
- Previous allogenic bone marrow transplant or (single) umbilical cord blood transplantation
- Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, as long as not received within 28 days of start of treatment.
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction within 14 days of treatment
- Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
- Subjects with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.
- Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician
- Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
- History of leptomeningeal carcinomatosis

Study Assessments and Criteria for Evaluation:

To assess change of tumor biology from the biopsied specimens;

Core biopsy of tumor (preferably 4 cores or more; 2 will be fresh-frozen, and 2 will be used for FFPE) and blood will be obtained. The items for analysis of the biopsied specimens will be determined later. Those could include, but not limited to;

Determination of tumor infiltrating lymphocytes by H&E stain

Immunohistochemistry of ATM, PDL-1, PDL-2, and others

NGS (exome sequencing) to detect mutational burden

Tumor immune signature

To assess tumor response;

Ultrasonography, CT and PET-MRI before and after study treatment (day 0 and day 29)

Physical examination (including manual measure of the tumor) on every visit (days 0, 15, 29, and thereafter)

To assess safety and toxicity;

Routine safety and toxicity assessment by NCI-CTCAE v.4.0.

Sample Size Determination/Statistical Analysis:

This is an exploratory serial biopsy trial, and a formal sample size calculation is not applicable. Considering the planned analyses and the number of patients expected to receive neoadjuvant chemotherapy, and with the failure rate of obtaining adequate tumor tissue during serial biopsy being approximately 50%, it is anticipated that enrollment of approximately 50–60 participants will be required to secure 25 analyzable paired specimens.

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ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
Cmax	peak concentration
Cmax,ss	peak concentration at steady state
Cmin	trough concentration
Cmin,ss	trough concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	disease control
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

Abbreviation or special term	**Explanation**
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IHC	immunohistochemistry
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody

Abbreviation or special term	**Explanation**
MDSC	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks

Abbreviation or special term	**Explanation**
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
t½	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
Tmax	time to peak concentration
Tmax,ss	time to peak concentration at steady state
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
WFI	water for injection
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and rationale for conducting this study

1.1.1 Background

Durvalumab is an anti-programmed death-ligand (PD-L1) antibody, which is being developed as a potential anticancer therapy for patients with advanced tumors.

1.1.1.1 Tumor immunotherapy and programmed death ligand 1

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung (Mu et al, 2011), renal (Thompson et al, 2005; Thompson et al, 2006; Krambeck et al, 2007), pancreatic (Nomi et al, 2007; Loos et al, 2008; Wang et al, 2010), ovarian cancer (Hamanishi et al, 2007), and hematologic malignancies (Andorsky et al, 2011; Brusa et al, 2013) tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir et al, 2008; Park et al, 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou and Chen, 2008).

1.1.1.2 Rationale for clinical development of durvalumab in solid tumors

Nonclinical data with durvalumab suggest that targeting PD-L1 with a biologic agent could be an effective antitumor therapy. Durvalumab is a human monoclonal antibody (mAb) that selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and CD80. PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal

immune responses by delivering inhibitory signals to T cells through the PD-1 and CD80 receptors. Blockade of PD-L1 with durvalumab relieved PD-L1-mediated suppression of human T-cell activation in vitro. In a xenograft model, durvalumab inhibited human tumor growth via a T-cell-dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in >50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and CTLA-4) resulted in tumor regression in a mouse model of colorectal cancer. In another combination therapy study, dual targeting of PD-1 and PD-L1 in a syngeneic model β of sarcoma in mice demonstrated statistically significant mean tumor growth delay relative to the control group.

Clinical studies of durvalumab, either as monotherapy or as combination therapy, are ongoing across various tumor indications including breast cancer. Encouraging clinical activity of durvalumab combined with acceptable and manageable safety has been demonstrated across the monotherapy and combination therapy studies. These data provide a sound rationale for further development of durvalumab in advanced solid tumors and hematologic malignancies. The rationale for combining durvalumab with olaparib in the current study is discussed in Section 1.4.

1.2 Background on individual investigational products

1.2.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent Polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor (PARP-1, -2 and -3) that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents.

PARP inhibition is a novel approach to targeting tumours with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks (SSBs). Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA double strand breaks (DSBs) during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by homologous recombination repair (HR). Tumours with HR deficiencies (HRD), such as ovarian cancers in patients with BRCA1/2 mutations, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumour types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

BRCA1 and BRCA2 defective tumours are intrinsically sensitive to PARP inhibitors, both in tumour models in vivo (Rottenberg et al 2008, Hay et al 2009) and in the clinic (Fong et al

2009). The mechanism of action for olaparib results from the trapping of inactive PARP onto the single-strand breaks preventing their repair (Helleday 2011; Murai et al 2012). Persistence of SSBs during DNA replication results in their conversion into the more serious DNA DSBs that would normally be repaired by HR repair. Olaparib has been shown to inhibit selected tumour cell lines in vitro and in xenograft and primary explant models as well as in genetic BRCA knock-out models, either as a stand-alone treatment or in combination with established chemotherapies.

1.2.2 Durvalumab

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1 and CD80.

To date durvalumab has been given to more than 1800 subjects as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 1.2.3 and Section 6.5. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.2.3 Durvalumab safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols

1.3 Research hypothesis

Olaparib could increase genomic instability and sensitize triple negative breast cancer or low ER positive tumors to durvalumab. The changes of tumor biology will be detected by serial biopsy of breast cancer before and after olaparib and durvalumab.

1.4 Rationale for conducting this study

Triple negative breast cancer is an aggressive subtype of breast cancer and associated with higher expression of PDL-1 compared with other subtypes of breast cancer (Sabatier et al. 2015; Muenst et al 2015). Olaparib increases genomic instability (O'Connor et al 2015) and could sensitize triple negative breast cancer to durvalumab.

We propose a window-of-opportunity, serial biopsy trial of olaparib and durvalumab before standard neoadjuvant chemotherapy for locally advanced breast cancer.

1. Rationale #1

Mutation burden and response to Immune checkpoint inhibitors

Tumors with high nonsynonymous mutation burden were associated with improved outcome with immune checkpoint inhibitors (antibodies to PD-1, PDL-1, or CTLA-4) in NSCLC (Rizvi et al 2015) and melanoma (Snyder et al 2014). Moreover, colorectal cancer with mismatch repair deficiency was also associated with better outcome with PD-1 blocker, suggesting the relationship high mutation burden and improved outcome (Le et al 2015). As olaparib increased the genomic instability by inhibiting PARP1, it is plausible that olaparib could enhance the sensitivity to durvalumab.

2. Rationale #2

Immunoregulatory effects of PARP inhibitors

Beyond the function of PARP-1 as a DNA nick sensor and signaling molecule binding to single and double stranded DNA breaks, diverse roles of PARP in immunity, inflammation, and cell death are being investigated (Laudisi et al 2011, Rosado et al 2013). Indeed a PARP inhibitor shown to increase peritoneal CD8 T cells and NK cells production of IFN-γ and TNF-α from the immune cells in a BRCA1-mutated ovarian cancer xenograft model (Huang et al 2015).

3. Rationale #3

Immunogenic cell death and local antigen release

Preclinical studies have shown that PARP inhibitors promote local antigen release, resulting in systemic antitumor response after tumor exposure to radiation or DNA-damaging agents or secondary to spontaneous or heritable defects in DNA (Kroemer et al 2013, Wu et al 2014).

1.5 Benefit/risk and ethical assessment

Olaparib benefit/risk

Olaparib has demonstrated statistically significant improvement in PFS as a maintenance monotherapy in a phase II study in platinum-sensitive ovarian cancer and statistically significant improvement in PFS in combination with carboplatin and paclitaxel in a phase II study in patients with platinum-sensitive relapsed serous ovarian cancer. Olaparib plus paclitaxel has demonstrated statistically significant improvement in overall survival, but not PFS, compared with paclitaxel alone in a phase II study in patients with recurrent/metastatic gastric cancer (Bang et al 2015). In addition, olaparib has demonstrated antitumor activity in non-comparative studies in patients with gBRCA mutated cancers including ovarian, breast, pancreatic, and prostatic. Olaparib is currently being studied in a phase III study in patients with ATM-negative gastric cancer (the "GOLD" study) and in a phase II study in patients with SCLC.

The olaparib capsule formulation was registered for use in the EU and US in December 2014, and Korea in August 2015, as a treatment for advanced recurrent BRCAm ovarian cancers. As of 31 March 2015 it is estimated that >750 patients have received commercial material.

The recommended olaparib monotherapy tablet dose is 300 mg bid. Olaparib monotherapy appears to be generally well tolerated across studies up to and including these doses and from the available data to date, there is no evidence of any unexpected toxicity following long-term olaparib (capsule) monotherapy exposure.

An analysis of data from 13 AstraZeneca-sponsored monotherapy studies in 1006 patients with ovarian cancer (634/1006 [63%]) and other non-ovarian solid tumors (372/1006 [37%]) who received olaparib capsule at a range of doses, estimated that 16.0% (161/1006) of patients had been exposed to olaparib (capsule) for >12 months, 8.3% (84/1006) for >18 months and 4.1% for >24 months at the time of database closure for the respective studies. Twenty-one patients (2.1%) had received ≥48 months of olaparib exposure.

As of 31 March 2015, 117 patients (117/883 [13%]) from 7 completed AstraZeneca-sponsored monotherapy studies had continued on olaparib treatment post-study closure because they continued to derive treatment benefit. Approximately half (63/117 [54%]) of these patients have received >24 months of olaparib capsule treatment, of which 39 (33%) have received >36 months of treatment and of the 39 patients, 16 (14%) have received >4 years treatment.

Data from phase I dose escalation studies of olaparib in combination with various chemotherapy agents indicated an increase in bone marrow toxicity (anemia, neutropenia, thrombocytopenia) greater than expected if the agents had been administered alone. However, tolerable regimens of a combination of olaparib with carboplatin/paclitaxel, paclitaxel alone, and liposomal doxorubicin have been established, supporting further studies in the combination setting.

Administration of olaparib in combination with dacarbazine, topotecan, gemcitabine, cisplatin, carboplatin + paclitaxel or paclitaxel resulted in a lower maximum tolerated dose compared with administration as a monotherapy.

