Document Coversheet

Study Title: A Phase I/II Evaluation of Olaparib in combination with Durvalumab and Tremelimumab in the Treatment of Recurrent Platinum Sensitive or Resistant or Refractory Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Patients who Carry a Germline BRCA1 or BRCA2 Mutation

Institution/Site:	Roswell Park Comprehensive Cancer Center
Document (Approval/Update) Date:	04/15/2021
NCT Number:	NCT02953457
Roswell Protocol ID:	I 288216

TITLE: A Phase I/II Evaluation of Olaparib in Combination with Durvalumab (Medi4736) and Tremelimumab in the Treatment of Recurrent Platinum Sensitive or Resistant or Refractory Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Patients Who Carry a BRCA1 or BRCA2 Mutation

Roswell Park Cancer Institute

Study Number:	**I 288216**
Initial Date:	**10 June 2016**
Amendment 1	**07 December 2016**
Amendment 2	**31 August 2017**
Amendment 3	**13 November 2017**
Amendment 4	**27 February 2018**
Amendment 5	**27 June 2018**
Amendment 6	**21 September 2018**
Amendment 7	**16 January 2019**
Amendment 8	**24 July 2019**
Amendment 9	**28 August 2019**
Amendment 10	**18 November 2019**
Amendment 11	**29 December 2020**
Amendment 12	**15 April 2021**
IND Holder:	**Roswell Park Cancer Institute**
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Sponsor:	**Roswell Park Cancer Institute**

Industry/Other Supporter: AstraZeneca

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FOR NETWORK SITES: Please contact the RPCI Network Monitor for any study-related questions regarding sample handling, processing or shipping.

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List of Abbreviations

AChE	Acetylcholine esterase
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
C_{max}	peak concentration
$C_{max,ss}$	peak concentration at steady state
C_{min}	trough concentration
$C_{min,ss}$	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
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
irRECIST	immune-related response criteria
IV	Intravenous(ly)
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
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
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
T_{max}	time to peak concentration
$T_{max,ss}$	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

SYNOPSIS

Title / Phase	A Phase I/II Evaluation of Olaparib in Combination with Durvalumab (Medi4736) and Tremelimumab in the Treatment of Recurrent Platinum Sensitive or Resistant or Refractory Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Patients Who Carry a BRCA1 or BRCA2 Mutation.
Roswell Park Cancer Institute Study Number	I 288216
Roswell Park Cancer Institute Investigator	Emese Zsiros, MD
Sponsor	Roswell Park Cancer Institute
Industry/ Other Supporter	AstraZeneca
Study Drugs	Olaparib Durvalumab Tremelimumab
Objectives	**Primary:** • **Phase I:** The primary objective of the phase I component of this study is: o To assess the safety and toxicity of the combination of PARP inhibitor olaparib with anti-PD-L1 antibody durvalumab and anti-CTLA4 antibody tremelimumab • **Phase II:** The primary objective of the phase II component of this study is: o To assess the impact of the combination of olaparib with durvalumab and tremelimumab on PFS rates. **Secondary:** • To assess the impact of the combination of olaparib with durvalumab and tremelimumab on anti-tumor immune responses in patients with recurrent platinum sensitive or resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer who carry a germline and/or somatic BRCA1 or BRCA2 mutation and/or a homologous recombination deficiency (HRD) • To assess the impact of the combination of olaparib with durvalumab and tremelimumab on PFS and OS in patients with recurrent platinum sensitive or resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer who carry a germline and/or somatic BRCA1 or BRCA2 mutation and/or a HRD.
Study Design	This is an open-label Phase I/II study for combination of the PARP inhibitor olaparib with anti-PD-L1 antibody durvalumab and anti-CTLA4 antibody tremelimumab, utilizing a 3+3 design followed by a Phase II study with a planned enrollment at a 2:1 ratio of platinum-resistant to platinum-sensitive disease. Patients

	must have platinum-sensitive or platinum-resistant recurrent or persistent or refractory ovarian, fallopian tube, or primary peritoneal carcinoma AND have one or more of the characteristics listed in the inclusion criteria documented on a validated platform (documented genetic test report is required). Historic report is permitted.
Target Accrual and Study Duration	A maximum of 36 participants at multiple sites, including RPCI will be enrolled. Accrual is expected to take up to 4 years.
Study Procedures	The following will be performed during the **pre-screening period Day -42 through Day -1)** for PD-L1 status only: • Informed Consent • Preliminary review of eligibility criteria (investigator's opinion) • Obtain archived tumor tissue for PD-L1 assay The following will be performed within 28 days prior to first dose of study drug (**Screening period**), unless otherwise specified: • Formal verification of eligibility criteria • Recording of concomitant medications • Recording of adverse events • Medical and surgical history/demographics • Complete physical exam (to include vital signs, height, and weight) • ECOG Performance Status • 12-lead ECG (in triplicate [2-5 minutes apart]) • Tumor/Disease Assessment by CT/MRI (including brain MRI only if clinically indicated) • Hematology (Table 6) • Chemistry (Table 7) • CA-125 level • Thyroid function tests: TSH level. If TSH is abnormal fT3 and fT4 will also be collected. • Coagulation (PT, PTT, INR) • Pregnancy test (serum βhCG for pre-menopausal women of childbearing potential only) • HIV/Hepatitis B, C serologies • Urinalysis (Table 8) **Cycle 1 Day 1:** • Pregnancy test (serum) in pre-menopausal women of child-bearing potential (only if not performed within 7 days of treatment start). • Physical examination • Vital signs • Weight • ECOG Performance Status • Single 12-lead ECG– on Cycle 1 Day 1 within 2-3 hours prior to start of the first treatment and 0-3 hours after

	administration of the combination is completed. In case of clinically significant ECG abnormalities, including a QTcF value ≥ 470ms, 2 additional 12-lead ECGs should be obtained over a brief period (e,g, 30 minutes) to confirm the finding. • Recording of adverse events • Recording of concomitant medications • Chemistry (Table 7) • CA-125 level • Thyroid function tests: TSH level. If TSH is abnormal, fT3and fT4 will also be collected. • Hematology (Table 6) • Urinalysis • PAXgene® RNA blood sample collection • Blood for immune monitoring • Blood for circulating soluble factors • Initial durvalumab, tremelimumab, and olaparib treatment • Vital Sign monitoring during the infusions **Treatment Phase:** Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Procedures and Observations (see Table 5). **End of Treatment**: End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab, tremelimumab, or olaparib prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit (see Table 5).
Statistical Analysis	**Sample Size Determination:** The potential Phase I study sample size ranges from a minimum of n=6 to a maximum of n=12. See Table 1 for the dose escalation schema. The phase II portion of the study will have a sample size of n=27. Subjects will be enrolled in the Phase II study at a ratio of 2:1 of platinum resistant to platinum sensitive disease. Depending on the incidence of DLT(s), following a 3+3 design, the sample size is estimated to be 33 to 36 patients. Assuming the true DLT rate is much less than 1/3rd, we anticipate enrolling 36 subjects (9+27) where the accrual is expected to take up to 4 years. **Efficacy Analysis:** Clinical efficacy evaluation will include tumor response assessed by irRECIST and RECIST, Progression-free Survival and Overall Survival. The primary endpoint will test the 3 months progression free survival rate in the platinum resistant group in conjunction with the 6-month progression free survival rate in the platinum sensitive group.

	Safety Analysis: The primary objective of the Phase I study is establishing safety. Assessment of safety and tolerability will be performed by closely monitoring the first 6 subjects in the safety lead-in cohort. The internal data safety monitoring panel will monitor on an ongoing basis, based on data review and regular conference calls with the investigators.

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

Title: A Phase I/II Evaluation of Olaparib in Combination with Durvalumab (Medi4736) and Tremelimumab in the Treatment of Recurrent Platinum Sensitive or Resistant or Refractory Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer in Patients Who Carry a BRCA1 or BRCA2 Mutation.

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Patients must have platinum-sensitive or platinum-resistant recurrent or persistent or refractory ovarian, fallopian tube, or primary peritoneal carcinoma AND have one or more of the following characteristics documented on a validated platform (documented genetic test report is required). Historic report is permitted. a) A germline *BRCA1* or *BRCA2* deleterious alteration. b) A somatic mutation in *BRCA1* or *BRCA2* detected in a tumor sample or on circulating tumor DNA. c) Carry a known or likely loss of function alteration in one or more of the homologous recombination or mismatch repair pathway genes (see section 5.1 for the list of genes). d) Demonstrate a genomic phenotype of HR deficiency as measured by a LOH-high score. **Recurrent ovarian cancer** is defined as recurrence of disease in a patient who achieved initial complete response to primary therapy. **Persistent ovarian cancer is** defined as having residual disease in the form of elevated tumor markers or microscopic or clinically evident disease in a patient who has completed and apparently responded to initial chemotherapy. **Refractory ovarian cancer is** defined as patients who have failed to achieve at least a partial response to therapy including patients with either stable disease or disease progression during primary therapy. **Platinum-sensitive** is defined as achievement of documented response to initial platinum-based treatment and has been off treatment for an extended period of time (more than 6 months) **Platinum-resistant** is defined as relapse within 6 months of last platinum-based chemotherapy or progression while on platinum-based therapy.	
☐	☐	☐	2. All patients must have measurable disease as defined by irRECIST. Measurable disease is defined as 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non- nodal lesions and ≥ 15 mm in short axis for nodal lesions, 20 mm by chest X-ray, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).	
☐	☐	☐	3. Must have archival tissue available for PD-L1 assessment.	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	4. Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).	
☐	☐	☐	5. Patients who have the following risk factors are considered to be at increased risk for cardiac toxicities and may be enrolled only with increased monitoring (refer to Table 5, footnote 5): i) prior treatment with anthracyclines, ii) prior treatment with trastuzumab, iii) a New York Heart Association classification of II controlled with treatment, iv) prior central thoracic radiation therapy (RT), including RT to the heart.	
☐	☐	☐	6. Any hormonal therapy being taken as a treatment for cancer must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy e.g. thyroid hormone replacement therapy is permitted.	
☐	☐	☐	7. Able to tolerate oral medications and no GI illnesses that would preclude absorption of olaparib.	
☐	☐	☐	8. Female patients, age ≥ 18 years at time of study entry.	
☐	☐	☐	9. Have an ECOG Performance Status of 0-1. Refer to Appendix B.	
☐	☐	☐	10. Life expectancy of > 6 months.	
☐	☐	☐	11. Adequate normal organ and marrow function as defined below: • Hemoglobin ≥ 10 g/dL (no blood transfusion in the 28 days prior to entry) (olaparib guidelines) • WBC > 3 x 10^9/L • 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). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician • AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN • Creatinine ≤ 1.5 x ULN or, serum creatinine CL >51 mL/min (by the Cockcroft-Gault equation: see Appendix L)	
☐	☐	☐	12. Female subjects must either be of non-reproductive potential (i.e., 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 within 28 days of study treatment, confirmed prior to treatment on day 1.	

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	13. Participants of child-bearing potential must agree to use two highly effective and acceptable forms of contraception from screening, throughout their participation in the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after last dose of durvalumab or olaparib, whichever is the longer time period (e.g., hormonal or barrier method of birth control). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	
☐	☐	☐	14. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	
☐	☐	☐	15. 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.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM

Participant Name: (Network sites use participant initials): _____

Medical Record No.: (Network sites use participant ID): _____

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EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrollment in the present study.	
☐	☐	☐	2. Participation in another clinical study with an investigational product during the last 4 weeks (prior use of bevacizumab in the upfront setting is allowed).	
☐	☐	☐	3. History of discontinuation of any previous treatment with PARP inhibitors, including olaparib, or a PD-1 or PD-L1 inhibitor, including durvalumab or anti-CTLA4 antibody, including tremelimumab due to toxicity.	
☐	☐	☐	4. Patients with myelodysplastic syndrome/acute myeloid leukemia.	
☐	☐	☐	5. History and/or confirmed ILD/pneumonitis, extensive bilateral lung disease on HRCT scan.	
☐	☐	☐	6. Concomitant use of a strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritonavir, lopinavir/ritonavir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) and moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole. Fosamprenavir, imatinib, verapamil).	
☐	☐	☐	7. Concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) and moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin).	
☐	☐	☐	8. History of another primary malignancy except for: • Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence. • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease (e.g. basal cell or squamous cell carcinoma of the skin). • Adequately treated carcinoma in situ without evidence of disease (e.g., breast and cervical cancer in situ).	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	9. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, radiotherapy or, other investigational agent) ≤ 21 days prior to the first dose of study drug and within 6 weeks for nitrosourea or mitomycin C).	
☐	☐	☐	10. Mean QT interval corrected for heart rate (QTcF) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.	
☐	☐	☐	11. Patients with history of myocardial infarction within 6 months.	
☐	☐	☐	12. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.	
☐	☐	☐	13. Any unresolved toxicity (CTCAE grade ≥2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).	
☐	☐	☐	14. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.	
☐	☐	☐	15. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.	
☐	☐	☐	16. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).	
☐	☐	☐	17. Patients with thyroid dysfunction if not adequately controlled.	
☐	☐	☐	18. History of primary immunodeficiency.	
☐	☐	☐	19. History of allogeneic organ transplant.	
☐	☐	☐	20. History of hypersensitivity to durvalumab, tremelimumab, olaparib or, any excipient.	
☐	☐	☐	21. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of, or test positive for, acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.	
☐	☐	☐	22. Known history of previous clinical diagnosis of tuberculosis.	
☐	☐	☐	23. History of leptomeningeal carcinomatosis.	

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	24. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab (e.g. LAIV, MMR, VAR, Zoster, yellow fever etc.)	
☐	☐	☐	25. Female subjects who are pregnant, breast-feeding, or of reproductive potential who are not employing an effective method of birth control from screening to 180 days after the last dose of durvalumab + tremelimumab + olaparib combination therapy or 90 days after the last dose of durvalumab and olaparib therapy, whichever is the longer time period.	
☐	☐	☐	26. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results or, is an unsuitable candidate to receive study drug (e.g. inability to tolerate oral medications which would preclude absorption of olaparib).	
☐	☐	☐	27. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.	
☐	☐	☐	28. Subjects with uncontrolled seizures.	
☐	☐	☐	29. Dependency on IV hydration or TPN.	

Participant meets all entry criteria: ☐ **Yes** ☐ **No**
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

TABLE OF CONTENTS

IN-TEXT TABLES

APPENDICES

1 BACKGROUND

1.1 Recurrent Ovarian Cancer

Most patients with epithelial ovarian cancer present with advanced disease at diagnosis (1). The standard of care for first-line treatment after primary cytoreductive surgery is the combination of a platinum drug with a taxane (2): This combination results in response rates (RR) of 70% in patients with suboptimally-debulked disease and, of 80% in optimally cytoreduced patients (2). However, disease recurrence is common in this patient population and most patients with recurrent ovarian cancer eventually develop platinum-resistant disease (defined as disease recurring within 6 months after the last treatment with platinum-based chemotherapy) (3).

Platinum-sensitive disease: Carboplatin and paclitaxel (CP) have emerged as standard for re-challenge in patients with platinum-sensitive recurrent ovarian cancer. Re-challenge with CP has been limited by the risk of cumulative peripheral neuropathy. Other carboplatin-based combinations, such as gemcitabine and carboplatin (4), and liposomal doxorubicin plus carboplatin (5) have been explored. The median PFS of the treatment regimens varies from 8.4 to 12.4 months, depending on the study (4-6). Unfortunately, these patients eventually develop platinum-resistant disease. Therefore, novel interventions are necessary for patients with platinum-sensitive recurrent ovarian cancer.

Platinum-resistant/refractory ovarian cancer is an unmet medical need: In women with platinum-resistant disease, RRs range from 10%-25% and duration of response is typically less than 6 months to chemotherapeutic agents, such as pegylated liposomal doxorubicin (PLD), topotecan, taxanes, etoposide, and gemcitabine (7). Thus, there is an urgent need for the development of alternative therapies given the poor response of recurrent disease to traditional cytotoxic agents. Two potential therapeutic targets are DNA damage repair and immune checkpoint pathways.

Ovarian Cancer and PARP Inhibition: PARP-1 is essential to the repair of DNA single-strand breaks via the base excision repair pathway. Poly (ADP-ribose) polymerase (PARP) plays a key role in DNA repair mechanisms by detecting and initiating repair after DNA strand breaks. Inhibition of PARP in DNA repair-defective tumors (like those with BRCA1 or BRCA2 mutations) can lead to gross genomic instability and cell death. Recent in vitro and in vivo evidence suggests that PARP inhibitors could be used not only as chemo/radiotherapy sensitizers, but also as single agents to selectively kill cancers defective in DNA repair, specifically cancers with mutation in the breast cancer-associated genes, BRCA1 and BRCA2.

Much of the proof of concept and proof of principle single agent studies performed to date have centered on olaparib. Objective responses were observed only in confirmed carriers of BRCA1 or BRCA2 mutation, apart from one patient with a strong family history of BRCA mutation who declined mutational testing. Of the 60 patients entered, there were 9 partial or complete responses by RECIST criteria (8 with ovarian cancer and 1 with breast cancer) (8). A phase II trial evaluating two sequential cohorts of women with recurrent ovarian cancer (with confirmed germline BRCA1 or BRCA2 mutation and measurable disease) enrolled 33 women treated at 400 mg BID and then 24 women treated at 100 mg BID. Objective response rate (RECIST) was 33% (11/33 patients) in

the 400 mg BID cohort and 13% (3/24 patients) in the 100 mg BID cohort (9). In a further phase I study, 50 patients with recurrent ovarian cancer, known BRCA1 or BRCA2 mutation and measurable disease were treated with doses of olaparib ranging from 40 mg daily for 2 of 3 weeks, to 600 mg BID (11 patients). There was then a dose expansion cohort, where all patients received olaparib at 200 mg BID (39 patients). Objective response rate was 28% (14/50 patients). Objective response rates were reported according to platinum-sensitivity: Platinum-sensitive 46% (6/13 patients); Platinum-resistant 33% (8/24 patients); and Platinum-refractory 0% (0/13 patients) (10). A potential explanation for the variable response according to platinum-sensitivity is the development of secondary mutations restoring BRCA 1/2 function (11-15).