Toxicities considered to be associated with administration of olaparib include hematological effects (anemia, neutropenia, lymphopenia, thrombocytopenia, mean corpuscular volume elevation), decreased appetite, nausea and vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, and dizziness.

In a small number of patients, pneumonitis, myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) and new primary malignancies have been reported. Evidence from the whole development program for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are important potential risks for olaparib and are being kept under close pharmacosurveillance.

Durvalumab benefit/risk

The majority of the safety and efficacy data currently available for durvalumab are based on the first-in-human, single-agent study (Study 1108) in patients with advanced solid tumors, which has treated the largest number of patients (N=414). Data from Study 1108 were presented at the European Society for Medical Oncology (ESMO) 2014 Congress. As of 21 August 2014, 162 patients with non-small cell lung cancer (NSCLC) were evaluable for response analysis. The DCR at 12 weeks in patients receiving 10 mg/kg durvalumab Q2W was 39%, and the overall response rate (ORR) was 15% (26% [12 out of 47 patients] with known PD-L1 -positive NSCLC [ie, ≥25% PD-L1 expression] and 10% [7 out of 74 patients] with known PD-L1 -negative NSCLC [ie, <25% PD-L1 expression]). A total of 24% of patients receiving 10 mg/kg durvalumab Q2W had stable disease (SD) for ≥12 weeks (including 21% [10 out of 47 patients]

with known PD-L1 -positive NSCLC and 32% [24 out of 74 patients] with known PD-L1 -negative NSCLC). Responses were ongoing in 88% of patients with NSCLC, with an objective response duration ranging from 0.1 to 32.4 weeks.

Potential risks, based on the mechanism of action of durvalumab and related molecules, include immune-mediated reactions, such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, and neuropathy or neurologic events. Additional important potential risks include infusion-related reactions, hypersensitivity, anaphylaxis or serious allergic reactions, serious infections, and immune complex disease.

Of the 393 patients with advanced solid tumors, including NSCLC, treated with 10 mg/kg Q2W in Study 1108 (as of IB Edition 7.0 cut-off date of 14 July 2014), 331 patients (84.2%) had at least 1 adverse event (AE) regardless of causality. Treatment-related AEs were reported for 162 of 393 patients (41.2%). The most frequently reported (≥2% of patients) AEs assessed by the investigator as treatment related (including all NCI Common Terminology Criteria for Adverse Events [CTCAE] grades) were fatigue (13.5%); nausea (8.4%); diarrhea, decreased appetite, and rash (5.3% each); vomiting (4.8%); pruritus (4.1%); dyspnea (3.8%); pyrexia (3.1%); hypothyroidism, increased alanine aminotransferase (ALT; also known as serum glutamate pyruvate transaminase [SGPT]), increased aspartate aminotransferase (AST; also known as serum glutamic-oxalo-acetic transaminase [SGOT]), and cough (2.5% each); myalgia (2.3%); and abdominal pain and dizziness (2.0% each). Two patients discontinued treatment due to AEs assessed by the investigator as treatment related (pneumonitis and increased transaminases). Grade 3 events assessed by the investigator as treatment related that occurred in 2 or more patients were fatigue (4 patients); increased gamma-glutamyltransferase (3 patients); and vomiting, increased ALT, increased AST, and arthralgia (2 patients each).

There were 2 patients with grade 4 events (hypercalcemia and fatigue) assessed by the investigator as treatment related and 1 patient with a grade 5 event assessed by the investigator as treatment related (angiopathy). For further details on the safety profile of durvalumab as monotherapy or combination therapy, please refer to the current IB.

Other mAbs targeting the PD-1/PD-L1 pathway are currently in clinical development. Among the most frequent AEs noted following treatment with these antibodies are fatigue, rash, diarrhea, and pruritus. Immune-mediated AEs of grade ≥3 reported include pneumonitis, diarrhea, increased ALT, and increased AST. Other relevant risks include those associated with biological and immunotherapeutic agents, including infusion reactions and acute immunoglobulin E-mediated allergic reactions.

Olaparib and durvalumab benefit/risk

The hypothesis to be tested is that increased DNA damage by PARP inhibition will induce changes in the tumor microenvironment that will complement the antitumor activity of an immune checkpoint inhibitor in triple negative breast cancer who receives neoadjuvant chemotherapy.

In order to test this hypothesis, patients will receive olaparib monotherapy in combination with durvalumab for a period of 4 weeks prior to commencing standard neoadjuvant chemotherapy.

Encouraging clinical activity, combined with acceptable and manageable safety, has been seen to date with durvalumab in combination therapy studies. In general, the toxicity profiles of durvalumab and of olaparib are nonoverlapping, therefore management of toxicities will be per the individual guidelines of the respective agents. Pneumonitis is considered to be the most important potential exception. The management guidelines for pneumonitis (see Section 6.5.3.5) integrate the guidance provided for these 2 agents. Please refer to the durvalumab IB for further details.

Monoclonal antibodies are not metabolized through classical hepatic enzymes pathways. Olaparib has previously been combined with another mAb (bevacizumab) without significant drug-drug interaction. Therefore no PK interaction is anticipated within this study.

Overall benefit/risk

There remains a significant unmet medical need for additional treatment options for patients with triple negative breast cancer, to achieve higher pathologic response after neoadjuvant chemotherapy and a chance of cure.

Based upon the available nonclinical and clinical safety data, the limited pathologic response to neoadjuvant chemotherapy in triple-negative breast cancers, and the hypothesis of the complementary effect of the 2 agents, the investigation of the potential therapeutic efficacy of the combination of durvalumab with olaparib in this population is acceptable, and the overall benefit/risk assessment supports the proposed study design.

2. STUDY OBJECTIVES

2.1 Primary objective(s)

The changes of tumor biology detected by serial biopsy of breast cancer before and after olaparib and durvalumab (exploratory serial biopsy study)

2.2 Secondary objective(s)

1. Number of participants with a pathological complete response (ypT0/Tis, ypN0).

2. Response rate by RECIST v.1.1

3. Safety and toxicity of olaparib and durvalumab

4. Adverse events of special interest and immune-mediated adverse events (AESI/imAEs), which include diarrhoea/colitis, pneumonitis/ILD, hepatitis and increases in transaminases, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis /hypopituitarism and Type 1 diabetes mellitus), dermatitis/rash and pruritus, nephritis and increases in serum creatinine, neuromuscular toxicity such as myasthenia gravis and Guillain-Barre, pancreatitis, other inflammatory responses that are rare with a potential immune-mediated aetiology (including myocarditis, pericarditis, and uveitis), infusion-related reactions and hypersensitivity/anaphylactic reactions.

3. STUDY DESIGN

This is a non-randomized, prospective, open label, window pilot study to evaluate the change of tumor biology after olaparib and durvalumab treatment by serial biopsy of breast cancer. Patients will be PARP-inhibitor and immunotherapy (IMT)-naïve (defined as no prior exposure to PARP inhibitors or IMT, including, but not limited to, other anti-CTLA-4, PD-1, anti-PD-L1 mABs or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

3.1 Overview of study design

3.1.1 Olaparib + Durvalumab treatment phase

Prior to the start of study medication, tumor tissue and blood will be collected as baseline. Olaparib 300mg bid will be started after the collection of tumor and blood. Olaparib will be given on days 1-28 days without rest.

Tumor tissue and blood will be collected on day 14 before administration of durvalumab, to see the change in biomarkers after 2 weeks of olaparib treatment. After the acquisition of tumor and blood, durvalumab will be given in a fixed one dose of 1.5 gram on day 15.

On day 29, there will be a third acquisition of tumor and blood, to see the change in biomarkers after combination treatment of olaparib and durvalumab. Tumor response will also be evaluated according to RECIST criteria version 1.1 based on CT.

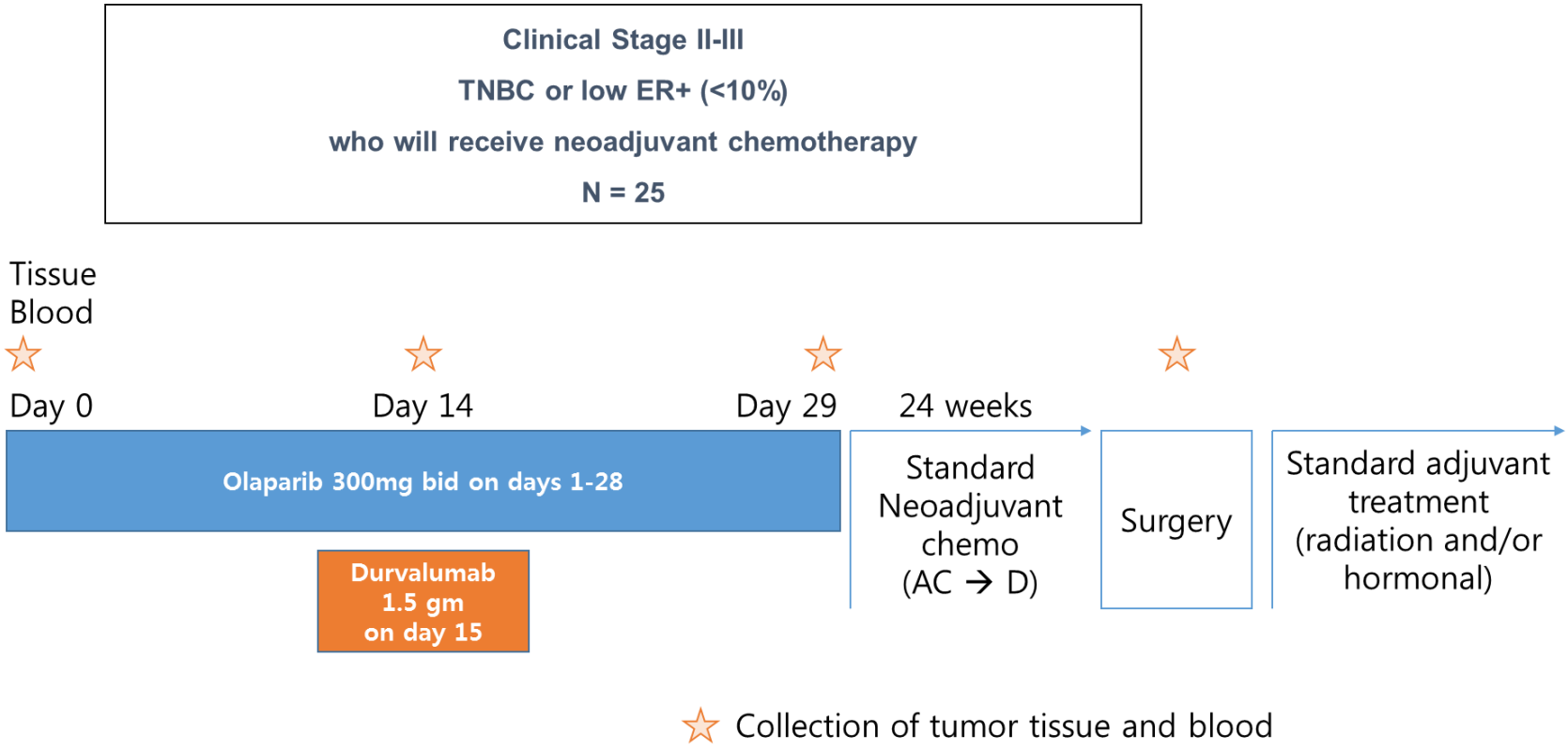
3.1.2 Standard neoadjuvant chemotherapy phase

After the study treatment, the subject will receive standard neoadjuvant chemotherapy (Adriamycin/cyclophosphamide for 4 cycles, followed by docetaxel for 4 cycles) for approximately 6 months. Standard neoadjuvant chemotherapy will be given within 2 weeks after completion of the study treatment unless grade 3 neutropenia or other grade 3 or greater AE present. Starting standard of neoadjuvant chemotherapy could be delayed upto 2 weeks from the date of planned day by hematologic or non-hematologic toxicities grade 3 or more. All subjects are to receive definitive local-regional therapy (surgery ± radiotherapy) at the completion of neoadjuvant systemic therapy.

3.2 Study schema

Figure 1 summarizes, in graphical form, the treatment and biopsy plans.

Figure 1. Schema of study flow



3.3 Study Oversight for Safety Evaluation

A data and safety review meeting will be convened when the first 10 patients have been followed for 4 weeks. The Committee deliberations will consider safety and pertinent tumor assessment data (at a minimum from radiologic imaging studies but also other data, such as relevant physical exam findings, etc.). All serious adverse events (SAEs), adverse events of special interest (AESI), discontinuations, dose reductions and dose interruptions will be reviewed, as well as any lesser-grade adverse events (AEs) that are considered by the study team to be of particular interest (based on emerging data from the ongoing safety monitoring and accumulating clinical experience in the first 10 patients, and other data from external sources as indicated). Participants of the review meetings discussed above will consist of the principal investigators and/or their delegates, other relevant clinical staff from the site. Safety data and pertinent tumor assessment data collected to date (including scans and other data eg, physical examinations if available) will be considered (and efficacy data as appropriate).

4. SUBJECT SELECTION

Each patient enrolled should meet all of the inclusion criteria and none of the exclusion criteria for this study.

4.1 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Nineteen years of age or older on the day of signing informed consent

2. Willing and able to provide written informed consent for voluntary participation in the trial

3. Has previously untreated, clinical stage II/III triple negative breast cancer (TNBC) or low estrogen receptor (ER) tumor where ER is expressed in ≤10% tumor cells) .

4. Willing to provide biopsy from the primary tumor or lymph nodes at screening to the central laboratory and agrees to have core needle biopsy or incisional or excisional tumor biopsy after 14 days and 28 days of olaparib treatment (before and after durvalumab treatment) if tumor biopsy is feasible as judged by the investigator

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1

6. Postmenopausal or evidence of non-child bearing status for women of childbearing potential: negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day1.

   Postmenopausal is defined as:

   - Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments.
   - Luteinizing hormone (LH) and Follicle stimulating hormone(FSH) levels in the post menopausal range for women under 50.
   - Radiation-induced oophorectomy with last menses >1 year ago
   - Chemotherapy-induced menopause with >1 year interval since last menses
   - Surgical sterilisation (bilateral oophorectomy or hysterectomy)

7. Adequate normal organ and marrow function as defined below:

   - Haemoglobin ≥ 10.0 g/dL with no blood transfusion in the past 28 days
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
   - Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
   - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN)
   - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional ULN unless due to Gilbert's syndrome
   - INR/PT/APTT each ≤ 1.5 x ULN
   - TSH within normal limits (TSH can be controlled with medication.)

- Serum creatinine < 1.5 x ULN or serum creatinine CL > 51 mL/min by the Cockcroft-Gault formula (Cockroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

  Males:

  $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

  Females:

  $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

8. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Underweighted populations - ≤30kg

2. Has evidence of metastatic breast cancer, inflammatory breast cancer, or concurrent bilateral invasive breast cancer where ER is expressed in >10% tumor cells.

(Note) Patients with bilateral invasive breast cancers can be enrolled if both tumors are TNBCs, including low estrogen receptor (ER) tumor where ER is expressed in ≤10% tumor cells.

3. Has another malignancy within the last 3 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and thyroid cancer that has undergone potentially curative surgery, or in situ cervical cancer.

(Note) These patients should be consulted to the principal investigator for a case-by-case decision before enrollment.

4. Has received prior chemotherapy, targeted therapy, radiation therapy, immunotherapy that targets immune checkpoints, co-stimulatory or co-inhibitory pathways for T cell receptors within the past 12 months.

5. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab

6. Is currently participating and receiving study therapy, or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks ot the first dose of study drug.

7. Has received a live vaccine within 30 days of the first dose of durvalumab.

(Note) Patients, if enrolled, should not receive live vaccine up to 30 days after the last dose of IP.

8. Has an active autoimmune disease or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea, systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]) that has required systemic treatment in past 2 years. The followings are exceptions to this criterion:

   - Patients with vitiligo or alopecia
   - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment.
   - Any chronic skin condition that does not require systemic therapy
   - Patients without active disease in the last 3 years may be included but only after consultation with the principal investigator.
   - Patients with celiac disease controlled by diet alone may be included but only after consultation with the principal investigator.

9. Has a diagnosis of immunodeficiency

10. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

    - Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)
    - Systemic corticosteroid at physiologic dose not to exceed 10 mg/day of prednisone or its equivalent
    - Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication)

11. Has a known history of Human Immunodeficiency Virus (HIV).

12. Active infection, including tuberculosis (clinical evaluation *that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice*), hepatitis B, hepatitis C, or human immunodeficiency virus (HIV, positive HIV 1 or 2 antibodies). Active hepatitis B virus (HBV) infection is defined by a positive HBV surface antigen (HBsAg) and positive HBV DNA quantitation result. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core IgG antibody and the absence of HBsAg, deoxyribonucleic acid [DNA] negative) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA)..

13. Has evidence of active, non-infectious pneumonitis.

14. Has history of pneumonitis requiring treatment with steroids or history of interstitial lung disease.

15. Has an active infection requiring systemic therapy.

16. Has significant cardiovascular disease, such as: History of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months; Congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF NYHA class III or IV

17. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.

18. Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of study drug.

19. Has a known hypersensitivity to the components of the study drug or its analogs.

20. Concurrent use of any medications or substances that are strong inhibitors of cytochrome P450 (CYP) 3A (CYP3A), such as ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir, or strong inducers of CYP3A4. A list of CYP3A4 inhibitors and induces is provided in Appendix G. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

21. Preivious allogenic bone marrow transplant or (single) umbilical cord blood transplantation

22. Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable, as long as not received within 28 days of start of treatment.

23. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction within 14 days of treatment

24. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

25. Subjects with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

26. Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician

27. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

28. History of leptomeningeal carcinomatosis

4.3 Withdrawal of Subjects from Study Treatment and/or Study

4.3.1 Permanent discontinuation of IP

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent or lost to follow-up

2. Adverse event that, in the opinion of the investigator or the AstraZeneca, contraindicates further dosing

3. Any AE that meets criteria for discontinuation as defined in Section 6.5

4. Pregnancy or intent to become pregnant

5. Non-compliance with the study protocol that, in the opinion of the investigator or AstraZenca, warrants withdrawal from study treatment (eg, refusal to adhere to scheduled visits)

6. Subject is determined to have met one or more of the exclusion criteria for study participation

7. Grade ≥ 3 infusion reaction

8. Initiation of alternative anticancer therapy including another investigational agent

9. Progressive disease and investigator determination that the subject is no longer benefiting from treatment with durvalumab and olaparib

4.3.2 Procedures for discontinuation of a patient from investigational product

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Appendix 4. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

4.3.3 Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

- Reasons for withdrawal of a patient from the study include:
- Voluntary withdrawal by the patient (all patients are free at any time to discontinue their participation in the study, without prejudice to further treatment)
- Incorrectly enrolled patients, ie, the patient does not meet the required inclusion/exclusion criteria for the study
- Patient is lost to follow-up
- Death

(Note) If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- further participation in the study including any further follow-up (eg, survival calls) the use of their study-generated data
- withdrawal to the use of any samples

4.3.3.1 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be enrolled.

4.3.3.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn his or her consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE(s). The investigator will follow-up AEs outside of the clinical study. If a patient withdraws from participation in the study, then his or her patient identification number cannot be reused. Withdrawn patients (who took <75% of planned Olaparib dose, who did not receive durvalumab, or who is not able to provide biopsies) will be replaced. Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and any evaluations should resume according to the protocol.

The vital status of ongoing, withdrawn (from the study) and "lost to follow-up" patients at the time of the final analysis for each cohort should be obtained by the site personnel by checking the patient notes, hospital records, contacting the patient's general practitioner and checking publicly available death registries. In the event that the patient has actively withdrawn consent

to the processing of their personal data, the vital status of the patient can be obtained by site personnel from publicly available resources where it is possible to do so under applicable local laws.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Identify of investigational products

AstraZeneca will supply the investigational sites with durvalumab and olaparib (Table 1). In this study protocol, the term "IP" refers to the combination treatment (durvalumab + olaparib).

Table 1. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	500 mg vial (50 mg/mL) solution for infusion after dilution	MedImmune/AstraZeneca
Olaparib	150mg and 100mg tablet	AstraZeneca

5.1.1 Durvalumab

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% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2℃ to 8℃ (36℉ to 46℉) and must not be frozen.