Olaparib has also been evaluated as a single agent in a trial that included patients without germline BRCA1 or BRCA2 mutation. In this phase II trial, 86 patients were treated and evaluable for response (63 with ovarian cancer and 23 with breast cancer). Patients were entered with recurrent high grade serous and/or undifferentiated ovarian cancer or triple negative breast cancer. Patients were stratified according to whether they had a BRCA1 or BRCA2 mutation or not. In ovarian cancer, objective responses were seen in 41% (7/17 patients) with BRCA1 or BRCA2 mutation and 24% (11/46 patients) without BRCA1 or BRCA2 mutation (16). A three-arm randomized, open label, phase II trial of olaparib 200 mg BID (n=32), olaparib 400 mg BID (n=32) and pegylated liposomal doxorubicin (PLD) (n=33), in women with recurrent ovarian cancer, germline BRCA1 or BRCA2 mutation and recurrence within 12 months of prior platinum therapy has been conducted. PLD was given at 50 mg/m2 every 4 weeks. The primary endpoint was investigator assessed progression-free survival. The progression free survival (PFS) and objective response rates (RR) were similar between the 3 arms (17). The efficacy of olaparib was consistent with previous studies. The efficacy of PLD was greater than expected.

A randomized phase II maintenance trial of olaparib (400 mg BID) vs placebo was conducted in women with platinum sensitive recurrent high grade serous ovarian cancer (with and without BRCA1 or BRCA2 mutation) who had achieved a response (partial or complete) following 2nd line (or greater) platinum-based therapy. The time to progression in the 265 patient cohort was extended from 4.8 months to 8.4 months (HR: 0.35, $P<0.001$). Patients were not required to undergo BRCA1 and BRCA2 testing and they were not stratified as to whether they had a BRCA1 or BRCA2 mutation or not (Ledermann et al, 2011).

Ovarian Cancer and the PD-1/PD-L1 pathway: Tumors employ the programmed cell death 1 and its ligand (PD-1/PD-L1) inhibitory pathway to paralyze antitumor immune response. PD-L1 (also known as B7-H1 or CD274) is a coregulatory molecule that is expressed on the surface of various types of cells, including immune cells and epithelial cells. By binding to its receptor PD-1 on lymphocytes, it generates an inhibitory signal toward the T-cell receptor (TCR)-mediated activation of lymphocytes. PD-L1 expression in tumor cells has been shown to be an independent unfavorable prognostic factor in human ovarian cancer (18). Importantly, PD-L1 expression showed the closest relation to unfavorable prognosis among other immunosuppressive molecules that have been tested in ovarian cancer (19). Moreover, direct ex-vivo analysis of tumor antigen specific CD8+ T cells from tumor-infiltrating lymphocytes (TILs) of ovarian cancer patients demonstrated impaired effector function, that was could be restored by blocking the PD-1/PD-L1 pathway (20). In preclinical models of ovarian cancer, PD-1/PD-L1 pathway blockade also enhanced the amplitude of tumor immunity by reprogramming suppressive and stimulatory signals

that yielded more powerful cancer control (21, 22). These data suggest that PD-L1 has a role in the clinical course of ovarian cancer by affecting the local immune microenvironment and that interruption of the PD-1/PD-L1 pathway could restore effective antitumor immunity in ovarian cancer patients.

Ovarian Cancer and the CTLA-4 pathway: Tremelimumab is a human monoclonal immunoglobulin G2 (IgG2) antibody specific for human cytotoxic T lymphocyte- associated antigen 4 (CTLA-4), a co-inhibitory receptor expressed on activated T cells. Tremelimumab has been shown to block the inhibitory signal mediated by interaction of human CTLA-4 on activated T cells with B7-1 and B7-2 on antigen-presenting cells. This is thought to maintain T cell activation in the tumor microenvironment and promote the establishment of tumor-specific immune responses. Inhibition of CTLA-4 signaling is a validated approach to cancer therapy, as shown by the approval in 2011 of ipilimumab for the treatment of metastatic melanoma based on statistically significant and clinically meaningful improvement in OS (23). Like melanoma, ovarian cancer is associated with significant tumor heterogeneity, and is also a rational target for immune therapy. Although antitumor effects have been observed in patients with epithelial ovarian cancer in response to anti-CTLA-4 antibody treatment, evidence of clinical disease regression has not been demonstrated.

1.2 Durvalumab, Tremelimumab and Olaparib Background

1.2.1 Durvalumab

The non-clinical and clinical experience is fully described in the current version of the durvalumab Investigator's Brochure (IB Version 15.0).

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.

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of patients with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of patients with tumors lacking PD-L1 (24). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of several non-clinical studies using mouse tumor models support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity (25-28).

Durvalumab has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of the data cut-off (DCO) date of (12 July 2019), across the entire clinical development program, approximately 8817 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumor types, stages of disease and lines

of therapy. Of these, 4067 patients received durvalumab monotherapy, 2423 patients received durvalumab in combination with tremelimumab, and 2327 patients received durvalumab in combination with an investigational and or an approved product. An estimated 8343 patients have been randomized to the various treatment/comparator arms in sponsor-blinded studies. In addition, 2482 patients have participated in the durvalumab Early Access Programme (EAP; Study D4194C00002) for patients with locally advanced, unresectable non-small cell lung cancer [NSCLC] whose disease has not progressed following platinum based chemoradiation therapy). The cumulative global-marketing patient exposure to durvalumab to (10 mg/kg) to 30 June 2019 has been estimated to be approximately 12,385 patient-years.

Durvalumab 50 mg/ml was first approved for the treatment of patients with locally advanced or metastatic UC in the US on 1 May 2017. On 16 February 2018, durvalumab was approved in the US for the treatment of patients with unresectable Stage III NSCLC. On 21 September 2018, durvalumab was approved in the EU for the treatment of locally advanced, unresectable NSCLC in adults whose tumors express PD-L1 on ≥1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy. As of 12 July 2019, durvalumab is approved in 18 countries for UC and over 45 countries for NSCLC.

Study CD-ON-MEDI4736-1108: As of 16 October 2017, PK data were available for 1009 patients following treatment with 0.1 to 10 mg/kg Q2W and 15 mg/kg Q3W (dose-escalation), 10 mg/kg Q2W (dose-expansion), and 20 mg/kg Q4W (dose-exploration) durvalumab administered as an IV infusion over 60 minutes. The C_{max} increased in an approximately dose-proportional manner over the dose range examined. The AUC0-14 increased dose-proportionally at doses of 3 to 20 mg/kg and more than dose-proportionally at doses of <3 mg/kg, likely due to saturable target-mediated clearance (CL). The steady state was achieved at approximately Week 16. Accumulation of durvalumab was observed following repeated dosing. Mean accumulation ratio (AR) ranged from 0.64 to 1.87 and 3.16 to 4.93 for C_{max} and C_{min}, respectively. Near complete target saturation (sPD-L1 and membrane bound) is expected with durvalumab ≥3 mg/kg Q2W.

As of 16 October 2017, a total of 849 patients provided evaluable samples for ADA analysis. The overall ADA prevalence (the proportion of patients who were evaluable for ADA and were positive for durvalumab ADA at any point in time) was 5.3% (45 of 849 patients). The overall ADA incidence (the proportion of the study population who were evaluable for ADA and were treatment-emergent ADA positive) was 3.1% (26 of 849 patients). Three patients (0.4%, in 3/810 patients) were neutralizing ADA (nAb) positive. Based on population PK covariate analysis, ADA positive status was not associated with a clinically relevant reduction of exposure to durvalumab. At the 10 mg/kg Q2W dose, sPD-L1 suppression in ADA positive patients was similar to that observed in ADA negative patients. The impact of treatment-emergent ADA on the clinical efficacy of durvalumab in urothelial carcinoma (UC) and non-small cell lung cancer (NSCLC) patients was not evaluable due to very few patient samples testing positive for treatment-emergent ADA.

Durvalumab + tremelimumab: Study D4190C00006: As of 28 February 2017, durvalumab PK (n=347) and tremelimumab PK (n=353) data were available from the dose-escalation and dose-expansion phases following durvalumab Q4W (3, 10, 15, or 20 mg/kg) or Q2W (10 mg/kg) in combination with tremelimumab Q4W (1, 3, or 10 mg/kg). An approximately dose-proportional

increase in PK exposure (C_{max} and AUC 0 to 28 days [AUC0-28]) of both durvalumab and tremelimumab was observed over the dose range of 3 to 20 mg/kg durvalumab Q4W and 1 to 10 mg/kg tremelimumab Q4W. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. The observed PK exposures of durvalumab and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

As of 28 February 2017, ADA data were available from 99 patients for durvalumab and95 patients for tremelimumab in Study D4190C00006. The ADA prevalence was 7.1% (7/99 patients) for durvalumab and 6.3% (6/95 patients) for tremelimumab. The ADA incidence was 2.0% (2/99 patients) for durvalumab and 5.3% (5/95 patients) for tremelimumab. No patients treated with durvalumab tested positive for the presence of nAb. There was no clear relationship between ADA and the dose of either durvalumab or tremelimumab, and no apparent association between ADA and safety.

1.2.2 Tremelimumab

Tremelimumab is an IgG 2 kappa isotype mAb directed against the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) also known as CD152 (cluster of differentiation 152). This is an immunomodulatory therapy (IMT) that is being developed by AstraZeneca for use in the treatment of cancer.

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures (29). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. (Refer to the tremelimumab IB, Edition 9.0, for more information). Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cutoff date (12 July 2018), approximately 1670 patients have been exposed to one or more doses of tremelimumab monotherapy across the program; 734 patients from AstraZeneca/MedImmune sponsored studies D4884C00001, D4880C00003 (DETERMINE), D4880C00010, D4193C00003 (CONDOR), D4881C00024, D4190C00022, D4191C00004 (ARCTIC) and D4191C00011; 967 patients from legacy studies (monotherapy). Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.3.

Refer to the current tremelimumab IB (IB Version 9.0) for a complete summary of non-clinical and clinical information.

Refer to Section 6.5 for guidance on management of tremelimumab-related toxicities.

Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22 days. Overall, a low incidence of ADAs (<6%) was observed for treatment with tremelimumab.

1.2.3 Durvalumab in combination with Tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (30) because the mechanisms of action of CTLA-4 and PD-1 are non-redundant; therefore, AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/PDx, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 weeks (Q2W) or every 4 weeks (Q4W) up to Week 50 and 48 (12 months), combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

Study D4190C00006: As of the DCO of 28 February 2017, the ORR per investigator assessment in the total dose-escalation group (patients with advanced NSCLC) was 16.7% (17/102; 95% CI: 10.0, 25.3). ORRs were 28.0% (7/25; 95% CI: 12.1, 49.4) in the PD-L1 high (TC ≥25%) and 14.0% (8/57; 95% CI: 6.3, 25.8) in the PD-L1 low/negative (TC <25%) group. No objective response (OR) was observed at the lowest dose-level combinations of durvalumab 3 or 10 mg/kg Q4W + tremelimumab 1 mg/kg. The median TTR was 7.1 weeks and the median DOR had not yet been reached. The DCR was 47%. Median OS in the combined tremelimumab 3 mg/kg group exceeded that in the tremelimumab 1 and 10 mg/kg groups (16.7 months vs 11.8 and 10.3 months, respectively).

In the dose expansion Cohort A (treatment-naive NSCLC selected by PD-L1 status), the ORR was 15.6% (7/45; 95% CI: 6.5, 29.5). ORRs were 16.7% (3/18; 95% CI: 3.6, 41.4) in the PD-L1 high and 12.0% (3/25; 95% CI: 2.5, 31.2) in the PD-L1 low/negative group. A DCR of 57.8% (26/45; 95% CI: 42.2, 72.3) was observed. The median TTR was 7.3 weeks with a median DOR of 24.4 weeks. Clinical response was observed in both the PD-L1 high and PD-L1 low/negative subgroups. In the As-treated Population, the median PFS was 3.5 months, with a PFS rate of 38.8% at 6 months. Median OS was not reached, with an OS rate at 6 months of 83.6%.

In the dose expansion Cohort B co-administration group (immunotherapy-naïve, 1L or 2L patients with NSCLC, N=19), no objective responses were observed per investigator assessment. A best overall response of SD was observed for 9 of the 19 patients (DCR, 47.4%; 95% CI: 24.4, 71.1).

In the dose expansion Cohort B sequential administration group (2L patients with non- squamous NSCLC), the ORR per BICR was 14.5% (30/207; 95% CI: 10.0, 20.0). ORRs were 33.9% (19/56; 95% CI: 21.8, 47.8) in the PD-L1 high and 6.8% (9/132; 95% CI: 3.2, 12.5) in the PD L1 low/negative subgroup. A DCR of 49.8% (103/207; 95% CI: 42.8, 56.8) was observed. The median TTR was 7.2 weeks. The median DOR was not reached. Among the 30 responders, 25 (83.3%) had an ongoing response and 11 (36.7%) patients responded for at least 24 weeks. Median PFS per BICR (As-treated Population) was 3.4 months (95% CI: 1.7, 3.5) in the total group, 5.4 months

(95% CI: 3.4, not estimable) in the PD-L1 high subgroup, and 1.7 months (95% CI: 1.7, 3.5) in the PD-L1 low/negative subgroup. The median OS was not reached; however, the overall OS rate at 6 months was 68.0% (95% CI: 60.3, 74.5) and higher in the PD-L1 high (81.2%) vs the PD L1 low/negative (61.3%) subgroup.

Study D4190C00022: As of the 13 January 2017, 40 patients with HCC were evaluable for response at ≥16 weeks follow-up. Confirmed ORR was 17.5% (95% CI: 7.3, 32.8). The median TTR was 8 weeks (range, 7.6 to 24 weeks). The DCR (defined as any CR + PR + SD >16 weeks) was 57.5% (95% CI: 40.9, 73.0).

1.2.4 Olaparib

Olaparib is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. The indication is approved under accelerated approval based on objective response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB version 17.0). Olaparib (AZD2281, KU-0059436) is a potent Poly-adenosine 5'diphosphoribose [poly (ADP ribose] polymerization (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 tumors 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). Tumors with HR deficiencies (HRD), such as serous ovarian cancers, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib has been shown to inhibit selected tumor 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. Cells deficient in homologous recombination DNA repair factors, notably BRCA1/2, are particularly sensitive to olaparib treatment.

PARP inhibitors such as olaparib may also enhance the DNA damaging effects of chemotherapy (31-33). For further information please refer to the current version of the olaparib IB (Version 17.0).

1.3 Risks and/or Benefits

The proposed study focuses on evaluating the safety of the combination of durvalumab and tremelimumab with olaparib and the expanded cohort will determine the efficacy of this

combination in treating recurrent ovarian cancer. There is a sound rationale to combine these drugs (**Section 2**) and the results from this study will form the basis for decisions for future studies.

1.3.1 Potential Benefits

1.3.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors.

NSCLC cohort: Overall, clinical activity was observed in both the PD-L1 high (defined as having tumor cells [TC] ≥25%) and PD-L1 low/negative (defined as TC <25%) subgroups, however, patients with PD-L1 high tumors had higher objective response rates (ORRs). The ORR per blinded independent central review [BICR] was 21.8% and 6.4% in patients with PD-L1 high and low/negative tumors, respectively and 15.3% in the overall population regardless of PD-L1 expression. ORR was 25.9%, 14.3% and 11.5% in the 1L, 2L and 3L+ cohorts, respectively. Median duration of response (DOR) was 17.74 months. Median overall survival (OS) was 12.4 months; median OS was 21.0, 11.8 and 9.3 months in the 1L, 2L and 3L+ cohorts, respectively. The OS rate at 24 months was 29.6%.

Head and neck squamous cell carcinoma (HNSCC) cohort: ORR per BICR was 7.3% across all patients, 16.7% in patients with PD-L1 high tumors and 2.9% in patients with PD-L1 low/negative tumors. Median OS was 8.4 months and the OS rate at 24 months was 24.2%.

UC cohort: The ORR per BICR was numerically higher in the PD-L1 high (TC ≥25% or IC ≥25%) subgroup (27.7%) compared with the PD-L1 low/negative (TC <25% and IC <25%) subgroup (5.9%); and 17.6% overall regardless of PD-L1 expression. The median OS was 10.5 months; the OS rate at 24 months was 30.0%.

Hepatocellular carcinoma (HCC) cohort: ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 10%. The median OS was 13.2 months; the OS rate at 24 months was 28.2%.

1.3.1.2 Tremelimumab

Across the clinical development program for tremelimumab, a pattern of efficacy has emerged that is similar to that of the related anti-CTLA-4 antibody, ipilimumab. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in patients who respond, the responses are generally durable, lasting several months even in those with aggressive tumors such as refractory metastatic melanoma. Summary efficacy data for completed studies are presented in Table 10 of IB Edition 9.

1.3.1.3 Durvalumab plus Tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.2.3 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, 2013 (38) suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma.

Study D4190C00006 (NSCLC): In the dose expansion Cohort A (treatment-naive NSCLC selected by PD-L1 status), the ORR was 15.6% (7/45; 95% CI: 6.5, 29.5). ORRs were 16.7% (3/18; 95% CI: 3.6, 41.4) and 12.0% (3/25; 95% CI: 2.5, 31.2) in the PD L1 high and PD-L1 low/negative groups, respectively. Median OS was not reached, with an OS rate at 6 months of 83.6%. In the dose expansion Cohort B co-administration group (immunotherapy-naïve, 1L or 2L patients with NSCLC), no objective responses were observed per investigator assessment. A best overall response of SD was observed for 9 of the 19 patients (DCR 47.4%; 95% CI: 24.4, 71.1). In the dose expansion Cohort B sequential administration group (2L patients with non-squamous NSCLC), the ORR per BICR was 18.8% (40/213; 95% CI: 13.8, 24.7); ORRs were 35.1% (20/57; 95% CI: 22.9, 48.9) and 11.8% (16/136; 95% CI: 6.9, 18.4) in the PD-L1 high and PD-L1 low/negative subgroups, respectively. Median PFS per BICR was 3.5, 7.1 and 3.3 months in the total, PD-L1 high and PD-L1 low/negative groups, respectively. The median OS was 15.4 months; the OS rate at 12 months was 53.8% and higher in the PD-L1 high (71.6%) vs the PD-L1 low/negative (47.3%) subgroup. In Cohort C (immunotherapy-pretreated, 2L to 4L patients with NSCLC), the ORR by investigator assessment was 5.1% (4/78; 95% CI: 1.4, 12.6); ORRs were 7.7% (2/26; 95% CI: 0.9, 25.1) and 2.9% (1/34; 95% CI: 0.1, 15.3) in the PD-L1 high and PD-L1 low/negative subgroups, respectively. Median PFS was 1.8, 1.7 and 1.7 months in the total, PD-L1 high and PD-L1 low/negative groups, respectively. The median OS was 8.4 months; the OS rate at 12 months was 34.1% and was similar in the PD-L1 high (31.5%) vs the PD-L1 low/negative (29.8%) subgroup.