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab 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 (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2℃ to 8℃ (36℉ to 46℉)
- 4 hours at room temperature

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

Doses of 1.5 g will be administered using an IV bag containing 0.9% (weight/volume) saline or 5% (weight/volume) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL and delivered through an IV administration set with a 0.2-μm or 0.22-μm in-line filter. Add 30.0 mL (for the 1.5 g dose) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 60 minutes (± 5 minutes). Less then 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline) 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 and document if the line was not flushed.

In the event that either preparation time or infusion time exceeds the time limits outlined, a new dose must be prepared from new vials. Durvalumab does not contain preservatives and any unused portion must be discarded. No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed

5.1.2 Olaparib

Olaparib is available as a film-coated tablet containing 150 mg or 100 mg of olaparib.

5.2 Olaparib and Durvalumab doses and treatment regimens

5.2.1 Olaparib

Treatment with olaparib commences on D1 following confirmation of eligibility into the study and continues on to Day 28. Patients will be administered study olaparib treatment orally at a dose of 300mg bid. The initial dose of 300mg bid will be made up of 2x150mg tablets bid. The 100 mg and 150 mg tablets will be used to dose reductions.

5.2.2 Durvalumab

A fixed dose of durvalumab 1500 mg (equivalent to 20mg/kg Q4W) (based on an average body WT of 75 kg) is given via IV infusion on Day 15.

5.3 Monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

5.4 Compliance and Accountability

5.4.1 Compliance

Treatment compliance will be assured by reconciliation of site drug accountability logs.

Patients should be given clear instructions on how and when to take their study treatment.

Patients will self-administer olaparib. Study site staff will make tablet counts at regular intervals during treatment. Compliance will be assessed by the tablet count and the information will be recorded in the appropriate section of the case record form (CRF). After the tablet count has been performed, the remaining tablets will not be returned to the patient but will be retained by the investigative site until reconciliation is completed by the study monitor. All patients must return their bottle(s) of olaparib at the appropriate scheduled visit. Patients will be instructed to notify study site personnel of missed doses.

Dates of missed or held doses will be recorded by the patient on their patient diary and by the site staff on the CRF. Patients must return all containers and any remaining tablets at the end of the study.

5.4.2 Accountability

The study drug provided for this study will be used only as directed in the study protocol.
The study personnel will account for all study drugs dispensed to and returned from the patient, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return (as applicable for particular study drug) should be signed.

5.5 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

6. TREATMENT PLAN

6.1 Enrollment/screening period

All screening and enrolment procedures will be performed according to the assessment schedule. Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply an archived sample of

their tumor (not more than 3 years old) for entry into this study. This consent is included in the main patient informed consent form (ICF).

Screening/baseline evaluations may be performed over more than one visit.

The timing of vital sign assessments should be such that it allows the blood draw to occur at the timepoints indicated in Table 6.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria.

Patients who do not meet these criteria must not be enrolled in the study

6.2 Treatment period

All procedures to be conducted during the treatment period will be performed according to the assessment schedule presented in Table 6.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw to occur at the time points indicated in Table 6.

6.3 Dosage and Administration

Describe the dosing schema for the administration of the full treatment regimen, including durvalumab and any other study drug given in combination or sequence.

Refer to Section 5.2, 5.3, and 5.4 for the administration and monitoring of administration of durvalumab and olaparib.

6.4 Dose Modification and Toxicity Management

6.4.1 Durvalumab

For adverse events (AEs) that are considered at least partly due to administration of durvalumab, the following management guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendix 1.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 6.5.3.4 and 6.5.3.5. All toxicities will be graded according to NCI CTCAE v4.03.

6.4.2 Olaparib

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed, as required, for a maximum of 2 weeks on each occasion. Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step. If the reduced dose of 200 mg bid is not tolerable, no further dose reduction is allowed and study treatment should be discontinued. Once dose is reduced, escalation is not permitted. Durvalumab can be administered in case of dose interruption of olaparib, at investigator's discretion.

6.4.3 Toxicity management guidelines

In general, the toxicity profiles of durvalumab and of olaparib are nonoverlapping, therefore, management of toxicities will be per the individual guidelines of the respective agents.

6.4.3.1 General comments

The following general guidance should be followed for management of toxicities.

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).

- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted. In addition, guidelines on dose modifications are provided in Appendix 1.

- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

6.4.3.2 Management of hematological toxicity

Management of anemia

Management of anemia is presented in Table 2.

Table 2. Management of anemia

Hemoglobin level	Action to be taken
Hb <10 but ≥8 g/dL	Give appropriate supportive treatment and investigate causality.
(CTCAE grade 2)	Investigator judgement to continue olaparib with supportive treatment (eg, transfusion) or interrupt dose for a maximum of 2 weeks. If repeat Hb <10 but ≥8 g/dL, dose interrupt (for max of 2 weeks) until Hb ≥10 g/dl and upon recovery dose reduction to 250 mg twice daily as a first step and to 200 mg twice daily as a second step may be considered.
Hb < 8 g/dL	Give appropriate supportive treatment (eg, transfusion) and investigate causality. Interrupt olaparib for a maximum of 2 weeks until improved to Hb ≥10 g/dL. Upon recovery dose reduce to 250 mg twice daily as a first step and to 200 mg twice daily as a second step in the case of repeat Hb decrease.

CTCAE=Common Terminology Criteria for Adverse Event; Hb=hemoglobin

Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. For cases were patients develop

prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTC grade 3 or higher anemia and/or development of blood transfusion dependence), refer to the section on Management of prolonged hematological toxicities while on study treatment for further information.

Management of neutropenia, leukopenia, and thrombocytopenia

Management of neutropenia, leucopenia, and thrombocytopenia is presented in Table 3.

Table 3. Management of neutropenia, leukopenia, and thromocytopenia

Hemoglobin level	Study treatment dose adjustment
CTCAE grade 1/2	Investigator judgment to continue treatment or if dose interruption, this should be for a maximum of 2 weeks; appropriate supportive treatment and causality investigation.
CTCAE grade 3/4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 2 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to 250 mg bid as a first step and 200 mg bid as a second step

CTCAE=Common Terminology Criteria for Adverse Event; Hb=hemoglobin

Adverse event of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended, however, if a patient develops febrile neutropenia, study treatment should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 h (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Study treatment can be interrupted for CTCAE grade 1/2 neutropenia or thrombocytopenia as per investigator's judgment. In case of CTCAE grade 3/4 neutropenia or thrombocytopenia, study treatment should be interrupted for a maximum of 2 weeks. Study treatment can be restarted at the same dose if an AE of neutropenia or leukopenia has been recovered up to

CTCAE grade 1 or better. Any subsequent interruptions will require study treatment dose reductions to 250 mg bid as a first step and to 200 mg bid as a second step.

Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC <1×109/L)
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets <50×109/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 2 weeks of dose interruption.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to AstraZeneca, Patient Safety. Olaparib treatment should be discontinued if patient's diagnosis of MDS and/or AML is confirmed.

6.4.3.3 Management of non-hematological toxicity

Repeat dose interruptions are allowed as required, for a maximum of 2 weeks on each occasion. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg bid as a first step and to 200 mg bid as a second step. Treatment must be interrupted if any CTCAE grade 3 or 4 AE occurs, which the investigator considers to be related to administration of study treatment

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib and durvalumabtreatment.

No routine prophylactic anti-emetic treatment is required at the start of study treatment, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients (ESMO, National Comprehensive Cancer Network), generally a single-agent anti-emetic should be considered eg, dopamine receptor antagonist, antihistamines or dexamethasone.

6.4.3.4 Management of immune-related adverse events

An irAE is defined as a clinically significant adverse event of unknown etiology of any organ that is associated with drug exposure and is consistent with an immune-mediated mechanism. Serologic, immunologic, imaging and histologic (biopsy) data should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies. These AEs are inflammatory in nature and can affect any organ. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in

Appendix 1, it is recommended that irAEs are managed according to the general treatment guidelines outlined in the Toxicity Management Guidelines. These guidelines recommend the following:

1. Patients should be evaluated to identify any alternative etiology.

2. In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.

3. Symptomatic and topical therapy should be considered for low-grade events.

4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.

5. More potent immunosuppressives should be considered for specific events not responding to systemic steroids (eg, infliximab or mycophenolate).

If the investigator has any questions in regards to an AE being an irAE, the investigator should immediately contact the Study Physician.

6.4.3.5 Management of AESI of Durvalumab

Definition of AESI for Durvalumab and Olaparib are detailed in 10.1.3.

AESIs observed with durvalumab include:

- diarrhoea/colitis, pneumonitis/ILD, hepatitis and increases in transaminases, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis /hypopituitarism and Type 1 diabetes mellitus), dermatitis/rash and pruritus, nephritis and increases in serum creatinine, neuromuscular toxicity such as myasthenia gravis and Guillain-Barre, pancreatitis, other inflammatory responses that are rare with a potential immune-mediated aetiology (including myocarditis, pericarditis, and uveitis), infusion-related reactions and hypersensitivity/anaphylactic reactions Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

Pneumonitis

If new or worsening pulmonary symptoms (eg, dyspnea or cough) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup should be performed to exclude pneumonitis. The differential diagnosis should include the possibility of both immune-related and non-immune related processes.

Initial work-up should consider the inclusion of a clinical evaluation, high-resolution CT scan, ruling out infection, pulse oximetry, and other appropriate laboratory workup. Pulmonary consultation is highly recommended. Guidelines for the management of patients with irAEs including pneumonitis are provided in Appendix 1.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study treatment can be restarted, if deemed appropriate by the

Investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Physician.

Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time.

Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in Appendix 1.

Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3×ULN and concurrent increase in total bilirubin to be greater than 2×ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder), alcohol, viral hepatitis, or an agent other than the IP. Guidelines for management of patients with hepatic function abnormality are provided in Appendix 1.

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix 1.

Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Appendix 1.

Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 1.

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

Contraception

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 2 **highly** effective method of contraception (**오류! 참조 원본을 찾을 수 없습니다.**) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + any drug combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should also refrain from breastfeeding throughout this period.

Male subjects with a female partner of childbearing potential

- Male patients must use a condom during treatment and for 3 months after the last dose of olaparib when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should also use a highly effective form of contraception if they are of childbearing potential (as listed below). Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib

Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in **오류! 참조 원본을 찾을 수 없습니다.**. Note that some contraception methods are not considered highly effective (eg male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

If applicable <<Subjects in the SoC (XX) group: Follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for agents in the SoC (XX) group.>>

Table 4. Highly Effective Methods of Contraception (<1% Failure Rate)

• Barrier/Intrauterine methods	• Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	• Etonogestrel implants: eg Implanon or Norplant • Intravaginal device: eg ethinylestradiol and etonogestrel • Medroxyprogesterone injection: eg Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

[a] This is also considered a hormonal method

Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab

7.2 Concomitant treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF.

Olaparib can inhibit CYP3A4 and uridine di-phosphoglucuronosyl transferase 1A1 (UGT1A1) enzyme in vitro. These findings suggest that olaparib has the potential to cause clinically significant interactions with other CYP3A4 substrates or UGT1A1 substrates in the liver or gastrointestinal tract. Therefore, caution should be exercised when substrates of CYP3A4 are combined with olaparib, in particular those with a narrow therapeutic margin (eg, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, and quetiapine). Substrates of UGT1A1 should also be given with caution in combination with olaparib (eg, irinotecan, nintedanib, ezetimibe, raltegravir, or buprenorphine).

7.2.1 Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 7.2.2.

7.2.2 Excluded Concomitant Medications

Restricted, prohibited, and permitted concomitant medications are described in the following tables.

Table 5. Prohibited and Rescue Medications

Prohibited medication/class of drug:	**Usage:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment through 90 days after the last dose of IP
Any concurrent chemotherapy, local therapy, biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment (concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications, including, but not limited to: systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given whilst the patient is on IP treatment (use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.)
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP during the study
Herbal medications	Should not be given through 30 days after the last dose of IP during the study
Rescue/supportive medication/class of drug:	**Usage:**

Table 5. Prohibited and Rescue Medications	
Prohibited medication/class of drug:	**Usage:**
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management)	Should be used when necessary for all patients

8. STUDY PROCEDURES

The procedures for the screening and the 4-week olaparib plus durvalumab treatment period are presented in Table 6; and the procedures to be followed after a patient has completed 4-week treatment with olaparib plus durvalumab are presented in Table 7. The procedures for a patient who discontinued early from 4-week olaparib plus durvalumab are presented in Table 8.

8.1 Schedule of study procedures

8.1.1 Screening Phase

All screening and enrolment procedures will be performed according to the assessment schedule presented in Table 6. Demographic data and other characteristics will be recorded including date of birth or age, gender, smoking history, and race/ethnicity, according to local regulations. A standard medical and surgical history will be obtained.

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply an archived sample of their tumor (not more than 3 years old) for entry into this study. This consent is included in the main patient informed consent form (ICF).

Screening/baseline evaluations may be performed over more than one visit.

The timing of vital sign assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in Table 6.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria.

Patients who do not meet these criteria must not be enrolled in the study.

8.1.2 Treatment Phase

All procedures to be conducted during the treatment period will be performed according to the assessment schedule presented in Table 6.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw to occur at the timepoints indicated in Table 6.

8.1.3 Follow-up period

All procedures to be conducted during the follow-up period will be performed according to the assessment schedule presented in Table 7 and Table 8.

Whenever vital signs, ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw to occur at the timepoints indicated in Table 7.

8.2 Description of study procedure

Table 6. SCHEDULE OF STUDY ASSESSMENTS: Screening and durvalumab + Olaparib 4-week treatment period

Procedure	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**				
		Baseline	**Durvalumab+ Olaparib treatment period: Weeks 1 to 4**			
Week	**-4 to -1**	**-1 to 0**	**W1**	**W2**	**W3**	**W4**
Day	**-28 to -1**	**-7 to 0**	**1**	**8**	**15**	**22**
Visit window			**±2**	**±2**	**±2**	**±2**
Written informed consent/assignment of E-code	X					
Verify eligibility criteria	X					
Enrollment	X					
Medical and surgical history	X					
Demographics (including date of birth, sex, race, ethnicity, tobacco use)	X					
Physical examination[a] , Weight, Height	X				X	
ECOG performance status	X					
Hepatitis B and C; HIV	X					
Urine hCG or serum βhCG[b]	X	As clinically indicated				
Electrocardiogram[c]	X	X then as clinically indicated				
Vital signs (pre- during and post-infusion vital signs assessments)[d]	X				X	
Adverse event/serious adverse event assessment	X	X	All visits			
Concomitant medications	X	X	All visits			

Procedure	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**				
		Baseline	**Durvalumab+ Olaparib treatment period: Weeks 1 to 4**			
Week	**-4 to -1**	**-1 to 0**	**W1**	**W2**	**W3**	**W4**
Day	**-28 to -1**	**-7 to 0**	**1**	**8**	**15**	**22**
Visit window			**±2**	**±2**	**±2**	**±2**
Serum Chemistry (complete clin chem. panel including Liver enzymes)[e]	X				X	
Thyroid function tests (TSH and fT3 and fT4)[f]	X					
HbA1C	X					
Hematology[e]	X			X	X	X
Urinalysis[h]	X					
Coagulation parameters[i]	X	As clinically indicted				
Durvalumab administration					X	
Olaparib administration			←----------	----------	----------	----------→
Obtain blood sample for confirmation of BRCA status	X					
Obtain whole blood for sequencing	X				X	
Obtain fresh tumour tissue for sequencing	X				X	
Tumor assessment (Physical examination)	X				X	
Tumor assessment (Ultrasonography and CT)	X					
Tumor assessment (PET-MRI)	X			X		X

[a] Full physical examination at baseline; targeted physical examination at other timepoints
[b] Pre-menopausal female subjects of childbearing potential only
[c]ECG during screening and at Day1 –baseline. Thereafter as clinically indicated.

[d] Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

  If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

[e] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

[f] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[h] Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

[i] Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

[j] Ultrasonography and PET-MRI are collected during screening (during baseline) as close to and prior to initiation of study treatment.

Table 7. SCHEDULE OF FOLLOW-UP SSESSMENTS: For patients who have completed 4-week olaparib + durvalumab treatment

Cycle	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**C8D22 (EOT)**	**Surgery**
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**23**	**26**	**27**
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**176**
Weeks(Days) since Durvalumab/Olaparib therapy	**5(29)**	**8(50)**	**11(71)**	**14(92)**	**17(113)**	**20(134)**	**23(155)**	**27(176)**	**30(197)**	**31(218)**
Visit window (days)	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±14**
Procedure										
Physical examination[a] , Weight, Height	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X	X	X	X	X	X	
Electrocardiogram[b]	X	As clinically indicated								
Vital signs (pre- during and post-infusion vital signs assessments)[c]	X	X	X	X	X	X	X	X	X	
Adverse event/serious adverse event assessment	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Serum Chemistry (complete clin chem. panel including Liver enzymes)[d]	X	X	X	X	X	X	X	X	X	
Thyroid function tests (TSH and fT3 and fT4)[e]	X	As clinically indicated								
Hematology[d]	X	X	X	X	X	X	X	X	X	
Coagulation parameters[f]	X	As clinically indicted								
Adriamycin + Cyclophosphamide administration	X	X	X	X						

Cycle	**C1D1**	**C2D1**	**C3D1**	**C4D1**	**C5D1**	**C6D1**	**C7D1**	**C8D1**	**C8D22 (EOT)**	**Surgery**
Week	**1**	**4**	**7**	**10**	**13**	**16**	**19**	**23**	**26**	**27**
Day	**1**	**22**	**43**	**64**	**85**	**106**	**127**	**148**	**169**	**176**
Weeks(Days) since Durvalumab/Olaparib therapy	**5(29)**	**8(50)**	**11(71)**	**14(92)**	**17(113)**	**20(134)**	**23(155)**	**27(176)**	**30(197)**	**31(218)**
Visit window (days)	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±3**	**±14**
Procedure										
Docetaxel administration					X	X	X	X		
Obtain whole blood for sequencing	X									X
Obtain fresh tumour tissue for sequencing	X									X
Tumor assessment (Physical examination)	X		X		X		X		X	
Tumor assessment (Ultrasonography and CT)[g]	X				X				X	

[a] Full physical examination at baseline; targeted physical examination at other timepoints

[b] ECG during screening and at Day1 –baseline. Thereafter as clinically indicated.

[c] Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

  If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

[d] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

[e] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[f] Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

[g] Ultrasonography and PET-MRI are collected during screening (during baseline) as close to and prior to initiation of study treatment.

Table 8. SCHEDULE OF FOLLOW-UP SSESSMENTS: For patients who have not completed 4-week olaparib + durvalumab treatment

Evaluation	**Time since last dose of investigational product**			
	Day (±3)	**Months (**± 2 week)		
	30	**2**	**3**	**4**
Physical examination[a] , Weight, Height	X			
Vital signs	X			
Adverse event/serious adverse event assessment	X		X	
Concomitant medications	X		X	
ECOG performance status	At timepoints consistent with tumor assessment			
Survival status	X		X	
Hematology	X		X	
Serum Chemistry (complete clin chem. panel including Liver enzymes)	X		X	
Thyroid function tests (TSH and fT3 and fT4)[b]	X			
Tumor assessment (Ultrasonography and CT)[c]	Every 6 weeks during neoadjuvant chemotherapy, then at the discretion of the physician			

[a] Full physical examination at baseline; targeted physical examination at other timepoints

[b] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[c] Only for patients yet to progress, RECIST 1.1 assessments will be performed using CT/MRI assessments of the chest, pelvis, and abdomen (including liver and adrenal glands). Additional anatomy should be imaged based on signs and symptoms of individual patients.

8.2.1 Medical history and physical examination, electrocardiogram, weight and vital signs

Physical examinations will be performed on study days noted in the Schedule of Assessments.

ECGs are required during screening, prior to starting study treatment on Cycle 1 Day 1, at week 5 (before start of standard neoadjuvant chemotherapy), at the end of treatment, as well as at any other time point when clinically indicated.