To date, no assay has been established or validated, and no single approach has proven accurate, for patient enrichment for checkpoint blockade. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor infiltrating cells may be associated with greater clinical benefit.

Data from ongoing studies with durvalumab and other agents targeting the PD-1/PD-L1 pathway suggest, as shown in a number of tumor types (e.g., NSCLC, renal cell carcinoma, and melanoma), that monotherapy may be more efficacious (in terms of ORR) in patients who are PD-L1-positive.

Given these findings, a number of ongoing studies are assessing the activity of agents in patients with PD-L1–positive tumors. There is also an unmet medical need in patients with PD-L1–negative tumors that needs to be addressed. Data, as of 27 January 2015 from Study 006 show that with the addition of tremelimumab to durvalumab, the ORR can be increased to 25% in patients with PD-L1 negative NSCLC. As patients with PD-L1 positive disease can also have an increase in ORR, from 25% with durvalumab monotherapy, to 36% with the combination of durvalumab and tremelimumab, the study will enroll all patients with NSCLC, with an emphasis on those determined to be PD-L1 negative.

1.3.1.4 Olaparib

The efficacy of olaparib was investigated in a single-arm study in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced cancers. A total of 137 patients with measurable, gBRCAm-associated ovarian cancer treated with three or more prior lines of chemotherapy were enrolled. All patients received olaparib at a dose of 400 mg (capsule) twice daily as monotherapy until disease progression or intolerable toxicity. Objective response

rate (ORR) and duration of response (DOR) were assessed by the investigator according to RECIST v1.1. ORR was 34%, complete response (CR) in 2%, partial response (PR) in 32% with a median DOR of 7.9 months.

The median age of the patients was 58 years, the majority were Caucasian (94%) and 93% had an ECOG PS of 0 or 1. Deleterious or suspected deleterious, germline BRCA mutation status was verified retrospectively in 97% (59/61) of the patients for whom blood samples were available by the companion diagnostic BRACAnalysis CDxTM, which is FDA approved for selection of patients for olaparib treatment.

1.3.2 Potential Risks

1.3.2.1 Durvalumab

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.

Monotherapy pool: Safety data have been pooled for 3 durvalumab monotherapy studies (CD-ON-MEDI4736-1108, PACIFIC, D4191C00003 [ATLANTIC], D4191C00004

[ARCTIC], D4190C00002, D4193C00001 [HAWK], D4193C00003 [CONDOR] and MYSTIC) for patients who received a durvalumab dose of 10 mg/kg Q2W or 20

mg/kg Q4W; a total of 2769 patients are included in this validated pooled data set.

- Overall, AEs reported in ≥15% of patients were fatigue, decreased appetite, cough, nausea dyspnea, constipation and diarrhea; AEs considered by the investigator as related to durvalumab in ≥5% of patients were fatigue, diarrhea, hypothyroidism, pruritus, nausea, decreased appetite and rash.
- A total of 44.5% patients reported AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher: Grade 3, 4 and 5 (fatal) events were reported in 34.5%, 4.7% and 5.2% patients, respectively; Grade 3, 4 and 5 (fatal) events considered related to durvalumab were reported in 9.9%, 1.0% and 0.6% patients, respectively.
- Grade 3 or 4 events occurring in ≥2% of patients were anemia, dyspnea, hyponatremia, fatigue, pneumonia and gamma-glutamyltransferase (GGT) increased; Grade 3 or 4 events considered related to durvalumab occurring in ≥0.5% patients were fatigue, GGT increased, pneumonitis and aspartate aminotransferase (AST) increased.
- The most common Grade 5 events were general physical health deterioration (0.5% patients), respiratory failure, pneumonia and sepsis (0.4% patients each). The only Grade 5 events considered related to durvalumab occurring in ≥2 patients were pneumonitis and respiratory failure.
- A total of 9.4% patients discontinued from study treatment due to an AE. The most common events leading to treatment discontinuation (≥5 patients) were pneumonitis,

pneumonia, dyspnea, general physical health deterioration, interstitial lung disease (ILD), radiation pneumonitis, sepsis and anemia.
- A total of 6.5% patients had serious AEs (SAEs) that were considered by the investigator as related to durvalumab.
- A total of 53.4% patients experienced an AESI. The most common grouped term AESI was diarrhea (16.9% patients; of whom 0.7% had events of Grade ≥3). Other common AESIs (>10%; grouped term) were dermatitis (15.1% patients; of whom 0.2% had events of Grade ≥3); rash (14.5% patients; of whom 0.6% had events of Grade ≥3); hypothyroid events (11.3% patients; of whom 0.2% had events of Grade ≥3); and hepatic events (10.9% patients; of whom 3.8% had events of Grade ≥3).

PACIFIC: Overall durvalumab monotherapy (10 mg/kg Q2W) was well-tolerated and had a manageable safety profile relative to the standard of care (SoC) in this placebo-controlled study where durvalumab or placebo was given to patients following concurrent chemoradiation to the chest for stage IIIA/IIIB unresectable NSCLC. Generally, the type, incidence, and severity of AEs were comparable between the durvalumab and placebo treatment groups. Where not comparable, the type, incidence, and severity of events were consistent with the established durvalumab safety profile to date (safety monotherapy pool). The exception to this was for events of pneumonitis/radiation pneumonitis, for which, as expected in this patient population, there was a high background incidence. However, despite a numerical increase in these events for patients receiving durvalumab over those receiving placebo, most of these events were low grade. Clinically important CTCAE Grade 3 or 4 events were infrequent and balanced between the 2 treatment groups.

The data incidences for this study are provided in the format of durvalumab vs placebo arms respectively. Safety data is presented based on a DCO of 22 March 2018.

- AEs experienced during the study with an incidence of >15% were cough (35.2% vs 25.2%); fatigue (24.0% vs 20.5%); dyspnea (22.3% vs 23.9%); radiation pneumonitis (20.2% vs 15.8%); and diarrhea (18.5% vs 19.7%) and pyrexia (15.2% vs 9.4%). Combined events of pneumonitis or radiation pneumonitis occurred in 33.9% vs 24.8% of patients.
- CTCAE Grade 3 or 4 AEs were reported in 32.6% vs 28.2% of patients. CTCAE Grade 3 pneumonitis or radiation pneumonitis occurred in 3.6% vs 3.0% of patients and there were no Grade 4 events.
- SAEs were reported in 29.1% vs 23.1% of patients.
- AEs with an outcome of death were comparable between treatment groups (4.4% vs 7.2%). The only AEs with an outcome of death experienced by >1 patient in the durvalumab arm were pneumonitis and cardiac arrest. Fatal events of pneumonitis or radiation pneumonitis were balanced between the 2 treatment groups.
- A total of 15.4% vs 9.8% of patients had an AE that led to permanent discontinuation of treatment. AEs leading to discontinuation reported in ≥2 patients were pneumonitis (4.8% vs 2.6%), radiation pneumonitis (1.3% vs 1.3%) and pneumonia (1.1% vs 1.3%).
- A total of 66.7% vs 49.1% of patients experienced an AESI. AESIs, grouped terms, with an overall incidence >15% were dermatitis or rash (33.1% vs 18.4%) and diarrhea (18.5%

vs 20.1%). A total of 9.1% vs 3.4% of patients experienced CTCAE Grade 3 or 4 AESIs. AESIs with an outcome of death occurred in 4 patients (0.8%) treated with durvalumab (all pneumonitis events) and 5 patients (2.1%) treated with placebo (4 patients [1.7%] with pneumonitis and 1 patient [0.4%] with eosinophilic myocarditis).

Consistent with the immune-mediated mechanism of action for durvalumab, there was a higher incidence of imAEs for patients receiving durvalumab (24.4% vs 8.1% of patients).

1.3.2.2 Tremelimumab

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include: potentially immune-mediated gastrointestinal (GI) events including enterocolitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; hepatitis including autoimmune hepatitis and increased serum ALT and AST; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratory tract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target.

To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma).

Based on a data cutoff date of 24 January 2016, in Study D4880C00003 (DETERMINE; mesothelioma), the proportion of patients with any AE (95.8% in the tremelimumab 10 mg/kg vs 94.7% in the placebo group) and with AEs with an outcome of death (9.5% vs 6.3%, respectively) were similar between tremelimumab and placebo groups. The proportion of patients with AEs ≥Grade 3 (64.7% in the tremelimumab 10 mg/kg group vs 48.1% in the placebo group), SAEs (57.4% vs 45.0%) and AEs leading to discontinuation of treatment (27.4% vs 5.3%) were higher compared with the placebo group.

In the TMMD pool, at the dose of tremelimumab 10 mg/kg Q4W used in Study D4880C00003 (DETERMINE), a lower proportion of patients in the melanoma group had AEs leading to discontinuation of treatment (18.2%) compared with patients in the mesothelioma group (27.4%). Overall, the incidence of AEs ≥Grade 3 (47.0% vs 64.7% in mesothelioma group) and SAEs (43.9% vs 57.4% in mesothelioma group) in patients with melanoma were generally lower than in patients with mesothelioma.

In the TST pool 15 mg/kg group, and overall, the proportion of patients with any AE was similar to the TMMD pool.

1.3.2.3 Durvalumab plus Tremelimumab

No safety studies in animals have been performed combining tremelimumab with durvalumab. As both CTLA-4 and PD-L1 have mechanisms of actions that enhance activation of immune cells, their potential to induce cytokine release was tested in a whole-blood assay system. Durvalumab and tremelimumab, either alone or in combination, did not induce cytokine release in blood from any donor.

Durvalumab + tremelimumab pool: Safety data have been pooled for 9 durvalumab and tremelimumab combination studies (D4190C00002, D4190C00006, D4190C00010, D4190C00011, D4190C00021, D4190C00022, CONDOR, MYSTIC, and ARCTIC) for patients who received a dose of 20 mg/kg durvalumab plus 1 mg/kg tremelimumab, or equivalent durvalumab 1500 mg + tremelimumab 75 mg fixed dose; a total of 1822 patients are included in this pooled data set.

- Overall, AEs reported in ≥15% of patients were fatigue, diarrhea, decreased appetite, nausea, pruritus, dyspnea, constipation, anemia, pyrexia and, vomiting. AEs reported in ≥5% of patients that were considered by the investigator as treatment-related were fatigue, pruritus, diarrhea, decreased appetite, rash, nausea, hypothyroidism, lipase increased, rash maculo-papular, hyperthyroidism, pyrexia, amylase increased and, asthenia.
- A total of 63.7% patients reported AEs of Grade 3 or higher: Grade 3, 4 and 5 (fatal) events were reported in 39.6%, 8.1% and 16.0% patients, respectively; Grade 3, 4 and 5 (fatal) events considered related to durvalumab were reported in 20.0%, 3.6% and 0.7% patients, respectively.
- AEs ≥Grade 3 occurring in ≥2% of patients were anemia, hyponatremia, lipase increased, pneumonia, dyspnea, diarrhea hypokalemia, fatigue, GGT increased, amylase increased, asthenia, AST increased, dehydration, colitis, pulmonary embolism, abdominal pain, hyperglycemia, nausea, alanine aminotransferase (ALT) increased and, back pain; ≥ Grade 3 events considered treatment-related occurring in ≥1% patients were lipase increased, diarrhea, amylase increased, colitis, fatigue, pneumonitis, hyponatremia, AST increased, ALT increased.
- A total of 17.1% patients had SAEs that were considered treatment-related by the investigators.
- A total of 15.5% patients discontinued from study treatment due to an AE. The most common events leading to treatment discontinuation were colitis, diarrhea, pneumonitis and bladder cancer.
- A total of 68.6% patients had AESIs. The most common grouped term AESI was dermatitis/rash (38.4% patients, of whom 1.4% had events of Grade ≥3). Other common (>10%) AESIs by grouped term were diarrhea/colitis (28.5% patients, of whom 5.8% had events of Grade ≥3); hepatic events (15.5% patients, of whom 5.7% had events of Grade ≥3); hypothyroid events (11.5% patients, of whom 0.2% had events of Grade ≥3); and pancreatic events (11.5% patients, of whom <6.9% had events of Grade ≥3).

In the literature (38), using the combination of the same class of drugs (e.g., anti PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with

malignant melanoma, the safety profile of this combination had shown occurrences of AEs assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with Grade 3 or 4 events assessed by the Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment-related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment-related in the combination therapy included hepatic events (in 15% of patients), GI events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

1.3.2.4 Olaparib

Olaparib 400 mg (capsule) twice daily as monotherapy, has been studied in 300 patients with gBRCA-mutated advanced ovarian cancer, and 223 of these patients had received 3 or more prior lines of chemotherapy. In the 223 patients with gBRCA-mutated ovarian cancer who received 3 or more prior lines of chemotherapy (including 137 patients in Study 1 with measurable disease) adverse reactions led to dose interruption in 40% of patients, dose reduction in 4%, and discontinuation in 7%. There were 8 (4%) patients with adverse reactions leading to death, two were attributed to acute leukemia, and one each was attributed to COPD, cerebrovascular accident, intestinal perforation, pulmonary embolism, sepsis, and suture rupture. Adverse reactions reported in ≥20% of 223 patients (in 6 studies) with gBRCA-mutated advanced ovarian cancer who had received 3 or more prior lines of chemotherapy who were treated with olaparib 400 mg twice daily were anemia, abdominal pain/discomfort, decreased appetite, nausea, vomiting, diarrhea, dyspepsia, fatigue/asthenia, nasopharyngitis, upper respiratory infection, arthralgia, and myalgia. Abnormal laboratory findings were decrease in hemoglobin, absolute neutrophil count, platelets, lymphocytes, mean corpuscular volume elevation and, increase in creatinine. The median exposure to olaparib in these patients was 158 days. The following adverse reactions and laboratory abnormalities have been identified in ≥10 to <20% of the 223 patients receiving olaparib and not included in the table: cough, constipation, dysgeusia, peripheral edema, back pain, dizziness, headache, urinary tract infection, dyspnea, and rash. The following adverse reactions and laboratory abnormalities have been identified in ≥1 to <10% of the 223 patients receiving olaparib and not included in the table: leukopenia, stomatitis, peripheral neuropathy, pyrexia, hypomagnesemia, hyperglycemia, anxiety, depression, insomnia, dysuria, urinary incontinence, vulvovaginal disorder, dry skin/ eczema, pruritis, hypertension, venous thrombosis (including pulmonary embolism), and hot flush.

In a randomized trial of olaparib 400 mg (capsule) twice daily as maintenance monotherapy (53 patients) compared to placebo (43 patients) in patients with platinum sensitive, relapsed, high-grade serous ovarian cancer following treatment with 2 or more platinum-containing regimens, the median duration on treatment with laparib was 11.1 months for patients with a gBRCA mutation compared to 4.4 months for patients with gBRCA mutation on placebo. Adverse reactions led to dose interruptions in 26% of those receiving olaparib and 7% of those receiving placebo; dose reductions in 15% of olaparib and 5% of placebo patients; and discontinuation in 9% of olaparib and 0% in placebo patients. One (2%) patient on olaparib died as a result of an adverse reaction.

Adverse Reactions Reported in ≥20% of Patients with gBRCA-Mutated Ovarian Cancer in the Randomized Trial were anemia, abdominal pain/discomfort, decreased appetite, nausea, vomiting, diarrhea, dyspepsia, fatigue/asthenia, nasopharyngitis, upper respiratory infection, arthralgia, myalgia, back pain, headache, cough and dermatitis/rash. Laboratory Abnormalities observed were decrease in hemoglobin, absolute neutrophil count, platelets, mean corpuscular volume elevation, and increase in creatinine.

Myelodysplastic syndrome/Acute Myeloid Leukemia (overall 22 out of 2618 patients i.e. 1%) and pneumonitis (<1%) occurred in patients exposed to olaparib, and some cases were fatal.

Potential overlapping toxicity between olaparib, durvalumab, and tremelimumab are: diarrhea, enterocolitis, myalgia, arthralgia, fatigue, and rash. However, based on published studies, anti-CTLA-4 appears to be associated with more frequent and severe side effects.

1.3.2.5 Fixed Dosing for Durvalumab and Tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) [Wang et al. 2014]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (39-42). Wang and colleagues (41) investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters (42).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a

fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Fixed dosing of durvalumab and tremelimumab is recommended only for subjects with > 30 kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule.

1.3.2.6 Dose for Olaparib

Olaparib capsule formulation is approved in the United States as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy at a dose of 400 mg BID (capsule form). The indication is approved under accelerated approval based on objective response rate and duration of response.

A tablet formulation of olaparib has been used in all newer clinical trials with a recommended monotherapy dose of 300 mg BID.

1.4 Research Hypothesis

The combination of olaparib, durvalumab, and tremelimumab will be safe and, tolerable with acceptable toxicity.

The combination of olaparib, durvalumab, and tremelimumab will improve the PFS in patients with BRCA germline and/or somatic mutations who have platinum- sensitive or platinum-resistant ovarian cancer.

The combination of olaparib, durvalumab, and tremelimumab will improve the antitumor response in patients with BRCA germline and/or somatic mutations who have recurrent platinum-sensitive or platinum-resistant ovarian cancer.

The combination of olaparib, durvalumab, and tremelimumab will have significant effects on the density, location, and antitumor properties of immune cells in the ovarian tumor microenvironment.

2 STUDY RATIONALE

Epithelial ovarian cancer (EOC) is the leading cause of mortality related to gynecologic cancer in USA with a majority of patients presenting with advanced disease at the time of diagnosis. There is an urgent need for the development of alternative therapies given the poor response of recurrent disease to available therapies. The current study focuses on evaluating the MTD and safety profile of a novel combination of three drugs.

PD-L1 has a role in the clinical course of ovarian cancer by affecting the local immune microenvironment and that interruption of the PD-1/PD-L1 pathway could restore effective antitumor immunity in ovarian cancer patients. The rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA 4 and PD-1 are non-redundant; suggesting that targeting both pathways may have additive or synergistic activity (30). In fact, combining

immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable (38). Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC (43), with further updated details presented in this clinical study protocol.

PARP inhibitors selectively kill cancer cells defective in DNA repair, specifically cancers with mutation in the breast cancer-associated genes, BRCA1 and BRCA2. Therefore, with non-redundant modes of action, targeting these three different pathways may have additive or synergistic activity leading to superior tumor control compared to monotherapy, thus improving progression free survival (PFS) and overall survival (OS) in women with recurrent/persistent platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers who carry a germline and/or somatic BRCA1 or BRCA2 Mutation.