ECGs recorded during the screening period will be obtained in triplicate (with 2-5 minute lag time between each); ECGs recorded during the treatment phase will be single tracing. All 12-lead ECGs should be recorded while the subject is in the supine position. A 12-lead ECG will be recorded for all subjects on study days noted in Section 8.2. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. On Day 1 and Week 16, ECGs will be recorded within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. On durvalumab treatment days, vital signs will be measured within an hour prior to start of durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses (at dose levels of 10 mg/kg or less), the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

8.2.2 Clinical laboratory tests

The following clinical laboratory tests will be performed.

Blood samples for determination of clinical chemistry and hematology will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 6, Table 7, and Table 8). Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

All clinical laboratory safety tests, including serum pregnancy tests, will be performed at a local laboratory at or near the investigational site. Sample tubes and sample sizes may vary depending

on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

If a patient shows an AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN, these cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria. Confirmed or potential Hy's law cases should be reported to the Health authorities. All patients with an elevated AST, ALT, or bilirubin value (the latter at ≥1.5×ULN) at the time of the last dose of study treatment should have a further liver chemistry profile (AST, ALT, bilirubin, and alkaline phosphatase) performed 30 days (±3 days) after permanent discontinuation of study treatment. These should be followed until normalized.

The investigator should make an assessment of the available results with regard to clinically relevant abnormalities. Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the CRF.

All patients with grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must have further tests performed until the laboratory values have returned to grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

Pregnancy tests on either urine (human chorionic gonadotropin [hCG]) or blood (serum β-hCG) samples will be performed for pre-menopausal women of childbearing potential as specified in the assessment schedule (see Table 6, Table 7, and Table 8). Tests will be performed by the hospital's local laboratory. If results are positive, the patient must not start or continue treatment. In the event of a suspected pregnancy during the study, the test should be repeated.
Other safety tests to be performed include assessment for hepatitis B surface antigen, hepatitis C antibodies, HIV antibodies, thyroid-stimulating hormone (TSH), free tri-iodothyronine (T3), and free thyroxine (T4).

8.2.2.1 Hematology

The following hematology variables will be measured:

Hb, Hematocrit, Mean cell volume, Mean cell hemoglobin, WBC, Platelets, Absolute differential white cell count (Neutrophils, lymphocytes, monocytes, eosinophils ad basophils and ANC or segmented neutrophil count and Band forms should be performed at each visit and

when clinically indicated. If absolute differentials are not available % differentials should be provided).

8.2.2.2 Coagulation

The following coagulation variables will be measured:

- activated partial thromboblastin time (APTT) will be performed at screening and if clinically indicated

- international normalized ratio (INR) will be performed at screening and if clinically indicated, unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and APTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

8.2.2.3 Clinical chemistry

The following clinical chemistry parameters will be measured:

Sodium, Potassium, Calcium, Chloride, Magnesiu, Creatinine, Total bilirubin[a], Glucose, Lipase, Alkaline phosphatase, Bicarbonate, AST, ALT, Amylase, Urea or blood urea nitrogen, Uric acid, Total protein, Albumin

[a]If total bilirubin is ≥2×ULN (and evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

8.2.3 *BRCA* status

BRCA gene testing for study inclusion purposes will be performed on a blood sample taken specifically for that purpose and all local guidelines for such genetic testing must be followed. Patients for whom *BRCA* status is already known, should be consented to the study within 28 days prior to Day 1 of the first dose of olaparib monotherapy and have a blood sample taken for confirmation of *BRCA* status at the Week 1/Day 1 visit. All patients must provide samples and consent to study-related *gBRCA* status testing, and must also have a blood sample taken at the same time for the purpose of developing and validating a diagnostic test for *BRCA* mutations.

8.3 Biological sampling procedures

8.3.1 Biomarker/Pharmacodynamic sampling and evaluation methods

Blood for gene expression and soluble factors

Blood samples (10 ml EDTA, 5 ml serum, and 5 ml whole blood) will be obtained pre- or post-treatment from all patients as described in Table 6 AND Table 7. Total RNA will be prepared for quantification of RNA and/or miRNA expression using RT-QPCR, microarray, sequencing, or similar technology.

Focus is likely to be given to the expression of immunomodulatory genes previously found to be up-regulated in response to durvalumab and/or olaparib (data not shown). This battery of genes is likely to be similarly up-regulated in response to durvalumab + olaparib combination therapy. Moreover, pre-treatment expression of such genes may indicate active immune responses that may be augmented by checkpoint inhibitor immunotherapies; correlations with outcome data will be completed on select candidate, predictive markers with the aim of identifying useful expression thresholds for identifying patients likely to receive benefit

8.3.2 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle.

The PI will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate). The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

- Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 9. Volume of Blood to Be Drawn From Each Subject

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Clinical chemistry (locally assessed)	5	12	60
Hematology (locally assessed)	5	14	70
Coagulation (locally assessed)	3	2	6
Serum pregnancy (locally assessed)		May use urine instead	N/A
Blood samples for confirmation of *BRCA* status	9	1	9
Whole blood for gene expression	20	4	80
Total			245

BRCA=breast cancer susceptibility gene; N/A=not available; PBMC=peripheral blood mononuclear cells; sPD-L1=soluble anti-programmed death-ligand 1.

All samples collected for biomarker analyses will be stored at the study site and may be used for subsequent research relevant to evaluating biological and/or clinical response to study treatment. Samples may be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. A full chain of custody should be maintained for all samples throughout their life cycle.

8.3.3 Fresh tumor biopsies

All patients must provide fresh tumor samples. Tumor samples should be collected via an imag-guided core-needle (18 gauge or larger, preferably 4 cores or more, 2 for fresh-frozen and 2 for FFPE) or be collected as an excisional or incisional tumor biopsy sample. When fresh tissue is obtained, effort should be made to maximize material for downstream analyses.

Biomarker analyses will be performed on the tumor tissues. Biomarker analyses may include, but are not limited to, CD8 and CD4/Foxp3 protein expression in an effort to enumerate cytotoxic versus Treg cells. A panel of additional, immune-relevant markers expressed on tumor-infiltrating lymphocytes or on tumor cells may be assessed. Markers of special interest include, but are not limited to, PD-1, PD-L1, OX40, OX40L, and B7H3.

Other tissue-based approaches will be pursued including reverse transcription quantitative polymerase chain reaction (RT-QPCR) nanostring, and/or in situ hybridization (eg, for detection of interferon [IFN] gamma signaling genes such as CXCL9, CXCL10, and IFN gamma itself), and/or somatic mutation detection methodologies.

Also, some tissue can be used for functional HRD assay, where fresh tumor tissue is irradiated and HRD markers, such as Rad51, BRCA1 and/or γH2AX foci are analyzed to discriminate HRD-deficient and –proficient tumors.

Baseline biopsy: the baseline tumor sample will be taken and may be used for analysis of several markers described above.

Subsequent biopsy: after 2 weeks of olaparib monotherapy, it is anticipated that sensitive tumor cells will have accumulated sufficient DNA damage to die and influence the tumor immune microenvironment. This is hypothesized to manifest in an increase in infiltrating lymphocytes and/or increased T-cell repertoire (visibility of the tumor to the immune system). The subsequent biopsies will be taken 2 weeks after the start of olaparib monotherapy (before durvalumab treatment, D15) and 2 weeks after durvalumab treatment (D29). After completion of standard neoadjuvant chemotherapy, tumor tissue will be obtained from the surgical specimen, if available.

8.3.4 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

9.1 Tumor assessment by ultrasonography, CT, and PET-MRI

At baseline and follow-up, the imaging modalities used for assessment should be ultrasonography and contrast enhanced CT. Whole body PET-MRI will be done at baseline, at week 2, and at week 4 (Table 6).

Radiological examinations performed in the conduct of this study should be retained at site as source data.

All treatment decisions will be based on site assessment of scans.

The baseline scan must be performed at screening unless obtained within 28 days prior to first dose of olaparib, as per standard of care. Following the baseline tumor assessment, the next tumor assessment will be 2 weeks after the first olaparib monotherapy dose and prior to the start of the standard neoadjuvant combination chemotherapy, as according to RECIST 1.1. All subsequent tumor assessments should be performed as stated in Table 7 and Table 8.

It is important to follow the assessment schedule as closely as possible.

9.2 Tumor evaluation

The RECIST 1.1 guidelines for measurable, non-measurable, target and nontarget lesions (NTL) and the objective tumor response criteria (CR, PR, SD or progression of disease [PD]). will be used for tumor evaluation.

10. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

10.1 Safety Parameters

10.1.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be

symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, ECG). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

10.1.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

10.1.3 Definition of adverse events of special interest (AESI)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

AESI for olaparib are the Important Potential Risks of MDS/AML, new primary malignancy (other than MDS/AML) and pneumonitis. ANY event of MDS/AML, new primary malignancy, or pneumonitis should be reported to AstraZeneca Patient Safety whether it is considered a non-

serious AE (eg, non-melanoma skin cancer) or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm. These adverse events must be reported according to the timelines for reporting an SAE to allow timely safety monitoring.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. "These AESIs may require close monitored in clinical studies with durvalumab monotherapy and combination therapy." An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

10.1.4 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs (Topalian et al, NEJM 2012). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Section 6.5.3.5, and Appendix 1.

10.1.5 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Appendix 1.

10.1.6 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct

obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Appendix 1.

Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs, These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria. Confirmed or potential Hy's law cases should be reported to the Health authorities.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

10.1.7 Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving durvalumab are provided in Appendix 1.

10.1.8 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix 1.

10.1.9 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Appendix 1.

10.1.10 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 1.

10.1.11 Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc) .

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 1.

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03.
The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgement and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).

Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

The Investigator will assess causal relationship between IP and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the IP/comparator/combination drug?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab (yes or no) <<and/or comparator/combination drug (yes/no)>>
- Action taken with regard to durvalumab /comparator/combination agent
- Outcome

In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to <<criteria>>
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab.

During the course of the study all AEs and SAEs should be proactively followed up for each subject. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the CRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post study events

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study subjects after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

10.3.2 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or

Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator and/or sponsor must report Suspected Unexpected Serious Adverse Reactions (SUSARs) to AstraZeneca as individual case reports as they occur and in parallel to reporting to the Regulatory Authority.