2.1 Durvalumab plus Tremelimumab Combination Therapy Dose Rationale

The durvalumab + tremelimumab doses and regimen selected for this study are based on the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

In order to reduce the dosing frequency of durvalumab to align with the Q4W dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety, and efficacy profile, cohorts were narrowed to 15 and 20 mg/kg durvalumab Q4W. PK simulations from the durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUCss; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W durvalumab. The observed durvalumab PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median C_{max} at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{min,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

Monotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented PDx activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 mg/kg and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the Q2W schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg

tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the Q4W regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥3 AEs or treatment-related SAEs. No dose-limiting toxicities were reported.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab Q4W cohorts demonstrated objective responses at all doses of tremelimumab and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR), 1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD) (The fifth patient had only a single scan, which was conducted outside the window for these evaluations).

Additionally, of all cohorts, the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

2.2 Rationale for 4 Cycles of Combination Therapy Followed by Durvalumab Monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [Q3W] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained

through 10 years of follow up (44). Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

- Nivolumab (anti-PD-1) was dosed Q2W for up to 96 weeks in a large Phase I dose escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis (45, 46)
- Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis (47).
- MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported (38, 48)

Similar long-term results may be expected with use of other immune-mediated cancer therapeutics including anti-CTLA-4 antibodies such as tremelimumab, anti PD-L1 antibodies such as durvalumab, or the combination of the two.

2.3 Rationale for Combination Therapy Doses in this Study

Therefore, in this study, durvalumab will be given Q4W for up to 1 year, tremelimumab Q4W for the 1st 4 cycles in combination with olaparib (300 mg [or lower in the case of de-escalation] BID for up to 1 year).

3 STUDY OBJECTIVES

3.1 Primary Objectives

Phase I: The primary objective of the Phase I component of this study is:

- To assess the safety and toxicity of the combination of PARP inhibitor olaparib with anti-PD-L1 antibody durvalumab and anti-CTLA4 antibody tremelimumab.

Phase II: The primary objective of the Phase II component of this study is:

- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on PFS rates.

3.2 Secondary Objectives

- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on anti-tumor immune responses in patients with recurrent platinum sensitive or resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer who carry a germline and/or somatic BRCA1 or BRCA2 mutation and/or a homologous recombination deficiency (HRD).

- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on PFS and OS in patients with recurrent platinum sensitive or resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer who carry a germline and/or somatic BRCA1 or BRCA2 mutation and/or a HRD.

4 METHODOLOGY

4.1 Study Design Overview

This is an open-label Phase I/II study for combination of the PARP inhibitor olaparib with anti-PD-L1 antibody durvalumab and anti-CTLA4 antibody tremelimumab, utilizing a 3+3 design. Fixed doses of durvalumab (1500 mg Q4W for up to 1 year) and tremelimumab (75 mg Q4W for 4 cycles) will be utilized with the recommended dose of olaparib for BRCA mutated ovarian cancer (300 mg BID for up to 1 year) in the first 6 patients in a Phase I safety run part of this study (Safety lead-in Cohort) followed by a Phase II part of the study (expansion cohort), enrolling 27 additional subjects. In case of >1 DLT out of the 6 patients, tremelimumab will be eliminated from this combination study as many of the toxicities from durvalumab and tremelimumab overlap but based on published studies, tremelimumab is associated with more frequent and severe side effects. Data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. The dose of tremelimumab utilized here is the lowest effective dose and therefore de-escalation not recommended. If the DLT is olaparib related, de-escalation plan is to decrease to 250 mg and then to 200 mg as shown in **Table 1**, following the 3+3 rule.

Update: The Phase 1 portion of this study has been completed and reviewed. 6 patients were treated at Dose level -1 (durvalumab 1500 mg + tremelimumab 75 mg + Olaparib 250 mg) with no dose limiting toxicities observed. Based on this, the dose for the Phase II Expansion cohort was determined as **durvalumab 1500 mg IV** Q4W up to 1 year + **tremelimumab 75 mg IV** Q4W 4 cycles + **olaparib 250 mg PO** BID up to 1 year.

Table 1 Treatment of Algorithm on True DLT Risk

Phase I:

<table>
<tr><th>Cohort</th><th>Dose Level</th><th>N</th><th># of DLTs*</th><th colspan="2">Action Based on # of DLTs</th><th>Total #</th></tr>
<tr><td rowspan="6">Phase I Lead-in cohort</td><td rowspan="6">durvalumab 1500 mg + tremelimumab 75 mg + olaparib 300 mg</td><td rowspan="6">3</td><td>0, 1</td><td>+ 3</td><td>1/6 DLT: Phase II Expansion cohort</td><td rowspan="6">6 to 12 depending on DLTs</td></tr>
<tr><td>≥ 2</td><td colspan="2">Eliminate tremelimumab: Phase II-T Expansion cohort
or
If DLT due to olaparib, dose de-escalate olaparib as follows:</td></tr>
<tr><td rowspan="4"></td><td rowspan="4">+3

durvalumab 1500 mg + tremelimumab 75 mg + olaparib 250 mg</td><td>0/3 DLT: Phase II-O Expansion cohort: durvalumab 1500 mg + tremelimumab 75 mg + olaparib 250 mg</td></tr>
<tr><td>1/3 DLT:
+3 at same dose</td></tr>
<tr><td>1/6 DLT: Phase II-O Expansion cohort: durvalumab 1500 mg + tremelimumab 75 mg + olaparib 250 mg</td></tr>
<tr><td>≥2/3 or ≥2/6 DLTs: +3 with further de-escalation: durvalumab 1500 mg + tremelimumab 75 mg + olaparib 200 mg</td></tr>
</table>

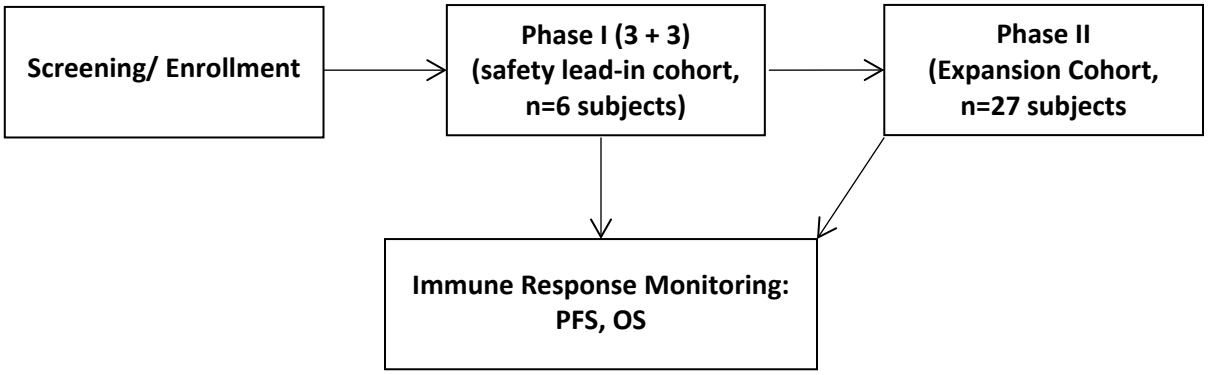
*DLT – dose limiting toxicity in the first two cycles of treatment.
For further description of Table 1, please refer to Section 6.3..

Phase II (Dose determined after completion of the Phase I portion of the study):

Cohort	Dose Level	N	# of DLTs	Action Based on # of DLTs	Total #
Phase II Expansion cohort (2:1 ratio of platinum-resistant to platinum-sensitive)	durvalumab 1500 mg + tremelimumab 75 mg + olaparib 250 mg	27	N/A	N/A	18 platinum-resistant and 9 platinum-sensitive)

The study schema is depicted in Figure 1.

Figure 1 Study Schema



Enrollment into the study will be at a 2:1 ratio of platinum-resistant to platinum-sensitive disease only in the Phase II study. Enrollment into the safety lead-in cohort of the Phase I part will not be constrained to a 2:1 ratio of platinum-resistant to platinum-sensitive disease. Estimated total sample size including the Phase I lead-in and Phase II expansion cohorts, n = 33 to 39. It has been observed that ovarian cancer patients with BRCA1 and BRCA2 mutations tend to be more sensitive to platinum agents and possibly PARP inhibitors than wild-type BRCA ovarian cancers. In an initial proof-of-concept study of 50 BRCA1/BRCA2-mutated patients treated with 200 mg BID olaparib, objective response rates for platinum-sensitive and platinum-resistant cases were 46% and 33%. Therefore, in this combination drug therapy study, the Phase II study is planned to enroll at a 2:1 ratio of platinum-resistant to platinum-sensitive disease.

Durvalumab will be administered every 4 weeks (Q4W) for up to 1 year (13 cycles) and tremelimumab will be administered every 4 weeks (Q4W) for up to 4 doses/cycles. Olaparib will be administered 300 mg BID (or lower in the event of de-escalation) for up to 1 year. Study treatments will be continued for up to 1 year or until disease progression, whichever occurs sooner. Each cycle for durvalumab and tremelimumab is 4 weeks. Olaparib is continuous dosing. For the first 4 cycles (16 weeks), a patient will receive all three drugs and then continue with only

durvalumab (9 more cycles) with daily olaparib. In the event of disease progression while the patient is receiving durvalumab and Ooaparib alone (i.e. after completion of the first 4 doses of tremelimumab), the patient may be given an additional 4 doses of tremelimumab per the investigator's discretion in combination with the ongoing durvalumab and olaparib.

Primary Endpoint

- Phase I component: Safety and tolerability: DLTs will be defined based on the rate of drug-related grade 3-5 adverse events. These will be assessed using the NCI CTCAE v4.0.
- Phase II component: To assess the impact of the combination of olaparib with durvalumab and tremelimumab on PFS rates compared the PFS achieved with the last treatment.

Secondary Endpoints

- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on anti-tumor immune responses
- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on OS
- Assessment of anti-tumor immune response of the treatment combination by evaluating translational and correlative biomarker endpoints. Archival tissue and on-treatment tumor biopsies and peripheral blood will be utilized for this assessment.
- Olaparib treatment of BRCA1/2+ve platinum resistant ovarian cancer patients leads to the release of a unique repertoire of tumor antigens that will be cross-presented to the immune system leading to generation of humoral and T cell responses. We will initially focus on auto-antibody analysis of pre- and post- treatment samples from the patients on the clinical trial, using a previously validated "seromics" approach by our group (Gnjatic et al, 2010)(49). The results generated by the analysis of pre- and post-treatment sera may be useful individually or as signature sets as (i) diagnostic markers, preferentially immunogenic in HR-deficient ovarian cancer, (ii) prognostic markers, associated with favorable or unfavorable clinical outcome in HR-deficient ovarian cancer, and (iii) potential targets of immune responses for the development of new immunotherapeutic reagents in HR-deficient ovarian cancer.
    - Immunoscore: archival and on-treatment biopsies.
    - Analysis of T-cell responses.
    - Analysis of potential resistance mechanism: sequencing studies (e.g. for HR deficiency), gene expression studies and analysis for secondary genetic and epigenetic events.

All participants will sign an informed consent prior to study related tests. All participants will meet the inclusion and exclusion criteria summarized in **Section 5.1** and **Section 5.2**.

4.2 Target Accrual and Study Duration

A maximum of 36 participants at multiple sites, including RPCI will be enrolled.

During the initial enrollment of the first two patients in dose level 1, due to the safety assessments after the first patients, there is a waiting period of at least 4 weeks before the second patient can be enrolled. Assuming an average enrollment of 1 patient per site per month:

- Enrollment Period: 12 months
- Duration of Treatment: 12 months
- Length of Study: 24 months.
- Accrual is expected to take up to 4 years.

4.3 Replacement of Participants

Patients who are not considered fully evaluable per protocol for the primary objective of safety and tolerability may be replaced. The period for evaluating DLTs will be from the time of first administration of durvalumab, tremelimumab, and olaparib until at least two cycles of durvalumab (8 weeks). Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. The compliance requirement for olaparib is 75% of the planned dose during the first 8 weeks. This applies to both Phase I and Phase II part of the study. There will be no replacement of patients during retreatment.

5 PARTICIPANT SELECTION

5.1 Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Patients must have platinum-sensitive or platinum-resistant recurrent or persistent or refractory ovarian, fallopian tube, or primary peritoneal carcinoma AND have one or more of the following characteristics documented on a validated platform (documented genetic test report is required). Historic report is permitted.
    a. A germline *BRCA1* or *BRCA2* deleterious alteration.
    b. A somatic mutation in *BRCA1* or *BRCA2* detected in a tumor sample or on circulating tumor DNA.
    c. Carry a known or likely loss of function alteration in one or more of homologous recombination or mismatch repair pathway genes (See Table below for the list of genes).
    d. Demonstrate a genomic phenotype of HR deficiency as measured by a LOH-high score.

Gene List			
ATM	CDKN2A	FANCO	PTEN
ATR	CHEK1	FANCP	RAD50
BAP1	CHEK2	FAM175A (ABRA1)(ABRAXAS)	RAD51
BARD1	FANCA	MLH1	RAD51B
BMPR1A	FANCB	MRE11A	RAD51C
BRCA1	FANCC	MSH2	RAP80
BRCA2	FANCE	MSH6	RAD51D
BRCC36	FANCD2	MUTYH	RBBP8
BRCC45 (MERIT 40)	FANCF	NBN	RET
BRIP1 (FANCJ)	FANCG	PALB2 (FANCN)	STK11
CDH1	FANCI	PI3K	VHL
CDK4	FANCL	PMS2	XRCC2
CDK12	FANCM	PRSS1	XRCC3

Recurrent ovarian cancer is defined as recurrence of disease in a patient who achieved initial complete response to primary therapy.

Persistent ovarian cancer is defined as having residual disease in the form of elevated tumor markers or microscopic or clinically evident disease in a patient who has completed and apparently responded to initial chemotherapy.

Refractory ovarian cancer is defined as patients who have failed to achieve at least a partial response to therapy including patients with either stable disease or disease progression during primary therapy.

Platinum-sensitive is defined as achievement of documented response to initial platinum-based treatment and has been off treatment for an extended period of time (more than 6 months).

Platinum-resistant is defined as relapse within 6 months of last platinum-based chemotherapy or progression while on platinum-based therapy.

2. All patients must have measurable disease as defined by irRECIST. Measurable disease is defined as 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non- nodal lesions and ≥ 15 mm in short axis for nodal lesions, 20 mm by chest X-ray, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).
3. Must have archival tissue available for PD-L1 assessment.
4. Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).

5. Patients who have the following risk factors are considered to be at increased risk for cardiac toxicities and may be enrolled only with increased monitoring (refer to Table 5, footnote 5): i) prior treatment with anthracyclines, ii) prior treatment with trastuzumab, iii) a New York Heart Association classification of II controlled with treatment, iv) prior central thoracic radiation therapy (RT), including RT to the heart.
6. Any hormonal therapy being taken as a treatment for cancer must be discontinued at least one week prior to registration. Continuation of hormone replacement therapy e.g. thyroid hormone replacement therapy is permitted.
7. Able to tolerate oral medications and no GI illnesses that would preclude absorption of olaparib.
8. Female patients, age ≥ 18 years at time of study entry.
9. Have an ECOG Performance Status of 0-1. Refer to Appendix B**.**
10. Life expectancy of > 6 months.
11. Adequate normal organ and marrow function as defined below:
    - Hemoglobin ≥ 10 g/dL (no blood transfusion in the 28 days prior to entry (olaparib guidelines)
    - WBC > 3 x 10^9/L
    - 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). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician
    - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
    - Creatinine ≤ 1.5 x ULN or, Serum Creatinine CL > 51 mL/min (by the Cockcroft-Gault equation: see Appendix L).
12. Female subjects must either be of non-reproductive potential (i.e., 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 within 28 days of study treatment, confirmed prior to treatment on day 1.
13. Participants of child-bearing potential must agree to use two highly effective and acceptable forms of contraception from screening, throughout their participation in the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after last dose of durvalumab or olaparib, whichever is the longer time period (e.g., hormonal or barrier method of birth control). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

14. Participant or legal representative must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.
15. 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.

5.2 Exclusion Criteria

Participants will be excluded from this study for the following:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrollment in the present study.
2. Participation in another clinical study with an investigational product during the last 4 weeks (prior use of bevacizumab in the upfront setting is allowed).
3. History of discontinuation of any previous treatment with PARP inhibitors, including olaparib, or a PD-1 or PD-L1 inhibitor, including durvalumab or anti-CTLA4 antibody, including tremelimumab due to toxicity.
4. Patients with myelodysplastic syndrome/acute myeloid leukemia.
5. History and/or confirmed ILD/pneumonitis, extensive bilateral lung disease on HRCT scan.
6. Concomitant use of a strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, ketoconazole, voriconazole, nefazodone, posaconazole, ritonavir, lopinavir/ritonavir, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) and moderate CYP3A inhibitors (e.g., amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole. Fosamprenavir, imatinib, verapamil).
7. Concomitant use of strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) and moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin).
8. History of another primary malignancy except for:
    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence.
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease (e.g. basal cell or squamous cell carcinoma of the skin).
    - Adequately treated carcinoma in situ without evidence of disease (e.g., breast and cervical cancer in situ).
9. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies,

radiotherapy or other investigational agent) ≤ 21 days prior to the first dose of study drug and within 6 weeks for nitrosourea or mitomycin C).

10. Mean QT interval corrected for heart rate (QTcF) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
11. Patients with history of myocardial infarction within 6 months.
12. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
13. Any unresolved toxicity (CTCAE grade ≥2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).
14. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.
15. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
16. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
17. Patients with thyroid dysfunction if not adequately controlled.
18. History of primary immunodeficiency.
19. History of allogeneic organ transplant.
20. History of hypersensitivity to durvalumab, tremelimumab, olaparib or, any excipient.
21. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of, or test positive for, acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
22. Known history of previous clinical diagnosis of tuberculosis.
23. History of leptomeningeal carcinomatosis.
24. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab (e.g. LAIV, MMR, VAR, Zoster, yellow fever etc.).
25. Female subjects who are pregnant, breast-feeding, or of reproductive potential who are not employing an effective method of birth control from screening to 180 days after the last

dose of durvalumab + tremelimumab + olaparib combination therapy or 90 days after the last dose of durvalumab and olaparib therapy, whichever is the longer time period.

26. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results or, is an unsuitable candidate to receive study drug (e.g. inability to tolerate oral medications which would preclude absorption of olaparib).
27. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
28. Subjects with uncontrolled seizures.
29. Dependency on IV hydration or TPN.

5.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this study.

6 TREATMENT PLAN

6.1 Dosing and Administration

Patients will receive IV infusions of fixed doses of durvalumab (1500 mg Q4W for up to 13 doses/cycles) and tremelimumab (75 mg Q4W for up to 4 doses) in combination with olaparib (300 mg BID or lower in case of de-escalation) orally. Study drugs will be continued for up to 1 year or until disease progression, whichever occurs sooner. After Phase I completion, dose of olaparib for Phase II was determined to be 250 mg BID.

For cohorts receiving all 3 drugs (durvalumab, tremelimumab, and olaparib):

In the event that the patient experiences disease progression during the time that they are receiving durvalumab and olaparib alone (i.e. after first 4 doses of tremelimumub have been completed), an additional 4 doses of tremelimumab may be added to ongoing durvalumab and olaparib at the investigator's discretion.

6.2 Treatment Regimens

6.2.1 Durvalumab + Tremelimumab + Olaparib Combination Therapy

Patients will receive 1500 mg durvalumab via IV infusion Q4W for up to 13 doses/cycles and 75 mg tremelimumab via IV infusion Q4W for up to 4 doses/cycles. Olaparib will be given orally, 300 mg BID (or lower in case of de-escalation), for up to 12 months. Tremelimumab + durvalumab should be given at least 1 hour after the patient has taken their olaparib morning dose. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion.

A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent

infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study. For participants weighing ≤ 30 kg, refer to Appendix C (Durvalumab) and Appendix E (Tremelimumab).

6.2.1.1 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

- 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 and re-initiated at 50% of the initial rate until completion of the infusion.
- For patients 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.

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 patients to an intensive care unit if necessary.

6.2.1.2 Duration of Treatment and Criteria for Retreatment

For patients receiving durvalumab + tremelimumab + olaparib, retreatment is allowed (once only) for patients meeting the retreatment criteria below. The same treatment guidelines followed during the initial 12-month treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments. Similar to the initial treatment, in the event of disease progression while the patient is receiving durvalumab and olaparib alone (i.e. after completion of the first 4 doses of tremelimumab), the patient may be given an additional 4 doses of tremelimumab per the investigator's discretion, in combination with the ongoing durvalumab and olaparib.

Patients receiving the combination of durvalumab, tremelimumab, and olaparib may undergo retreatment in the clinical scenarios described below:

- Patients who achieve and maintain disease control (i.e., irCR, irPR, or irSD) through to the end of the 12-month treatment period may restart treatment with the combination upon evidence of PD according to irRECIST during follow-up.

- Before restarting their assigned treatment, the Investigator should ensure that the patient:
  - Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient.
  - Still fulfills the eligibility criteria for this study, including re-consenting to restart durvalumab, tremelimumab, and olaparib.
  - Has not have received an intervening systemic anticancer therapy after their assigned treatment discontinuation.
  - Has had a baseline tumor assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial 12 months of treatment (relative to the date of randomization) until study treatment is stopped (maximum of 12 months of further treatment).

During the retreatment period, patients receiving durvalumab + tremelimumab + olaparib may resume durvalumab dosing at 1500 mg Q4W with 75 mg of tremelimumab Q4W for 4 doses each. Patients will then continue with durvalumab monotherapy at 1500 mg Q4W, beginning at Week 16, 4 weeks after the last dose of combination therapy (a total of 9 additional doses). Olaparib will be administered throughout this retreatment period at 300 mg BID (or the MTD in case of dose de-escalation) for up to 1 year.

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. A patient with a confirmed progression receiving durvalumab + tremelimumab + olaparib cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy (Q4W dosing) and progression occurs in a target lesion that has previously shown a confirmed response.

Patients who AstraZeneca and/or the Investigator determine may not continue treatment will enter follow-up. There will be no replacement of patient during retreatment.

6.2.2 Olaparib

Subjects will be administered olaparib in line with normal clinical practice, at 300 mg BID, in combination with fixed doses of durvalumab and tremelimumab. It is expected that subjects will receive this combination therapy for up to 1 year or until disease progression, whichever occurs sooner. After completion of the Phase I portion of the study, the safe dose of olaparib to be used in the Phase II study for this combination therapy was determined to be 250 mg BID.

6.2.2.1 Dose administration

Patients will take 2 tablets of 150 mg each (total 300 mg), orally, twice daily. In case of the reduced 200 mg dose group, patients will take 2 tablets of 100 mg and for the 250 mg dose group, one 150 mg and one 100 mg tablet. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Durvalumab + tremelimumab should be given at least 1 hour after the patient has taken their olaparib morning dose.

6.2.2.2 Monitoring of dose administration

Patients will be monitored for the first dose, similar to as described for durvalumab and tremelimumab (refer to Section 6.2.1.1) and subsequent doses will be taken by the patient at home.

Reported adverse events (AEs) and potential risks are described in Section 1.3.2. Appropriate dose modifications are described in Section 6.5.

6.3 Cohort Management: Dose Escalation Decision Rules

Refer to **Section 4.1**

Fixed doses of durvalumab, tremelimumab, and olaparib will be used in the first 6 patients in a Phase I safety run part of this study (Safety lead-in Cohort) followed by a Phase II part of the study (expansion cohort), enrolling 27 additional subjects (18 platinum-resistant patients and 9 platinum-sensitive patients). In case of >1 DLT out of the 6 patients, tremelimumab will be eliminated from this combination study (The DLT must be related to tremelimumab). The dose of tremelimumab utilized here is the lowest effective dose and therefore de-escalation not recommended. If the DLT is olaparib related, de-escalation plan is to decrease to 250 mg and then to 200 mg as shown in **Table 1**, following the 3+3 rule.

6.4 Definition of Dose-Limiting Toxicity

Dose-limiting toxicities (DLTs) will be evaluated during the Phase I portion of the trial. The period for evaluating DLTs will be from the time of first administration of durvalumab, tremelimumab, and olaparib until two cycles of durvalumab (8 weeks). Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 5 × ULN or total bilirubin > 5 × ULN
- Bone marrow findings consistent with myelodysplastic syndrome/acute myeloid leukemia
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

6.5 Dose Modifications and Toxicity Management

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab or tremelimumab or olaparib along with appropriate continuing supportive care. If ≥2 DLTs due to tremelimumab, tremelimumab will be eliminated for the Phase II expansion cohort. There will be no dose adjustment.

In addition, there are certain circumstances in which durvalumab or tremelimumab should be permanently discontinued.

Management of toxicity of durvalumab and tremelimumab

Based on the mechanism of action of durvalumab or tremelimumab 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 closely 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 G.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 10.2. All toxicities will be graded according to NCI CTCAE v4.03.

Management of toxicity of olaparib

Any toxicity observed during the course of the study could be managed by interruption and/ or dose reduction of the dose if deemed appropriate by the Investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer than this the AstraZeneca study team must be informed. Olaparib must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (current version) grade 1 or less.

Where toxicity reoccurs following re-challenge with olaparib, 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 treatment with olaparib. Dose de-escalation will be to 250 mg BID and then to 200 mg BID if needed.

Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 adverse event occurs which the Investigator considers to be at least possibly related to administration of olaparib.

Management of anemia

Adverse events of anemia CTCAE grade 1 or 2 (Hemoglobin (Hb) > 8 g/dL) should be investigated and managed as deemed appropriate by the investigator with or without interruption of study drug or change in dose, taking into account previous history of anemia. Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded. In some cases, management of anemia may require blood transfusions. However, if a patient develops anemia CTCAE grade 3 (Hb < 8 g/dL) or worse, study treatment should be interrupted for up to maximum of 4 weeks to allow for bone marrow recovery and the patient should be managed appropriately. Study treatment can be restarted at the same dose if Hb has recovered to > 10 g/dL. Any subsequently required anemia related interruptions, considered likely to be dose related, or coexistent with newly developed neutropenia, and or thrombocytopenia, will require study treatment dose reductions by 250 mg bd as a first step and to 200 mg bd as a second step.

If a patient has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by investigator, study treatment should be permanently discontinued.

Management of neutropenia and leukopenia

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 CTC 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 of the last dose of study treatment.

Study treatment can be restarted at the same dose if an adverse event of neutropenia or leukopenia have been recovered up to CTC AE grade >1 (ANC > 1.5 x 109/L). Growth factor support should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF).

Any subsequent interruptions will require study treatment dose reductions.

Management of thrombocytopenia

An adverse event of thrombocytopenia should be managed as deemed appropriate by the investigator. If a patient develops thrombocytopenia CTCAE grade 3 or worse study treatment should be interrupted for a maximum of 4 weeks. In some cases, management of thrombocytopenia may require platelet transfusions. Platelet transfusions should be done according to local hospital guidelines.

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 CTC grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse neutropenia (ANC < 1 x 10^9/L)
- ≥2 week interruption/delay in study treatment due to CTC grade 3 or worse thrombocytopenia (Platelets < 50 x 10^9/L)

Weekly differential blood counts including reticulocytes (calculate reticulocyte index (RI), RI = reticulocyte count x hematocrit (Hct)/normal Hct; a value of 45 is usually used for normal Hct) and peripheral blood smear should be performed. 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.

Myelodysplastic syndrome and/or Acute Myeloid Leukemia (MDS/AML is an important potential risk for olaparib. 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. Study treatment should be discontinued if diagnosis of MDS/AML is confirmed.

The dose of olaparib **must not** be adjusted under any other circumstances unless the AstraZeneca Study Physician gives prior agreement.

Management of new or worsening pulmonary symptoms

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality occurs, an interruption in olaparib dosing is recommended and a diagnostic workup (including a high-resolution CT scan) should be performed, to exclude pneumonitis. Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then olaparib treatment can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the AstraZeneca Study Physician.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the eCRF.

Olaparib should be stopped before surgery and re-started after wound has healed following recovery.

No stoppage of olaparib is required for any biopsy procedures.

Olaparib should be discontinued for a minimum of 7 days before a patient undergoes therapeutic palliative radiation treatment.

Management of nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. They are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment with the incidence of nausea and vomiting not showing an increase over the treatment cycles.

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.

6.6 Restrictions, General Concomitant Medication and Supportive Care

6.6.1 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 1 **highly** effective method of contraception (Table 2) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab 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 patients should also refrain from breastfeeding throughout this period.

N.B.: Females of childbearing potential are defined as those who are not surgically sterile (i.e., 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 (i.e., less than 1% per year) when used consistently and correctly, are described in Table 2. Note that some contraception methods are not considered highly effective (e.g. 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).

Table 2 Highly Effective Methods of Contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[a]	• Etonogestrel implants (e.g. Implanon or Norplant) • Intravaginal device (e.g., ethinylestradiol and etonogestrel) • Medroxyprogesterone injection (e.g., 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 dose of durvalumab or tremelimumab or olaparib concomitant treatments.

Food Intake Restrictions

Avoid grapefruit and Seville oranges during olaparib treatment and 3 months following the last dose of trial treatment, which may increase olaparib plasma concentrations. Olaparib tablet formulation can be taken with no regard to food.

The Principal 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 eCRF.

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

6.6.2 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 6.6.3 below.

6.6.3 Excluded Concomitant Medications

The following medications are considered exclusionary during the study:

1. Any investigational anticancer therapy other than the protocol specified therapies
2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy).
3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
4. Live attenuated vaccines within 30 days of durvalumab and tremelimumab dosing (i.e., 30 days prior to the first dose, during treatment with durvalumab and tremelimumab for 30 days post discontinuation of durvalumab and tremelimumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.
5. Use of strong CYP3A inhibitors **must** be avoided: The use of any natural/herbal products or other "folk remedies" should be discouraged but use of these products, as well as use of all vitamins, nutritional supplements and all other concomitant medications must be recorded in the eCRF.
    - Olaparib is an FDA approved drug for the treatment of patients with deleterious germline BRCA mutated advanced ovarian cancer. Based on in vitro data and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. In vitro data have, however, also shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A4 and consequently, to ensure patient safety, the following potent inhibitors of CYP3A4 must not be used during this study for any patient receiving olaparib.
    - While this is not an exhaustive list, it covers the known potent inhibitors, which have most often previously been reported to be associated with clinically significant drug interactions: ketoconazole, itraconazole, ritonavir, idinavir, saquinavir, telithromycin, clarithromycin and nelfinavir. For patients taking any of the above, the required wash-out period prior to starting olaparib is one week.
6. Use of strong CYP3A inducers **must** be avoided: In addition, to avoid potential reductions in exposure due to drug interactions and therefore a potential reduction in efficacy, the following CYP3A4 inducers **must** be avoided: Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (*Hypericum perforatum*). For patients taking any of the above, the required wash-out periods prior to starting olaparib are: phenobarbitone 5 weeks, and for any of the others, 3

weeks. After randomization, if the use of any potent inducers or inhibitors of CYP3A4 are considered necessary for the patient's safety and welfare, the Investigator must contact the AstraZeneca Study Physician. A decision to allow the patient to continue in the study will be made on a case-by-case basis.

7. Olaparib in combination with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Table 3 Prohibited Medications

Prohibited Medication/ Class of Drug	Usage
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given while 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 (except palliative radiotherapy for non-target lesions, e.g., radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment (including SOC). Concurrent use of hormones for non-cancer related conditions (e.g., 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 (including SOC). 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 (including SOC) during the study

6.6.4 Supportive Care

Table 4 Rescue Medications

Rescue and Supportive Care Medication/ Class of Drug	Usage
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "excluded" 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 [including palliative radiotherapy, etc.]).	Should be used when necessary for all patients

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

6.7 Duration of Treatment

Participants may remain on study for up to 1 year from the time of first treatment administration receiving a total of 13 doses of durvalumab and 4 doses of tremelimumab at Q4W and daily olaparib in the absence of disease progression (irRECIST), unacceptable toxicity and withdrawal from study, intercurrent illness that prevents further administration of treatment, participant demonstrates an inability/refusal to comply with oral medication regime or, participant withdraws from study.

6.8 Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

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.
    a. If consent is withdrawn, the subject will not receive any further investigational product or further study observation.
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
4. Pregnancy or intent to become pregnant.

5. Any AE that meets criteria for discontinuation as defined in Section 10.1.
6. Adverse Event or DLT that, in the opinion of the Investigator, contraindicates further dosing (See Section 6.4 for definition of DLT).
7. Grade ≥ 3 infusion reaction.
8. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits.
9. Initiation of alternative anticancer therapy including another investigational agent.
10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment.
11. Development of intercurrent, non-cancer related illnesses that prevent either continuation of therapy or regular follow up.

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10 and Appendix H or Appendix I, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or started on standard therapy or enrolled in another clinical study. 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.

6.9 Compliance

Participants will be provided with a medication diary for olaparib to monitor compliance (Appendix J). The compliance requirement for olaparib is75% at any time on study treatment.

7 INVESTIGATIONAL PRODUCTS

7.1 Durvalumab

7.1.1 Active Substance and Source

Durvalumab (MEDI4736), IMFINZI™, 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 and density of 1.054 g/mL. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

7.1.2 Drug Shipment

Durvalumab will be provided by the Investigational Products Supply section of AstraZeneca/MedImmune and shipped to the participating site.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

7.1.3 Preparation

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 vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500 mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final durvalumab concentration ranging from 1 to 20 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. 30 mL of durvalumab (i.e., 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

For patients < 30 kg: Calculate the dose volume of durvalumab and tremelimumab and number of vials needed for the subject to achieve the accurate dose (Appendix C and Appendix E).

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

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.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined in the table, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

7.1.4 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified by the Sponsor and in accordance with the applicable regulatory requirements.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Drug storage temperature will be maintained and recorded, as applicable.

7.1.5 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by the sponsor exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

7.2 Tremelimumab

7.2.1 Active Substance and Source

Tremelimumab will be supplied by AstraZeneca either as a 400-mg or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02%

weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

7.2.2 Drug Shipment

Tremelimumab will be provided by the Investigational Products Supply section of AstraZeneca/MedImmune and shipped to the participating site.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

7.2.3 Preparation

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab 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 tremelimumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

It is recommended that the prepared final IV bag be stored in the dark at 2ºC-8°C (36°F-46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Doses of 75 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter. 3.8 mL of tremelimumab (i.e., 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/mL to 10 mg/mL (IV bag volumes 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

For patients <30 kg, Calculate the dose volume for tremelimumab and number of vials needed for subject to achieve the accurate dose (Appendix C and Appendix E).

Tremelimumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of tremelimumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of 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.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

Tremelimumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined in the table, a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

7.2.4 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified by the Sponsor and in accordance with the applicable regulatory requirements.

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab vials must be protected from light.

Drug storage temperature will be maintained and recorded, as applicable.

7.2.5 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by the sponsor exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug) will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

7.3 Olaparib

7.3.1 Active Substance and Source

Olaparib will be supplied as film-coated 100 mg and 150 mg tablets for oral administration (100 mg tablets to be used for dose reduction).

7.3.2 Drug Shipment

Olaparib will be provided by the Investigational Products Supply section of AstraZeneca/MedImmune and shipped to the participating site. Olaparib tablets are supplied in high-density polyethylene (HDPE) bottles containing desiccant. Bottles contain 32 tablets in each.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

7.3.3 Preparation

Tablet taken orally, no preparation needed. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Durvalumab + tremelimumab should be given at least 1 hour after the patient has taken their olaparib morning dose.

7.3.4 Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified by the Sponsor and in accordance with the applicable regulatory requirements.

Store olaparib at controlled room temperature (15°C - 25°C). Excursion data available to confirm tablets suitable for use if stored up to 50°C for 7 days.

Drug storage temperature will be maintained and recorded, as applicable.

7.3.5 Handling and Disposal

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by the sponsor exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Excess drug will be destroyed according to standard practices after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other participants.

Under no circumstances will the Investigator supply investigational drug to a third party or allow the investigational drug to be used in a manner other than as directed by this protocol.

8 STUDY PROCEDURES

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided in Table 5.

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with RPCI Clinical Research Services Standard Operating Procedures.

8.1 Participant Randomization and Registration

Enrollment will be non-randomized, competitive multicenter, sequential enrollment with central patient registration. Enrollment will be under ongoing review by an internal data safety-monitoring panel.

Eligibility of each participant will be established prior to enrollment.

Informed consent MUST be completed prior to receiving any study related procedures.