Serious adverse events that do not require expedited reporting to the Regulatory Authority still need to be reported to AstraZeneca using the MedDRA coding language for serious adverse events. This information can be reported on a quarterly basis.

A cover page and a copy of the SAE report written in English must be sent to AstraZeneca at the time the event is reported to the Regulatory Authority. To meet data privacy and confidentiality requirements AE information (both individual case reports and listings) must be sent from the investigator and/or sponsor to AstraZeneca by **secure e-mail**, if secure email is not available AE information must be sent by fax. For methods of achieving secure email data exchange, via encrypted email or password protected attachment.

*** AstraZeneca's contact details for AE reporting**
- Designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com
- Fax: +1 302 886 4114

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the Regulatory Authority.

A cover page should accompany the AE report form indicating the following:

- Notification from an Investigator Sponsored Study
- The investigator's name and address
- The trial name/title and AstraZeneca ESR reference number (ESR-16-11923/D4191C00071)

10.3.3 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as a SAE.

10.3.4 Overdose

An overdose is defined as a subject receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported **within 24 hours** of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 10.1.2 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

10.3.5 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune.

10.3.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

Should pregnancy occur, the physician should discuss with the patient the potential hazard to the fetus or potential risk of loss of the pregnancy.

10.3.7 Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

All statistical analyses will be performed by the the investigator-initiated trial team in Seoul National University Hospital. The primary aim of the study is to describe the change of tumor

biology by serial biopsy with whole genome/exome sequencing, immune signature, immunohistochemical analysis, and functional RAD51 assay. .

11.1 Description of analysis sets

11.1.1 Safety analysis set

The safety analysis set will consist of all patients who received at least 1 dose of olaparib.

11.1.2 Efficacy analysis set

The efficacy analysis set will consist of all patients who completed 4-week olaparib/durvalumab treatment.

11.1.3 Exploratory analysis set (To assess change of tumor biology)

The exploratory analysis set will consist of all patients who provided serial tumor biopsies (baseline, on-treatment 1 (OT1) and on-treatment 2 (OT2)) before and during olaparib /durvalumab window of opportunity treatment)..

11.2 Methods of statistical analyses

11.2.1 Safety Analyses

Safety and tolerability will be assessed in terms of AEs, deaths, laboratory data, vital signs and ECGs. These will be collected for all patients. Appropriate summaries of these data will be described.

11.2.2 Efficacy Analyses

Efficacy endpoint: rate of pathologic complete remission (pCR), response rate (RR) by RECIST v.1.1 and metabolic response using FDG-PET/MRI will be reported.

FDG-PET/MRI scans will be performed at baseline, 2 weeks (on-treatment 1; OT1), and 4 weeks (on-treatment 2; OT2); CT scans will be performed at baseline, OT2 and before surgery.

Percentage change in tumor size at OT2 and before surgery and best overall percentage change from baseline in tumor size will be reported.

The pCR is defined as the absence of residual invasive cancer on hematoxylin and eosin evaluation of the completed resected breast specimen and all sampled regional lymph nodes

following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 in the current AJCC staging guideline).

Response rate is defined as the number (%) of patients with at least 1 visit response of CR or PR. Data obtained up until progression, or the last evaluable assessment before surgery in the absence of progression, will be included in the assessment of response rate. The patient who can't finish the 4-week olaparib/durvalumab will be replaced and will not be included in the denominator, but the patient who progressed during standard of neoadjuvant chemotherapy will be included as denominator.

In the case where a patient has 2 non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there is no PD between the PR visits, the patient will be defined as a responder. Similarly, if a patient has visit responses of CR, non-evaluable, CR, then, as long as the time between the 2 visits of CR is greater than 4 weeks, then a best response of CR will be assigned.

The percentage change from baseline in tumor size at D29 (on-treatment 2: OT2) and before surgery is based on modified RECIST 1.1 target lesion measurements taken at baseline and at D29 (OT2), and prior curative surgery. Tumor size is the sum of the longest diameters of the target lesions. Target lesions are measurable tumor lesions. Baseline for modified RECIST 1.1 is defined to be the last evaluable assessment prior to starting olaparib treatment. The percentage change in target lesion tumor size will be obtained for each patient taking the difference between the sum of the target lesions on day 29 (OT2) or prior surgery, and the sum of the target lesions at baseline divided by the sum of the target lesions at baseline times 100; ie, for D29 (OT2) (D29 (OT2) - baseline) / baseline x 100).

The best percentage change from baseline in tumor size is based on modified RECIST 1.1 target lesion measurements taken at each modified RECIST 1.1 assessment. All measurements up until modified RECIST 1.1 progression or the last evaluable assessment in the absence of modified RECIST 1.1 progression will be included in the calculation

The metabolic response (mRes) is defined as a ≥ 30% decrease in FDG standardized uptake value (SUV) by FDG-PET/MRI at OT1 and OT2 compared with baseline.

11.2.3 Exploratory Analyses

Whole exome sequencing, and RNA sequencing analysis will be applied on tumor tissue obtained by serial biopsy and surgery. Functional RAD51 foci assay will be performed using baseline biopsy tissues.

Tumor infiltrating lymphocytes (TILs) as well as specific immune subset markers (CD3, CD4, CD8, CD68, Foxp3, etc.) will be assessed by multiplex immunohistochemistry on tumor tissue. The expression profile of these molecules of tumor specimen acquired on OT1(D15), OT2(D29), and at the time of surgery will be compared to those of baseline tumor samples.

BRCA gene testing will be performed on a blood sample taken specifically for that purpose and all local gidelines for such genetic testing must be followed. All patients must provide samples and consent to study-related gBRCA status testing, and must also have a blood sample taken at the same time for the purpose of developing and validating a diagnostic test for BRCA mutations.

Categorical variables will be compared using the chi-square test or Fisher's exact test as appropriate. For paired comparisons across longitudinal timepoints (baseline, OT1, OT2), Wilcoxon signed-rank tests will be used. Unpaired group comparisons will be assessed using the Wilcoxon rank-sum test. P values will be adjusted for multiple testing; Bonferroni correction will be applied for predefined pairwise comparisons, whereas BH correction will be used for analyses involving GSVA and fGSEA. All statistical analyses will be performed using R software (version 4.5.0; R Foundation for Statistical Computing, Vienna, Austria).

PD-L1 Testing

To ensure comparability of data across all studies of durvalumab and/or tremelimumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the clone 22C3 (Dako, Carpinteria, CA, USA) on the DAKO Link 48 Autostainer (Dako), and the results will be interpreted using the combined positive score (CPS). Testing should be restricted to the clone 22C3 and should be performed in accordance with the package insert on the DAKO platform (DAKO Link Autostainer).

The clone 22C3 PD-L1 IHC assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and breast cancer. For these tumors, the 22C3 IHC assay has a full reproducibility data package supporting cut-off and CPS scoring algorithm. Following completion of KEYNOTE-522 clinical trials, the assay will be associated with clinical utility.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.

- In AstraZeneca studies, the preferred sample for PD-L1 testing was less than or equal to 3 months old. In cases where a sample a less than 3 months old was not available, patients were asked to undergo a new biopsy if considered clinically appropriate by their treating physician.

- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.

- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age. When archival samples are used to assess PD-L1 status, the age of the sample / date of collection should be captured.

- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 testing

The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (ecode or unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location

- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The PD-L1 IHC 22C3 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the Bio-Bank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.

- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same

block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.

- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended

Storage of tumor blocks for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 testing.

- Each sample should be reviewed for:

    - Adequate fixation
    - Good preservation of morphology
    - Presence of tumor tissue
    - Histopathology consistent with indication
    - Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

If indicated, shipping samples to a PD-L1 testing laboratory

- When submitting sample to for PD-L1 testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks should be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 micron thick) to be used for PD-L1 testing.

  Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for PD-L1 testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:

  - A minimum of 5-10 x 4 micron (μm) thick, unstained sections should be provided for PD-L1 testing
  - A new disposable microtome blade must be used for each block to prevent contamination between patient samples
  - Slides are stable under these conditions for 6 months.
  - Apply one section per slide to positively-charged Superfrost glass slides
  - The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status

11.3 Determination of sample size

This is an exploratory serial biopsy trial, and formal sample size calculation is not applicable. Considering further analysis plan and number of patients receiving neoadjuvant chemotherapy in the study sites, twenty-five patients who completed pre-treatment and post-treatment tumor biopsy sample which will be compatible for translational analysis. This sample size could detect a standardized difference of 0.6 or more as statistically significant ($p<0.05$) with 80% power, using a paired t-test. Enrollment will continue until **25 patients** who have completed both pre- and post-treatment serial tumor biopsies (OT1 and OT2), undergone the planned surgical procedure, and have **evaluable tumor tissue samples** available for analysis are accrued.

In the initial pathologic analysis of enrolled patients (n=25), residual cancer was absent in 16.0% of OT1 biopsies and 60.0% of OT2 biopsies. Because tumor-containing OT2 specimens were required for planned translational analyses, enrollment was continued to ensure an overall OT2 tumor-

positivity rate of approximately 50%. Based on an anticipated approximately 50% failure rate in obtaining adequate viable tumor tissue during serial biopsy procedures, it is estimated that approximately between 50 and 60 patients will need to be enrolled.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization (ICH)/GCP, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples

12.2 Ethics and regulatory review

An EC/IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The investigator will ensure the distribution of these documents to the applicable EC/IRB, and to the study site staff.

The opinion of the EC/IRB should be given in writing. The investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. The EC/IRB should approve all advertising used to recruit patients for the study. AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually. Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, EC/IRB and PIs with safety updates/reports according to local requirements.

Each PI is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. AstraZeneca will provide this information to the PI so that he/she can meet these reporting requirements.

12.3 Informed consent

The PI at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

12.4 Changes to the protocol and informed consent form

The PI at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

12.5 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an EC/IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

Before the first patient is entered into the study, the PI will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures. The PI will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The PI will maintain a record of all individuals involved in the study (medical, nursing and other staff).

13.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the CRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (eg, clinic charts)
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

13.3 Study timetable and end of study

The end of the study is defined as the date of the last visit of the last patient occurring when all patients have completed study therapy.