8.1.1 Pre-Screening Phase (Day -42 to Day -1)

- Written Informed Consent and assignment of subject identification number
- Preliminary eligibility fulfillment (investigator's opinion)
- Obtain archived tumor tissue for PD-L1 assay

8.1.2 Screening Phase (Day -28 to Day -1)

Screening procedures will be performed up to 28 days before Cycle 1 Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Formal verification of eligibility criteria
- Medical and surgical history/demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height

- 12-lead ECG (in triplicate [2-5 minutes apart])
- Recording of concomitant medications
- Disease assessment imaging by CT/MRI (including brain MRI only if clinically indicated)
- Clinical laboratory tests for:
    - Hematology (see Table 6)
    - Clinical chemistry with creatinine clearance (see Table 7)
    - TSH, (fT3 & fT4 if TSH is abnormal)
    - Coagulation (PT, PTT, INR)
    - Serum pregnancy test for pre-menopausal women of childbearing potential only
    - HIV/Hepatitis B, C serologies
    - CA-125 level
    - Urinalysis (Table 8)
- Recording of Adverse events

8.1.3 Cycle 1 Day 1

- Serum hCG pregnancy test for premenopausal women with child-bearing potential. Does not need to be repeated if performed within 7 days of Cycle 1 Day 1.
- Targeted Physical examination
- Vital signs
- Weight
- ECOG Performance Status
- Single 12- lead ECG– within 2-3 hours prior to the start of the first study treatment and 0-3hrs after administration of the combination is completed. In case of clinically significant ECG abnormalities, including a QTcF value ≥ 470ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g. 30 minutes) to confirm the finding.
- Recording of Adverse events
- Recording of Concomitant medications
- Clinical Chemistry (Table 7)
- Thyroid function tests: TSH. If TSH is abnormal, then fT3 and fT4 will also be collected.
- Hematology (Table 6)
- CA-125 level
- Urinalysis (Table 8)

- PAXgene® RNA blood sample
- Blood for immune monitoring
- Blood for circulating soluble factors
- Initial durvalumab, tremelimumab, and olaparib treatment
- Vital Sign monitoring during infusions (see Table 5 for time points)

8.1.4 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Procedures and Observations (Table 5). Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

8.1.5 End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab or tremelimumab or olaparib prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Follow-up assessments for subjects who have completed durvalumab, tremelimumab, and olaparib treatment and achieved disease control, or have discontinued durvalumab or tremelimumab or olaparib due to toxicity in the absence of confirmed progressive disease are provided in Appendix H.

Follow-up assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in Appendix I.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

8.2 Schedule of Procedures and Observations

The schedule of procedues and observations for this study is summarized in Table 5 below.

Screening and Treatment Period (up to 12 months):

- Durvalumab 1500 mg Q4W, maximum of 13 doses, IV administration, last infusion Cycle 13 Day 1.
- Tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W), maximum of 4 doses, IV administration, last infusion Cycle 4 Day 1. In the event of progressive disease on durvalumab and olaparib alone (i.e. after completion of initial 4 doses of tremelimumab), an additional 4 doses of tremelimumab may be added to the ongoing durvalumab and olaparib per the investigator's discretion. See section 6.1. Patients receiving additional tremelimumab doses will be monitored for toxicity.
- Olaparib 300 mg BID (or lower in the event of de-escalation), oral administration, up to 1 year. (After Phase I completion, Phase II dose was determined to be 250 mg BID for this combination).

Tremelimumab + durvalumab should be given at least 1 hour after the patient has taken their olaparib morning dose. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion.

Table 5 Schedule of Procedures and Observations

Evaluation[1]	Pre-Screening (Day -42 to Day -1)	Screening (Day -28 to Day -1)	All assessments to be performed pre-infusion unless stated otherwise.			End of Treatment Visit[19] (± 7 days)
			Cycle 1 Day 1	Cycle 1 Day 15 (± 3 days)	Cycle 2-13, Day 1 (± 3 days)	
Written Informed Consent and assignment of subject identification number	X					
Preliminary eligibility fulfillment (investigator opinion)	X					
Formal verification of eligibility criteria		X				
Recording of Concomitant Medications		X	X	X	X	X
Recording of Adverse Events[8]		X	X	X	X	X
Clinical Assessments						
Medical & Surgical History		X				
Physical Examination including vital signs, height and weight[5]		X	X		X	X

Evaluation[1]	Pre-Screening (Day -42 to Day -1)	Screening (Day -28 to Day -1)	All assessments to be performed pre-infusion unless stated otherwise.			End of Treatment Visit[19] (± 7 days)
			Cycle 1 Day 1	Cycle 1 Day 15 (± 3 days)	Cycle 2-13, Day 1 (± 3 days)	
Vital Sign Monitoring during infusions[6]			X		X	
ECOG Performance Status		X	X	X	X	X
Laboratory Procedures						
Hematology[10]		X	X		X	X
Serum Chemistry[18, 10]		X	X		X	X
CA-125 level[10]		X	X[20]		X[20]	
Obtain archived tumor tissue for PD-L1 assay (see section 8.5.1.1 for further detail)	X					
Hepatitis B & C; HIV		X				
Serum hCG[3]		X	X[3]			
Thyroid function tests[9, 10]		X	X[20]			
Urinalysis[11, 10]		X	X		X	
Coagulation parameters[12]		X				

Evaluation[1]	**Pre-Screening (Day -42 to Day -1)**	**Screening (Day -28 to Day -1)**	**All assessments to be performed pre-infusion unless stated otherwise.**			**End of Treatment Visit[19] (± 7 days)**
			Cycle 1 Day 1	**Cycle 1 Day 15 (± 3 days)**	**Cycle 2-13, Day 1 (± 3 days)**	
PAXgene® RNA tube (whole blood sample for mRNA/miRNA profiling)[13]			X		X[13]	
Blood for immune monitoring[14]			X	X	X	
Blood for circulating soluble factors[15]			X		X[15]	
Imaging/Other Procedures						
Brain MRI		X[2]				
12-Lead Electrocardiogram (see section 8.3.3 for further detail)[7]		X[7]	X[7]		X[7]	
Tumor Biopsy					X[16]	

Tumor/Disease Assessment by irRECIST (CT or MRI)		X[17]			X[17]	X[17]
Evaluation[1]	**Pre-Screening (Day -42 to Day -1)**	**Screening (Day -28 to Day -1)**	**All assessments to be performed pre-infusion unless stated otherwise.**			**End of Treatment Visit[19] (± 7 days)**
			Cycle 1 Day 1	**Cycle 1 Day 15 (± 3 days)**	**Cycle 2-13, Day 1 (± 3 days)**	
Study Drug Administration						
Durvalumab administration			X		X	
Tremelimumab administration			X		X[4]	
Olaparib administration			X ---------- BID continuous dosing, up to 1 year----------			

1. Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.
2. To be done only if clinically indicated.
3. Serum hCG to be obtained at screening, on Cycle 1 Day 1 and as clinically indicated once on treatment in pre-menopausal women of child-bearing potential only. Serum hCG only needs to be repeated on Cycle 1 Day 1 if screening test is not done within 7 days of treatment start.
4. Cycle 2, 3 and 4 only.
5. Full physical exam at screening; targeted physical exam at other time points. Patients with increased risk for cardiac toxicities (listed as inclusion criteria #9) will undergo targeted physical exam every 2 weeks and echocardiography if clinically indicated. Refer to section 8.3.2. Height required at screening visit only. Vital signs include blood pressure, pulse, temperature and respiratory rate.
6. Subjects will have their blood pressure, pulse, temperature and respiratory rate measured before, during and after the infusion at the following times (based on a 60-minute infusion for both durvalumab and tremelimumab). Refer to Section 8.3.4.
   - 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 post the end 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 the vital signs measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.
7. 12-lead ECG will be obtained at the following time points:
   - Screening (3 ECGs will be done 2-5 minutes apart during the screening visit)

- On Cycle 1 Day 1, a single ECG should be performed within 2-3 hours prior to the start of the first study treatment and 0-3hrs after administration of the combination is completed.
- On Treatment ECG: On Cycle 5 Day 1 OR at least one time after starting study treatment, a single ECG will be performed prior to administration of study treatment.
- Any other time point as clinically indicated.

In case of clinically significant ECG abnormalities, including a QTcF value ≥ 470ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g. 30 minutes) to confirm the finding.

8. For AEs/SAEs reported during pre-screening, additional information such as medical history and concomitant medications may be needed.
9. TSH level will be obtained at screening, on Cycle 1 Day 1 and as clinically indicated. Free T3 and free T4 level will only be measured if TSH is abnormal. Thyroid function tests should also be measured if there is clinical suspicion of an adverse event related to the endocrine system. Refer to Section 8.3.4.
10. Refer to Table 6 in Section 8.3.4. If screening laboratory assessments are performed within 3 days prior to Cycle 1 Day 1, they do not need to be repeated. Results for safety bloods must be available and reviewed before commencing an infusion.
11. Refer to Table 8 in Section 8.3.4. Urinalysis to be performed at screening, on day 1 of each cycle and as clinically indicated.
12. Prothrombin time, APTT and INR to be performed at screening and as clinically indicated. Refer to Section 8.3.4.
13. PAXgene® RNA tube will be collected on day 1 of cycles 1 & 2 (±3 days) and day 1 of cycles 3, 5, 7, 9, 11, & 13 (±7 days). Refer to Section 8.4.2.2.
14. Blood for immune monitoring will be collected on Cycle 1 Day 1, Cycle 1 Day 15, and Day 1 of cycles 2-13. Refer to Section 8.4.2.1.
15. Refer to Section 8.4.2.3. Blood for Circulating Soluble Factors will be collected on Cycle 1 Day 1, Cycle 2 Day 1 and Cycle 4 Day 1 only.
16. Tumor biopsy will be performed on cycle 4 day 1 (± 7 days and if clinically appropriate) after completion of CT scan for biopsy site determination or at the time of progression (if clinically appropriate). Refer to Section 8.5.1.2.
17. CT (preferred) or MRI scans, preferably with IV contrast, are collected during screening (for baseline), as close to and prior to initiation of study treatment. Timing of on-treatment CT/MRI scans is pre-dose C4D1 (± 7 days) for biopsy site determination and every 3 cycles thereafter (i.e. Day 1 of Cycles 7, 10, 13 ± 7 days) or as clinically indicated until progressive disease or off-study. Response according to irRECIST criteria (irCR, irPR) requires a confirmatory scan preferably at the next regularly scheduled imaging visit and no earlier than 6 weeks after the prior assessment of CR, PR, or SD is deemed by irRECIST. End of Treatment disease assessment does not need to be repeated if performed within 28 days prior to end of treatment.
18. Refer to Table 7 for details.
19. Refer to Appendix H and Appendix I for follow-up visits.
20. Results from CA-125 and thyroid function test do not need to be available prior to dosing patient on dosing days.

8.3 Description of Study Procedures

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

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

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

8.3.2 Physical Examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at Screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10.

8.3.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening, on Cycle 1 Day1 within 2-3 hours prior to the start of the first study treatment and 0-3hrs after administration of the combination is completed, on Cycle 5 day 1 OR at least one time after starting study treatment and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

At Screening, triplicate ECGs (2-5 minutes apart) will be obtained on which QTcF must be <470 ms.

For all other time points, a single ECG will be performed. In case of clinically significant ECG abnormalities, including a QTcF value ≥ 470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 10.

8.3.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules.

On infusion days, patients receiving durvalumab + tremelimumab + olaparib treatment will be monitored during and after infusion of IP as presented in the bulleted list below:

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP, pulse, temperature and respiratory rate will be collected from patients receiving durvalumab + tremelimumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]).
- Approximately 30 minutes during the infusion (halfway through infusion).
- At the end of the infusion (approximately 60 minutes ±5 minutes).
- A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab.

Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and of tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

If the infusion takes longer than 60 minutes, then vital signs measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Only the first dose of olaparib (oral) will be administered and monitored as above at the clinic. Subsequent doses will be taken by the patient and will keep a log book.

Situations in which vital signs results should be reported as AEs are described in Section 10. Clinical Laboratory Tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments):

- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at screening and as clinically indicated
- Pregnancy test (pre-menopausal female subjects of childbearing potential only)
    - Serum beta-human chorionic gonadotropin (at screening visit within 7 days prior to first treatment and as clinically indicated thereafter
- Thyroid Stimulating Hormone
    - Free T3 and free T4 only if TSH is abnormal
- Other laboratory tests
    - Hepatitis B surface antigen, hepatitis C antibody
    - HIV screening test

Table 6 Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

Table 7 Clinical Chemistry (serum or plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin [a]
Chloride	Total protein
Creatinine[c]	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase [b]	Uric acid

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

[b] At baseline and as clinically indicated

[c] Creatinine ≤ 1.5 x ULN or, Serum Creatinine CL > 51 mL/min (by the Cockroft-Gault equation). Refer to Inclusion Criterion #10.

Table 8 Urinalysis Tests

Bilirubin	pH
RBC, WBC	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

Table 9 Tumor Marker

Tumor Marker	CA-125 Level

8.4 Biological Sampling Procedures

8.4.1 Biomarker Sampling and Evaluation Methods

Tumor samples will be examined to evaluate biomarkers by immunohistochemistry (IHC) and mRNA/miRNA expression profiling. This may include but is not limited to, the expression level and localization of immunosuppressive proteins such as PD-Ll on tumor cells, tumor infiltrating lymphocytes (TlLs), and/or markers of inflammatory/immune cell signatures, e.g. CTLA-4 CD3, CD4, CDS, CD45RO, IFN-gamma, FoxP3, and granzyme Band OX40. Any relationships between biomarker expression with subject response to treatment with durvalumab, tremelimumab, and olaparib will be evaluated. Additionally, analyses of tumor mutations and polymorphisms using archival tumor tissue may be performed through relevant methodologies in order to assess genetic alterations and their potential relationships with treatment outcome to durvalumab, tremelimumab, and olaparib. Further, selected gene sequencing of samples may be employed to evaluate genetic alterations and relationships with treatment outcome with durvalumab, tremelimumab, and olaparib.

8.4.1.1 PD-L1 Testing

To ensure comparability of data across all studies of durvalumab 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 Ventana SP263 assay. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV+ cancers), the Ventana SP263 assay has only limited clinical performance data.

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.

- Archived tissue will be utilized for PD-L1 testing as assessment. The age of the sample / date of collection should be captured.

- Patients will be asked to undergo one fresh biopsy for on-treatment assessment on Cycle 4 Day 1 (± 7 days) if considered clinically appropriate by their treating physician or at time of progression (if considered clinically appropriate).

- 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.

- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) 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 shipping the samples:

- Patient identifier (e-code 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 or 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

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

Preparing Stored samples for testing

- Archived sample should be retrieved from the Paraffin Archive/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

- Tumor biopsy will be performed according to institutional practice on Cycle 4 Day 1 (± 7 days) (if clinically appropriate), or time of progression (if clinically appropriate). Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 4 cores is advised in order to provide sufficient tissue for PD-L1 assessment (2 for FFPE and 2 for flash freezing (refer to Laboratory Manual, version 2.0 for processing instructions). Archived tissue will be utilized for assessment. Tumor biopsy samples will be examined to evaluate the correlation between clinical activity and the expression level of PD-Ll and tumor-infiltrating lymphocytes changes in biopsies pre and post treatment.

Flash Frozen Tissue for DNA (refer to Section 8.5.1.2)

- Samples collected at RPCI will be processed and stored (-80°C) at the Correlative Science Pathology Office and will be batch shipped on dry ice to the RPCI Immune Analysis Facility.
- **NETWORK SITES:** Follow directions above for sample collection and processing. The cryogenic tubes will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, and protocol day. The samples will immediately be frozen in liquid nitrogen as per the lab manual and stored at -80ºC until requested for batch mailing. Samples are to be batch shipped frozen, on dry ice.
    - *Note*: Samples cannot be frozen in glass tubes – cryogenic vials must be used.
    - Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.
    - Address shipments and any questions regarding specimen processing to:

Roswell Park Cancer Center
Immune Analysis Facility at the Center for Immunotherapy
CCC Bldg. 4th Floor, Rm. 416
Attn: Study Number – I 288216
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716-845-8459

Junko.Matsuzaki@RoswellPark.org

- 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 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 (as per institutional guidelines)

- 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.

PD-L1 testing laboratory (Department of Pathology in the Pathology Resource Network at RPCI):

Roswell Park Cancer Institute
Elm & Carlton Streets
Correlative Science Pathology Office
Gratwick Basic Science Building, S-636
Attn: Protocol Lab Team, I 288216 Samples
Buffalo, NY 14263
(716) 845-8917
Email: CRSLabPathTeam@RoswellPark.org

For **Network Sites**, samples are to be sent to the central lab (Immune Analysis Facility). Additional details for sample collection, processing, storage, and shipment is provided in the ***Laboratory Manual [RPCI Immune Analysis Facility study Laboratory Manual (Version 2.0)].*** Samples will be analyzed in RPCI's Core Pathology Laboratory (Pathology Resource Network).

- When submitting sample 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.
- 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.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens.

This is required for both observational and interventional clinical studies collecting clinical samples.

8.4.2 Estimate of Volume of Blood to be Collected

Table 10 Volume of Blood to be drawn from each Participant

Assessment	Sample volume (mL)	No. of samples	Total volume 1 Year (mL)	Collection tube
Clinical chemistry	4	14	56	gold top
Hematology	4	14	56	purple top
Thyroid Function test	4	14	56	gold top
Coagulation	4	1	4	light-blue top
PAXgene® RNA tube	2.5	8	20	PAXgene® tube
Blood for Immune Monitoring	70	15	1050	6 green tops and 1 red top
Circulating soluble factors	5	3	15	purple top
Total	93.5	69	1257	

Please refer to the study **Laboratory Manual (version 2.0)** for additional details on processing and storage.

Samples will be kept at room temperature prior to processing.

8.4.2.1 Blood for Immune Monitoring

Blood samples will be collected via venipuncture for immune monitoring (to check for T cell phenotype, humoral and T cell responses using flow cytometry, ELISPOT and ELISA). Samples will be collected using (6) 10 mL green-top collection tubes and, (1) 4 mL red-top collection tube.

Samples will be obtained, prior to infusion, on:

- Cycle 1 Day 1
- Cycle 1 Day 15 (± 3 days)
- Day 1 of Cycles 2-13 (± 3 days)
- At the follow up visit if the patient discontinued durvalumab treatment due to confirmed progression of disease, at the discretion of the investigator.

Samples will be kept at room temperature prior to processing.

Samples collected at RPCI will be sent to the Immune Analysis Facility for processing (refer to Laboratory Manual, version 2.0 for additional details).

Roswell Park Cancer Center
Immune Analysis Facility at the Center for Immunotherapy
CCC Bldg. 4th Floor, Rm. 416
Attn: Study Number – I 288216
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716-845-8459

Junko.Matsuzaki@RoswellPark.org

NETWORK SITES: Follow directions above for sample collection and processing. The cryogenic tubes will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at -80ºC or below (samples are to be stored until requested for batch mailing), unless otherwise indicated. Samples are to be batch shipped frozen, on dry ice, unless otherwise indicated.

Note: Samples cannot be frozen in glass tubes – cryogenic vials must be used.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Address shipments and any questions regarding specimen processing to:

Junko Matsuzaki PhD, Director-Immune Analysis Facility
Immune Analysis Facility at the Center for Immunotherapy
Cancer Cell Center, Room 416
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263
junko.matsuzaki@roswellpark.org

Samples will be analyzed at the IAF, where all samples will be archived.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

8.4.2.2 Blood for mRNA/miRNA Profiling

Blood samples will be collected via venipuncture for mRNA/miRNA profiling. Samples will be collected using (1) 2.5 mL PAXgene® RNA tube.

Samples will be obtained, prior to infusion, on:

- Cycle 1 Day 1 (± 3 days)
- Cycle 2 Day 1 (± 3 days)

- Day 1 of Cycles 3, 5, 7, 9, 11 &13 (± 7 days)

Samples will be kept at room temperature prior to processing.

Samples collected at RPCI will be sent to the Immune Analysis Facility for processing (refer to Laboratory Manual, version 2.0 for additional details).

Roswell Park Cancer Center
Immune Analysis Facility at the Center for Immunotherapy
Cancer Cell Center, Room 416
Attn: Study Number – I 288216
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716-845-8459
junko.matsuzaki@roswellpark.org

NETWORK SITES: Follow directions above for sample collection and processing. The cryogenic tubes will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will be frozen following the procedure outlined in Appendix M (samples are to be stored until requested for batch mailing). Samples are to be batch shipped frozen, on dry ice.

Note: Samples cannot be frozen in glass tubes – cryogenic vials must be used.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Address shipments and any questions regarding specimen processing to:

Junko Matsuzaki PhD, Director-Immune Analysis Facility
Immune Analysis Facility at the Center for Immunotherapy
Cancer Cell Center, Room 416
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263
junko.matsuzaki@roswellpark.org

Samples will be analyzed at the IAF, where all samples will be archived.

8.4.2.3 Blood for Circulating Soluble Factors

Blood samples will be collected via venipuncture for analysis of circulating soluble factors. Samples will be collected using (1) 5 mL purple top EDTA collection tube. Samples will be obtained, prior to infusion, on:

- Cycle 1 Day 1
- Cycle 2 Day 1 (± 3 days)
- Cycle 4 Day 1 (± 3 days)

Samples will be kept at room temperature prior to processing.

Samples collected at RPCI will be sent to the Immune Analysis Facility for processing (refer to Laboratory Manual, version 2.0 for additional details).

Roswell Park Cancer Center
Immune Analysis Facility at the Center for Immunotherapy
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Tel: 716-845-8459
junko.matsuzaki@roswellpark.org

NETWORK SITES: Follow directions above for sample collection and processing. The cryogenic tubes will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. The samples will immediately be frozen at -80ºC or below (samples are to be stored until requested for batch mailing). Samples are to be batch shipped frozen, on dry ice.

Note: Samples cannot be frozen in glass tubes – cryogenic vials must be used.

Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. Do not ship on a Friday or the day before a holiday.

Address shipments and any questions regarding specimen processing to:

Junko Matsuzaki PhD, Director-Immune Analysis Facility
Immune Analysis Facility at the Center for Immunotherapy
Cancer Cell Center, Room 416
Roswell Park Cancer Institute
Elm and Carlton Streets
Buffalo, NY 14263
junko.matsuzaki@roswellpark.org

Samples will be analyzed at the IAF, where all samples will be archived.

8.5 Pathology

8.5.1 Archival Tumor Samples and Fresh Tumor Biopsies

8.5.1.1 Archival tumor samples

Archival tumor samples are required for all subjects and must be deemed available during the screening period. The quantity (5-10 unstained slides with tissue sections of 4µm thick on charged glass slides), and quality of archival tumor samples should be confirmed during screening period.

For **Network Sites**, de-identified tissue samples using study-specific subject ID number and tissue accession# (GCP requires at least 2 identifiers) are to be sent to the central lab (Immune Analysis Facility). Additional details for sample collection, processing, storage, and shipment is provided in the ***Laboratory Manual [RPCI Immune Analysis Facility study Laboratory Manual (Version 2.0***)]. Samples will be analyzed in RPCI's Core Pathology Laboratory.

8.5.1.2 Fresh tumor biopsies

Tumor lesions planned for biopsy must not be used as index lesions for assessment of disease and tumor response. Excisional biopsies are preferred where clinically appropriate. Otherwise, subjects will undergo 4 image-guided core biopsies (18 g or larger, if clinically appropriate). Two tissue cores will be placed in formalin and processed to FFPE. The remaining 2 cores will be immediately frozen in liquid nitrogen and then stored at -80°C. Network sites will ship the samples in formalin at room temperature on the same day as collection to the central lab (IAF) as per lab manual. Flash frozen samples can be batch shipped to the Central Lab on dry ice.

Additional details for sample collection, processing, storage, and shipment is provided in the ***Laboratory Manual [RPCI Immune Analysis Facility study Laboratory Manual (Version 2.0)]***.

Tumor biopsy will be performed on Cycle 4 Day 1 ± 7 days (if clinically appropriate), or at time of progression (if clinically appropriate). Archived sample will be utilized for baseline assessment.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

8.5.2 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 EFFICACY EVALUATIONS

Disease Evaluation and Methods

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy, including the following (50, 51):

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (52) for immune modulating anti-cancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria (53):

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab, tremelimumab, and olaparib would continue between the initial assessment of progression and confirmation for progression.
- In addition, subjects may continue to receive durvalumab, tremelimumab, and olaparib beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab/olaparib and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than durvalumab/olaparib or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.1 Efficacy Assessment by irRECIST

Tumor response will be assessed using the Immune-Related Response Criteria (irRECIST) as described by Nishino et al, 2013 (54) and Bohnsack et al, 2014 (55). The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

Tumor response will be assessed by irRECIST. Conventional RECIST 1.1 (53) will also be documented during the trial, however; RECIST 1.1 will not be used to determine disease progression.

Refer to Appendix K for a summary of irRECIST.

10 SAFETY EVALUATION

10.1 Adverse Events

10.1.1 Definition

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

10.1.1.1 Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

10.1.1.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

10.1.1.3 Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as "hyperkalemia"

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

10.1.1.4 Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.1.2 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 judgment 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.

10.1.3 Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP

Version 4 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

N.B.: When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in "Background" of this protocol may support these evaluations.

10.1.4 Reporting Adverse Events

Table 11 Guidelines for Routine Adverse Event Reporting for Phase 1 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated	X	X	X	X
Unlikely	X	X	X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Table 12 Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring between the start date of intervention until 90 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

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 eCRF. 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 + tremelimumab+ olaparib. 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.

10.2 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 and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

10.2.1 Durvalumab + Tremelimumab AESIs

AESIs for durvalumab and tremelimumab 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 are being closely 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 etiology. 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 regard to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Sponsor.

AESIs observed with durvalumab and tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- ALT/AST increases / hepatitis / transaminase increases / 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 / hypopituitarism, adrenal insufficiency, and hyper- and hypothyroidism and type I diabetes mellitus)

- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)
- Myocarditis
- Myositis / Polymyositis
- Intestinal Perforation
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye (e.g., keratitis and optic neuritis) skin (e.g., scleroderma, vitiligo and pemphigoid) , hematological (e.g., hemotological anemia and immune thrombocytopenic purpura) and rheumatological events (polymyalgia rheumatic and autoimmune arthritis), vasculitis, non-infectious meningitis and non-infectious encephalitis.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator Brochure. For durvalumab and tremelimumab, AESIs will comprise the following:

Pneumonitis

AEs of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Appendix G.

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. For all infusion reactions, SAEs should be reported to AstraZeneca Patient safety as described in Section 10.4.

Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (45). 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 (IgE-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 Section 6.2.1.1.

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 (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the IP. Guidelines for management of patients with hepatic function abnormality are provided in Appendix G.

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 tremelimumab are provided in Appendix G.

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 G.

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 G.

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 G.

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 G.

10.2.2 Olaparib Adverse Events of Special Interest (AESIs)

Adverse Events of Special Interest (AESIs) 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 [e.g. non-melanoma skin cancer] or SAE, and regardless of investigator's assessment of causality or knowledge of the treatment arm.

A questionnaire will be sent to any investigator reporting an AESI, as an aid to provide further detailed information on the event. During the study there may be other events identified as AESIs that require the use of a questionnaire to help characterize the event and gain a better understanding regarding the relationship between the event and study treatment.

10.2.3 Immune-related Adverse Events

Based on the mechanism of action of durvalumab and tremelimumab 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 (23, 45, 56) These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., 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 G – Table A), it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (57). These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (e.g., infliximab or mycophenolate).
- If the Investigator has any questions in regard to an AE being an irAE, the Investigator should immediately contact the Study Sponsor.

10.3 Serious Adverse Events

10.3.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical 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.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

10.3.2 Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 90 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs that are unexpected and possibly, probably or definitely related must be reported as an Unanticipated Problem. Please refer to **Section 10.6** for details on reporting Unanticipated Problems.

10.4 Investigator Reporting: Notifying the Study Sponsor

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 + tremelimumab + olaparib 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 inform the FDA, via a MedWatch form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A ***cover page*** should accompany the ***MedWatch*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-16-11751)

* Sponsor must also indicate, either in the SAE report or the cover page, the ***causality*** of events ***in relation to all study medications*** and if the SAE is ***related to disease progression***, as determined by the principal investigator.

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:***

AEMailboxClinicalTrialTCS@astrazeneca.com

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

Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

10.5 Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

10.6 Unanticipated Problems

10.6.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:

a) The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.

b) The characteristics of the participant population being studied.

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 10.3**.

10.6.2 Reporting Unanticipated Problems

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the IRB in accordance with their local institutional guidelines.

10.7 Reporting of Deaths

All deaths that occur during the study, or within the protocol defined 90 day post last dose of durvalumab + tremelimumab + olaparib (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 10.3.2for 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.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab + tremelimumab + olaparib follow-up period will be documented as events for survival analysis but will not be reported as an SAE.

10.8 Other Events Requiring Reporting

10.8.1 Overdose

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

Any overdose of a study subject with durvalumab + tremelimumab + olaparib, 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 10.4 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.1). 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 10.3). There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab or olaparib.

The investigator will use clinical judgment to treat any overdose.

10.8.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.2.1) 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 investigation 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.

10.8.3 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, i.e., 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.

10.9 FDA Reporting

When RPCI is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening;

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS QA Office via email to CRSQA@RoswellPark.org. Network sites: See Appendix A.

11 DATA AND SAFETY MONITORING

The Phase 1 portion of this study will be reviewed at the scheduled RPCI Early Phase Clinical Trial (EPCT) Program meetings and the minutes are forwarded to the IRB for review.

During the Phase II portion of this study, The RPCI Data, Safety Monitoring and Accrual Board (DSMAB) will assess the progress of the study, the safety data, and critical efficacy endpoints. The DSMAB will review the study annually and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design, (c) suspension of, or (d) or termination of the study.

12 STATISTICAL METHODOLOGY

Phase I: The primary objective of the Phase I component of this study is:

- To assess the safety and toxicity of the combination of PARP inhibitor olaparib with anti-PD-L1 antibody durvalumab and anti-CTLA4 antibody tremelimumab

Phase II: The primary objective of the Phase II component of this study is:

- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on PFS rates.

The secondary objectives of the Phase II component of study are:

- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on anti-tumor immune responses in patients with recurrent platinum sensitive or resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer who carry a germline and/or somatic BRCA1 or BRCA2 mutation.
- To assess the impact of the combination of olaparib with durvalumab and tremelimumab on PFS and/or OS in patients with recurrent platinum sensitive or resistant or refractory epithelial ovarian, fallopian tube, or primary peritoneal cancer who carry a germline and/or somatic BRCA1 or BRCA2 mutation.

12.1 Sample Size Determination

The potential Phase I study sample size ranges from a minimum of n=6 to a maximum of n=12. See Table 1 for the dose escalation schema. The Phase II portion of the study will have a sample

size of n=27. Subjects will be enrolled in the Phase II study at a ratio of 2:1 of platinum resistant to platinum sensitive disease.

Depending on the incidence of DLT(s), following a 3+3 design, the sample size is estimated to be 33 to 36 patients. Assuming the true DLT rate is much less than 1/3rd, we anticipate enrolling 36 subjects (9+27) where the accrual is expected to take up to 4 years.

12.2 Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

12.3 Safety and Tolerability

The primary objective of the Phase I study is establishing safety. Assessment of safety and tolerability will be performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the investigators.

DLT: All patients who receive at least two cycles of durvalumab + tremelimumab and 8 weeks of olaparib treatment and respective safety assessments, as well as, all patients who discontinue the study prematurely due to DLT are considered fully evaluable per protocol for DLT (see Section 4.3 for patient replacement). Patients must also have received at least 75% of the planned dose of olaparib during the DLT evaluation period (except for patients who discontinued prematurely due to DLT) to be evaluable for DLT.

Safety set: All patients who received at least one dose of durvalumab + tremelimumab + olaparib will be evaluated for safety and tolerability.

Appropriate summaries of AEs, laboratory data and vital sign data will be presented. AEs will be listed individually per patient according to CTCAE version 4.03, and the number of patients experiencing each AE will be summarized using descriptive statistics.

The MTD is defined as the highest dose studied, for which the observed incidence of DLT is less than 33%. Frequencies of toxicities will be tabulated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

12.4 Clinical Efficacy

Clinical efficacy evaluation will include tumor response assessed by irRECIST, Progression-free Survival and overall survival.

The primary endpoint will test the 3-month progression free survival rate in the platinum resistant group in conjunction with the 6-month progression free survival rate in the platinum sensitive group. The overall test follows the approach of London and Change(58) Let π_1 denote the 3 month progression free response rate for the platinum-resistant strata and let $\pi_2$denote the 6 month progression free response rate for the platinum sensitive strata. Our overall test is of the form H_0:$\pi_1 = 0.55,\ \pi_2 = 0.65$ versus the alternative H_1:$\pi_1 > 0.55,\ \pi_2 > 0.65$. Using the approach of

London and Chang our test statistic takes the form $T = \frac{R - \sum_i^2 N_i \pi_{i0}}{\sqrt{N \sum_{i=1}^2 \pi_{i0}(1-\pi_{i0}) P_i}}$, where R denotes the combined number of non-progressors across strata, $\pi_{10} = 0.55$ and $\pi_{20} = 0.65$ represent the null values for strata 1 and 2 above, $N = N_1 + N_2$ $N_1 = 18$ and $N_2 = 9$ represent the strata sample sizes and $P_1 = 2/3$ and $P_2 = 1/3$ represent the strata distribution proportions, respectively. The distributional properties of T are given in London and Chang (58). Given $\alpha = 0.10$ and a fixed sample size of $N = 27$ we will be able to detect a difference of 0.2 and 0.15 between the null and alternative progression free survival rate values per strata one and two, respectively at 0.72 power based on an exact multinomial test about T.

All patients who received at least two cycles of durvalumab + tremelimumab and 8 weeks of olaparib, as well as baseline and at least one post-baseline disease assessment will be evaluated for clinical efficacy. Tumor Responses by irRECIST and RECIST, progression free survival and overall survival will be summarized and analyzed descriptively via summary frequencies and Kaplan-Meier estimators.

12.5 Interim Analysis and Criteria for Early Termination of the Study

This is a Phase I/II study and as such will be monitored and discussed by RPCI's Phase 1 Committee, which meets on a regular basis per the RPCI Data Safety Monitoring Plan. Drug safety will be monitored and evaluated continuously throughout the study including 30-day safety follow-up period by obtaining, reviewing and analyzing data on AEs, changes in laboratory values, vital signs, electrocardiograms (ECGs), and physical examination findings. Potential early termination decisions are an inherent part of the Phase 1 study monitoring. The Phase II study does not have an interim analysis point.

13 CORRELATIVE DATA ANALYSIS

13.1 Translational and Correlative Biomarker Endpoints

Archival and on-treatment tumor biopsies and peripheral blood will be utilized for this assessment.

- Olaparib treatment of BRCA1/2+ve platinum resistant ovarian cancer patients leads to the release of a unique repertoire of tumor antigens that will be cross-presented to the immune system leading to generation of humoral and T cell responses. We will initially focus on auto-antibody analysis of pre- and post- treatment samples from the patients on the clinical trial, using a previously validated "seromics" approach by our group (49). The results generated by the analysis of pre- and post-treatment sera may be useful individually or as signature sets as (i) diagnostic markers, preferentially immunogenic in HR-deficient ovarian cancer, (ii) prognostic markers, associated with favorable or unfavorable clinical outcome in HR-deficient ovarian cancer, and (iii) potential targets of immune responses for the development of new immunotherapeutic reagents in HR-deficient ovarian cancer.
- Immunoscore: pre- and post-treatment biopsies.
- Analysis of T-cell responses.

- Analysis of potential resistance mechanism: sequencing studies (e.g. for HR deficiency), gene expression studies and analysis for secondary genetic and epigenetic events.

14 ETHICAL AND REGULATORY STANDARDS

14.1 Ethical Principles

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

14.2 Informed Consent

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant or the participant's legally authorized representative in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

15 STUDY RESPONSIBILITIES

15.1 Data Collection

Data entry into the database is to be completed in a timely fashion (within 30 days) after the participant's clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Source Form, which is handled in an expedited fashion.

Data management activities will be performed using eClinical. eClinical is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the eClinical Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs (via the EXPeRT Module). eClinical is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

15.2 Maintenance of Study Documents

Essential documents will be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI.