There will be a final data cut-off defined as the time when all patients receiving IP have completed standard neoadjuvant chemotherapy and curative surgery. At this timepoint, the clinical study database will close to new data. Patients are, however, permitted to continue to receive study treatment beyond the closure of the database if, in the opinion of the investigator, they are continuing to receive benefit from treatment. Patients who remain on study treatment after this time point will be monitored according to routine clinical practice as defined by the Investigator. At routine clinic visits, patients will return used medication packaging and unused medication, and a thorough drug accountability assessment will be performed. However, where local regulations allow, patients may be switched from clinical trial supplies to marketed IP in those territories where IP is approved for the disease under study.

For patients who do continue to receive treatment beyond the time of this data cut-off, investigators will continue to report all SAEs and AESI to AstraZeneca, Patient Safety until 90 days after study treatment is discontinued. If an investigator learns of any SAEs, including death,

at any time after a patient has completed the study, and he/she considers there is a reasonable possibility that the event is causally related to the IP, the investigator should notify AstraZeneca, Patient Safety. Additionally, any SAE or non-serious AE that is ongoing at the time of this data cut-off, must be followed up to resolution unless the event is considered by the investigator to be unlikely to resolve, or the patient is lost to follow-up. For pharmacovigilance purposes and characterization of AESIs, ANY case of MDS/AML, new primary malignancy occurring after the 90-day follow up period should be reported to AstraZeneca Patient Safety whether is its considered a non-serious AE (eg, non-melanoma skin cancer) or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

The study may be terminated if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with olaparib and durvalumab.

14. DATA MANAGEMENT

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities. Medications will be classified according to the AstraZeneca Drug Dictionary.

The data collected through third party sources will be obtained and reconciled against study data.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

15. LIST OF REFERENCES

Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, and Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res. 2011. 17(13):4232-4244.

Bellati F, Napoletano C, Ruscito I, et al: Past, present and future strategies of immunotherapy in gynecological malignancies. Curr Mol Med 2013; 13:648-69.

Bookman MA, Brady MF, McGuire WP, et al: Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol 2009; 27:1419-25.

Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65.

Brusa D, Serra S, Coscia M, Rossi D, D'Arena G, Laurenti L, et al. The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia. Haematologica. 2013 Jun; 98(6):953-963.

Burger RA, Brady MF, Bookman MA, et al: Incorporation of bevacizumab in the primary treatment of ovarian cancer. The New England journal of medicine 2011; 365:2473-83.

Callahan MK and Wolchok JD. CTLA-4 and PD-1 blocking antibodies in cancer immunotherapy. J Leukoc Biol. 2013; 94(1):41-53.

Chow et al. Exploring novel immune-related toxicities and endpoints with immune-checkpoint inhibitors in non-small cell lung cancer. Am Soc Clin Oncol Educ Book. 2013

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Coleman RL, Monk BJ, Sood AK, et al: Latest research and treatment of advanced-stage epithelial ovarian cancer. Nature Reviews Clinical Oncology 2013; 10:211-224.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4)

Fagotti A, Ferrandina G, Fanfani F, et al: A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. Ann Surg Oncol 2006; 13:1156-61.

Fellman, B. M. Stata command for calculating adverse event and efficacy stopping boundaries for phase II single-arm trials. *Stata Journal.* 2014; 14(2):407-417.

Food and Drug Administration Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf. Accessed 10 December 2013.

Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Nat Acad Sci U S A. 2007;104(9):3360-5.

Hamid et al Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013 Jul 11;369(2):134-44

Huang J, Wang L, Cong Z, Amoozgar Z, Kiner E, Xing D, Orsulic S, Matulonis U, Goldberg MS: The PARP1 inhibitor BMN 673 exhibits immunoregulatory effects in a Brca1(-/-) murine model of ovarian cancer. Biochem Biophys Res Commun 2015, 463(4):551-556.

Kaehler et al. Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns, immune-related adverse events, and their management. Semin Oncol. 2010 Oct;37(5):485-98

Kandalaft LE, Motz GT, Duraiswamy J, et al: Tumor immune surveillance and ovarian cancer: lessons on immune mediated tumor rejection or tolerance. Cancer Metastasis Rev 2011; 30:141-51.

Katsumata N, Yasuda M, Takahashi F, et al: Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009; 374:1331-8.

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.

Kim KW, Ramaiya NH, Krajewski KM, et al. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. Invest New Drugs. 2013;31:1071.

Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al. Survivin and B7-H1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. Clin Cancer Res. 2007;13(6):1749-56.

Kroemer G, Galluzzi L, Kepp O, Zitvogel L: Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013, 31:51-72.

Kryczek I, Wei S, Zhu G, et al: Relationship between B7-H4, regulatory T cells, and patient outcome in human ovarian carcinoma. Cancer Res 2007; 67:8900-5.

Laudisi F, Sambucci M, Pioli C: Poly (ADP-ribose) polymerase-1 (PARP-1) as immune regulator. Endocr Metab Immune Disord Drug Targets 2011, 11(4):326-333.

Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D et al: PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med 2015, 372(26):2509-2520.

Lenz. Management and preparedness for infusion and hypersensitivity reactions. Oncologist. 2007 May;12(5):601-9.

Loos M, Giese NA, Kleeff J, Giese T, Gaida MM, Bergmann F, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic adenocarcinoma. Cancer Lett. 2008;268(1):98-109.

Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011 Sep;28(3):682-8.

Muenst S, Soysal SD, Gao F, Obermann EC, Oertli D, Gillanders WE: The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat 2013, 139(3):667-676.

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH and Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul; 19(14):3936-3943.

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic adenocarcinoma. Clin Cancer Res. 2007 Apr 1;13(7):2151-7.

O'Connor MJ: Targeting the DNA Damage Response in Cancer. Mol Cell 2015, 60(4):547-560.

Park J, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood. 2010;116(8):1291-8.

Perren TJ, Swart AM, Pfisterer J, et al: A phase 3 trial of bevacizumab in ovarian cancer. The New England journal of medicine 2011; 365:2484-96.

Peshkin BN, Alabek ML, Isaacs C. BRCA1/2 mutations and triple negative breast cancers. Breast Dis. 2010;32(1-2):25-33.

Raja FA, Chopra N, Ledermann JA. Optimal first-line treatment in ovarian cancer. Ann Oncol 2012 Sep; 23 Suppl 10:x118-27.

Rosado MM, Bennici E, Novelli F, Pioli C: Beyond DNA repair, the immunological role of PARP-1 and its siblings. Immunology 2013, 139(4):428-437.

Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, Lee W, Yuan J, Wong P, Ho TS et al: Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015, 348(6230):124-128.

Sabatier R, Finetti P, Mamessier E, Adelaide J, Chaffanet M, Ali HR, Viens P, Caldas C, Birnbaum D, Bertucci F: Prognostic and predictive value of PDL1 expression in breast cancer. Oncotarget 2015, 6(7):5449-5464.

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2015. CA Cancer J Clin 2015 Jan-Feb; 65(1): 5-29.

Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, Walsh LA, Postow MA, Wong P, Ho TS et al: Genetic basis for clinical response to CTLA-4 blockade in melanoma. N Engl J Med 2014, 371(23):2189-2199.

Sznol M and Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. 2013; 19(5):1021-1034.

Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo). 2013;2013:857519

TCGA. Integrated genomic analyses of ovarian carcinoma. Nature 2011; 474:609-15.
Thall PF, Simon R. Practical Bayesian guideline for phase IIB clinical trials. Biometrics 1994 Jun;50(2):337-49.

Thall PF, Wooten LH, and Tannir NM. Monitoring Event Times in Early Phase Clinical Trials: Some Practical Issues, Clinical Trials 2005; 2, 467-478 (2005).

Thompson RH, Gillett MD, Chevillem JC, Lohsem CM, Dong H, Webster WS, et al.

Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005;104(10):2084-91.

Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 2006;66(7):3381-5.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012 Jun 28;366(26):2443-54.

US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events Version 4.03. http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RHM, van der Burg MEL, Lacave AJ, Bendetti Panici P, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GCE, Pecorelli S, Reed NS. Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIc or IV Ovarian Cancer. NEJM 2010; 363; 10: 943-53.

Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. World J Surg. 2010;34(5):1059-65.

Weber et al. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012 Jul 20;30(21):2691-7

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-20.

Wu CY, Yang LH, Yang HY, Knoff J, Peng S, Lin YH, Wang C, Alvarez RD, Pai SI, Roden RB et al: Enhanced cancer radiotherapy through immunosuppressive stromal cell destruction in tumors. Clin Cancer Res 2014, 20(3):644-657.

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008;8(6):467-77.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) 19August 2016 Version

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	It is recommended that management of irAEs follows the guidelines presented in this table: – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections). – In the absence of a clear alternative etiology, all events should be considered potentially immune related. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) 19August 2016 Version

Dose Modifications	Toxicity Management
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; irAE Immune-related adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	**Any Grade**	General Guidance	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider pulmonary and infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		completion of steroid taper.	– If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain pulmonary and infectious disease consult. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			and refer to infliximab label for general guidance before using infliximab. – Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Enterocolitis	**Any Grade**	General Guidance	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1:**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	(stool frequency of <4 over baseline per day)		– Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (stool frequency of 4 to 6 over baseline per day)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeksa. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Consult study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			[Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × ULN)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			(mycophenolate mofetil)[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 ×	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 ×	No dose modifications.	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptoms.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	baseline; > ULN to 1.5 × ULN)		• If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			[Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days,	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines].

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	− Consider skin biopsy (preferably more than 1) as clinically feasible. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] − Discuss with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** − Consult endocrinologist. − Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness. − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). − Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. − If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or	**For Grade 2 (including those with symptomatic endocrinopathy):** – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Initiate hormone replacement as needed for management. – Evaluate endocrine function, and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.	**For Grade 3 or 4:** – Consult endocrinologist. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Neurotoxicity	**Any Grade**	General Guidance	**For Any Grade:**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
(to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	(depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)		− Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). − Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). − Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). − Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** − See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** − Discuss with the study physician. − Obtain neurology consult. − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). − Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For Grade 3:**	**For Grade 3 or 4:**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Discuss with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of	**For Grade 2:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		respiratory insufficiency or autonomic instability.	– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:*

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Discuss with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.

[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; irAE Immune-related adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PCP ; PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM Intramuscular; IV Intravenous; NCI National Cancer Institute.

Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.