15.3 Study Governance and Oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

16 ADMINISTRATIVE RULES

16.1 Revisions to the Protocol

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

16.2 Termination of the Study

It is agreed that, for reasonable cause, either the RPCI Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

16.3 Confidentiality

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

17 APPENDICES

Appendix A Instructions for Network Sites

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Quality Assurance (QA) Network Office
CRSNetworkCoordinators@RoswellPark.org
1930 GBSB Buffalo, New York 14263
Telephone:
Monday - Friday; 8:00 AM to 4:30 PM EST
716-845-3155
After hours, weekends, and holidays request the RPCI Investigator
716-845-2300
Fax: 716-845-8743

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any procedures or treatment**.
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park CRS QA Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park CRS QA Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 1 Protocol Registration Instructions

Contact the RPCI Network Monitor to verify that a slot is available in the open cohort when a participant has been identified. **Do not have the participant sign consent prior to verifying an open slot.**

- After the participant signs consent, the Subject Screening and Enrollment Log must be faxed or emailed CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park QA Coordinator Monitor within 1 business day. The Roswell Park QA Coordinator/Monitor will confirm receipt of the Subject Screening and Enrollment Log and email the participant ID number.
- When the participant has met eligibility, a signed eligibility checklist and other requested documentation will be faxed or emailed to the Roswell Park Network QA Coordinator.
- Within 1 business day of receipt of the eligibility check list, the Roswell Park Network QA Coordinator will fax or email the cohort assignment and dose level.
- An email must be sent by the site to confirm receipt of the cohort assignment and to provide the planned treatment start date.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be faxed or emailed (CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park CRS QA Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and fax or email it to the Roswell Park Network QA Coordinator at 716-845-8743.

4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the RPCI Network, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

The Reportable New Information (RNI) Form will be submitted to the CRS Network QA Coordinator within 1 business day of becoming aware of the Unanticipated Problem.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park Network QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of RPCI to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no

longer maintain the study records, they may be transferred to another institution, another investigator, or to RPCI upon written agreement between the Investigator and RPCI.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

If any questions regarding study drugs associated with this trial, network sites should contact:

Denise Wells-Johnson

716-845-3298

Denise.WellsJohnson@roswellpark.org

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park Network QA Coordinator within 1 business day of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- RPCI SAE Source form
- MedWatch 3500A

A complete follow-up report must be sent to the RPCI Network Monitor when new information becomes available.

- If this is a Phase 1 study the site Investigator or designated research personnel will complete and send the **Serious Adverse Event / Possible Dose Limiting Toxicity Memo** to notify the appropriate RPCI personnel of an SAE or potential DLT via email: Phase1DLTnetwork@Roswellpark.org.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 10.6**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park Network QA Coordinator within 1 business day of being made aware of the Unanticipated Problem by completing the **RPCI Unanticipated Problem Report Form** and faxing or emailing it to the Roswell Park Network QA Coordinator.

9. DATA AND SAFETY MONITORING

Weekly or bi-weekly teleconferences will be scheduled to review participant adverse events and study status. The site Investigator and study coordinator are expected to attend.

Appendix B ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

Appendix C Durvalumab: Dose Calculations

For durvalumab dosing done depending on subject weight ≤ 30 kg:

1. Cohort dose: X mg/kg
2. Subject weight: Y kg
3. Dose for subject: XY mg = X (mg/kg) × Y (kg)
4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle only needed for greater than 10% change in weight.

5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10 (mL/vial)

Example:

1. Cohort dose: 10 mg/kg
2. Subject weight: 30 kg
3. Dose for subject: 300 mg = 10 (mg/kg) × 30 (kg)
4. Dose to be added into infusion bag:

Dose (mL) = 300 mg / 50 (mg/mL) = 6mL

5. The theoretical number of vials required for dose preparation:

Number of vials = 6 (mL) / 10 (mL/vial) = 1 vial

Appendix D Durvalumab: Dose Volume Calculations

For durvalumab flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000 / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL).

3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 10 (mL/vial)

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

Dose (mL) = 1.5 g ×1000 / 50 (mg/mL) = 30mL

3. The theoretical number of vials required for dose preparation:

Number of vials = 30 (mL) / 10 (mL/vial) = 3 vials

Appendix E Tremelimumab: Dose Calculations

For tremelimumab dosing done depending on subject weight (≤ 30 kg):

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 20 (mL/vial)

Example:

1. Cohort dose: 1 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 30 mg = 1 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 30 mg / 20 (mg/mL) = 1.5 mL

5. The theoretical number of vials required for dose preparation:

Number of vials = 1.5 (mL) / 20 (mL/vial) = 1 vials

Appendix F Tremelimumab: Dose Volume Calculations

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

Dose (mL) = X mg / 20 (mg/mL)

where 20 mg/mL is tremelimumab nominal concentration

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL).

3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials = Dose (mL) / 20 (mL/vial)

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

Dose (mL) = 75 mg / 20 (mg/mL) = 3.8 mL

3. The theoretical number of vials required for dose preparation:

Number of vials = 3.8 (mL) / 20 (mL/vial) = 1 vial

Appendix G 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): 17 October 2019 Version 4.03

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. (unless indicated otherwise) 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 of the start of the immune-mediated adverse event (imAE)** • Grade 3 recurrence of a previously experienced Grade 3 treatment-related imAE 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. • **Note: For asymptomaticamylase or lipase levels of >2.0×ULN, 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: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: • It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines • Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. . In the absence of a clear alternative etiology; all events should be considered potentially immune related. General recommendations follow • 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. • Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. • If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., 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 (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. • With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carnii* pneumonia) prophylaxis, gastrointestinal protected, and glucose monitoring. • Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study

• Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e. hyperthyroidism, hypothyroidism, Type I diabetes mellitus)	drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE Immune-mediated 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/Interstitial Lung Disease (ILD)	**Any Grade**	**1.1.1.1.1 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 consults.
	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 completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** • Monitor symptoms daily and consider hospitalization. • Promptly start systemic steroids (e.g., 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 • If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] • Consider pulmonary and infectious Disease consults. • 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 [e.g., 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 consults Consider as necessary, discussing with study physician. • Hospitalize the patient. • Supportive care (e.g., 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 (e.g., infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis 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-PJP treatment (refer to current

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			NCCN guidelines for treatment of cancer-related infections). [a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** • Monitor for symptoms that may be related to diarrhea/colitis (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). • When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., 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, including perforation. • Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** • Monitor closely for worsening symptoms. • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: 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.	**For Grade 2:** • Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	(Colitis: abdominal pain; mucus or blood in stool) (Perforation: symptomatic; medical intervention indicated*) * "medical intervention" is not invasive	• If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	(e.g., 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 weeks a. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. • Consider, as necessary, discussing with 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3: Diarrhea stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences)	Permanently discontinue study drug/study regimen- for Grade 3 if toxicity does not improve to Grade <1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4**	**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.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	Grade 3 Colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs Grade 4: Colitis: life-threatening consequences, urgent intervention indicated (Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated) *This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective	Permanently discontinue study drug/study regimen	• If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. 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. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** • Monitor and evaluate liver function test: AST, ALT, ALP, and TB. • Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	(AST or ALT > to 3 × ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB > to 1.5 × ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	No dose modifications. • If it worsens, then treat as described for elevations in the row below.	• Continue LFT monitoring per protocol.
	(AST or ALT > 3 to 5 × ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5 to 3.0 × ULN if baseline normal, >1.5- 3.0×baseline if baseline abnormal	Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal. • If toxicity worsens, then treat as described for elevation in the row below. • If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB	• Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. • If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal in 1 to 2 days, consider, as necessary, discussing with study physician.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		≤1.5×baseline if baseline abnormal , resume study drug/study regimen after completion of steroid taper.	• 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 work-up 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 (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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	AST or ALT >5.0×ULN if baseline normal, >5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal; >3.0×baseline if baseline abnormal	For elevations in transaminases ≤8×ULN and/or in TB ≤5×ULN if baseline normal, or for elevations in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal: • Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline	• 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.** • Request Hepatology consult, and perform abdominal workup, and imaging as appropriate. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		abnormal, within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days • For elevations in transaminases >8×ULN or elevations in TB >5×ULN if baseline normal, or for elevations in transaminases >8×baseline and/or TB >5×baseline if baseline abnormal, permanently 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 (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Hepatitis (elevated LFTs) **<u>Infliximab should not be used for management of immune-related hepatitis</u>** **See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting**	**Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** • Monitor and evaluate liver function test: AST, ALT, ALP, and TB. • Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). • For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg • For HCV+ patients: evaluate quantitative HCV viral load • Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml • Consider consulting hepatologist/Infectious Disease specialist regarding

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
of either increasing bilirubin or **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** **signs of DILI/liver decompensation**			change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold • For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution toAST or ALT ≤5.0×ULN. • If toxicity worsens, then treat asdescribed for elevations in the rows below. • If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	• Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. • Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. • Consider, as necessary, discussing with study physician. • If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to 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 treatment with IV methylprednisolone 2 to 4 mg/kg/day.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			• If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN Grade ≤1 • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	• Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. • Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. • Consider, as necessary, discussing with study physician. • If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. • If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate 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

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			NCCN guidelines for treatment of cancer-related).[a]
	(Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	• Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** - **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, 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 (e.g., 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 (e.g., 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 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** • Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a • When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** • Carefully monitor serum creatinine on daily basis.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
	(Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN) (Grade 4: serum creatinine >6.0 × ULN)		• 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or dermatitis (including Pemphigoid)	**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. IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** • Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., 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.	**For Grade 2:** • Obtain Dermatology consult. • Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (.e.g., urea cream).

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		• If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	• 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, consider, as necessary, discussing 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, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**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]. • 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).[a] • Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**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:** • Consider consulting an endocrinologist for endocrine events. • Consider, as necessary, discussing with study physician. • Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			pain, unusual bowel habits, polydipsia, polyuria. hypotension, and weakness. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). • Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). • For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. • If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** • Monitor patient with appropriate endocrine function tests. • For suspected hypophysitis/hypopituitariusm, consider consultation of an endocrinologist to guide assessment of early morning ACTH, cortisol, TSH, and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). • If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, 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 (e.g. adrenal insufficiency) 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 ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** • Consult endocrinologist to guide evaluation of endocrine function, and , as indicated by suspected endocrinolopathy and as clinically indicated, consider pituitary scan. • For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type I DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., , hydrocortisone, sex hormones). • Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. • Isolated Type I diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. • Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] • For patients with normal endocrine workup (laboratory

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type I diabetes mellitus, 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g. adrenal insufficiency) can be treated 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 < 10 mg/day or equivalent	**For Grade 3 or 4:** • Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended • For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type I DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). • For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. • Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. • Isolated Type I diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. • Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** • Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). • Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). • Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). • Perform symptomatic treatment with Neurology 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:** • Consider, as necessary, discussing with the study physician. • Obtain Neurology consult. • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., 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 (e.g., 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 imAE does not resolve to Grade ≤1 within 30 days.	**For Grade 3 or 4:** • Consider, as necessary, discussing with study physician. • Obtain Neurology consult. • Consider hospitalization.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
		For Grade 4: Permanently discontinue study drug/study regimen.	• 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 (e.g., 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 (e.g., 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 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 Neurology consult. • Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			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:** • Consider, as necessary, discussing 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.
	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 respiratory insufficiency or autonomic instability.	**For Grade 2:** • Consider, as necessary, discussing 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 • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). • MYASTHENIA GRAVIS: • 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.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			• 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. • 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: • 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 imAE 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):** • Consider, as necessary, discussing with study physician. • Recommend hospitalization. • Monitor symptoms and obtain Neurology 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.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**

			• If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.
			• GUILLAIN-BARRE:
			  • 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.

Myocarditis	**Any Grade**	**General Guidance** <u>Discontinue drug permanently if biopsy-proven immune-mediated myocarditis</u>	**For Any Grade:** • The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function • Consider, as necessary, discussing with the study physician. • Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures.

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			• Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** • Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. • Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	**For Grade 2:**Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. **For Grade 3-4:** permanently discontinue study drug/study regimen.	**For Grade 2-4:** • Monitor symptoms daily, hospitalize. • Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. • Supportive care (e.g., oxygen). • If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). **Caution:** It is important to rule out sepsis and refer to infliximab label

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			for general guidance before using infliximab. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** • Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. • If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. • Consider, as necessary, discussing with the study physician. • Initial work-up should include clinical evaluation, creatine

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. • Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	No dose modification	**For Grade 1:** • Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated • Consider neurology consult. • Consider, as necessary, discussing with the study physician
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	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 respiratory insufficiency.	**For Grade 2:** • Monitor symptoms daily and consider hospitalization. • Obtain Neurology consult, and initiate evaluation. • Consider, as necessary, discussing with the study physician. • If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant • If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** • Monitor symptoms closely; recommend hospitalization. • Obtain Neurology consult, and complete full evaluation. • Consider, as necessary, discussing with the study physician. • Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. • If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no

Specific Immune-mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 4.03)**	**Dose Modifications**	**Toxicity Management**
			improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., 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. • Consider whether patient may require IV IG, plasmapheresis. • Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[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; C Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated 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; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia) ; 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 (e.g., 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 (e.g., 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 (e.g., 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 (i.e., 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.

Appendix H Schedule of study procedures: Follow-up for subjects who have completed durvalumab, tremelimumab and olaparib treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued study treatment due to toxicity in the absence of confirmed progression of disease

Evaluation	Time Since Last Dose of Durvalumab or Tremelimumab or Olaparib							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination [a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse) [b]	X							
Weight	X							
Urine hCG or serum βhCG	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
ECOG performance status	X	X	X		X (and month 9)			X
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology [c]	X	X	X					
Chemistry [d]	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4)[e]	X							

Evaluation	Time Since Last Dose of Durvalumab or Tremelimumab or Olaparib							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 12 weeks relative to the date of **first infusion** thereafter until confirmed PD by irRECIST by investigational site review. Please refer to Table 5 for timings of confirmatory scans. For subjects who **discontinue durvalumab + tremelimumab due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the date of **first infusion** as follows: every 12 weeks until confirmed PD by irRECIST by investigational site review or started on standard therapy or another clinical study. Please refer to Table 5 for timings of confirmatory scans. Upon confirmed PD or initiation of standard therapy, scans should be conducted according to local standard clinical practice.							

a Full physical exam (refer to Section 8.3.2).

b Refer to Section 8.3.4.

c Refer to Section 8.3.5, Table 6..

d Refer to Section 8.3.5, Table 7.

c 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.

Appendix I Schedule of study procedures: follow-up for subjects who have discontinued study treatment due to confirmed progression of disease at the investigator discretion

Evaluation	Time Since Last Dose of Durvalumab or Tremelimumab or Olaparib							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination [a]	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse) [b]	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X							
Palliative radiotherapy	As clinically indicated →							
ECOG performance status [c]	X							
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology [d]	X							
Chemistry [e]	X							
Thyroid function tests (TSH, and fT3 and fT4) [f]	X							
miRNA/mRNA (to examine immune cell gene expression profiles in circulation), if applicable	X							
blood for immune monitoring	X							
Tumour assessment (CT or MRI)	For subjects who **continue on durvalumab + tremelimumab post-confirmed progression** at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of **first infusion** per Table 5 until durvalumab + tremelimumab is stopped. For subjects who **discontinue durvalumab + tremelimumab following confirmed progression**, **scans should be conducted according to local clinical practice** and submitted for central review until a new treatment is started (these scans are optional).							

a Full physical exam (refer to Section 8.3.2)
b Refer to Section 8.3.4.
c Refer to Section 8.3.4, Table 6.
d Refer to Section 8.3.4, Table 7.
e PS to be collected if available at the 2 monthly calls to obtain subsequent anti-cancer therapy and survival status
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.

Appendix J Diary for Medication (Olaparib)

Study No.: _____ **Patient Name:** _____

Drug Name: _____

Cycle (Please circle one.): 1 2 3 4 5 6
7 8 9 10 11 12

Medical Record No.: _____

Study Medication Calendar

Please complete this calendar on a daily basis immediately after you take your pills. Fill in the date for each day and the time the pill is taken in the AM and PM space (not check mark) and write the total number of pills you take each day.

Start Date: _____

Cycle Day		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Date								
Dose								
Number of pills taken (Please Note time)	AM							
	PM							

Cycle Day		Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Date								
Dose								
Number of pills taken(Please Note time)	AM							
	PM							

Cycle Day		Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Date								
Dose								
Number of pills taken(Please Note time)	AM							
	PM							

Cycle Day		Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Date								
Dose								
Number of pills taken(Please Note time)	AM							
	PM							

Please remember to bring this calendar and your pill bottle (including any unused pills) with you to your next clinic appointment.

Coordinator's Use Only

$$\%\ Compliance = \left(\frac{Number\ of\ Pills\ Dispensed - Number\ of\ Pills\ Returned}{Number\ of\ Pills\ Scheduled}\right) \times 100$$

$$\_\_\_\_\%\ Compliance = \left(\frac{\_\_\_\_\_}{\_\_\_\_\_}\right) \times 100$$

Patient signature: _____ Date: _____

CRC signature: _____ Date: _____

Investigator signature:

Appendix K irRECIST Summary

Tumor response assessment using the Immune-Related response Criteria as described by Nishino et al, 2013* and Bohnsack et al, 2014**.

1.0 Baseline

1.1 Measurable Lesion Definitions and Target Lesion Selection

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline
- Measurable lesions must be accurately measured in at least one dimension with a minimum size of:
    - 10 mm in the longest diameter by CT or MRI scan (or no less than double the slice thickness) for non- nodal lesions and ≥ 15 mm in short axis for nodal lesions.
    - 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
    - 20 mm by chest X-ray
- A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

1.2 Non-measurable Lesion Definitions

- Non-target lesions will include:
    - Measurable lesions not selected as target lesions
    - All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is < 10 mm (or < two times the axial slice thickness), i.e., the longest perpendicular diameter is ≥ 10 and < 15 mm.
    - Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.
- All lesions or sites of disease not recorded as target lesions (e.g., small lesions and non-measurable lesions) should be identified as non-target lesions and indicated as present in the source documents at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline. The general location will also be documented on the images, drawing a regularly-shaped Region of Interest.
- Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

1.3 Target and Non-Target Lymph Node Lesion Definitions

- To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.4 Non-Target Lesion Selection

- All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number on non-target lesions that can be recorded at baseline.

1.5 Bone Lesions

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Regardless of the imaging modality blastic bone lesions will not be selected as target lesions. Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥ 10 mm can be selected as target lesions.

1.6 Brain Lesions

- Brain Lesions detected on brain scans can be considered as both target or non-target lesions.

1.7 Cystic and Necrotic Lesions as Target Lesions

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Lesions that are partially cystic or necrotic can be selected as target lesions.
- The longest diameter of such a lesion will be added to the ***Total Measured Tumor Burden (TMTB)*** [1] of all target lesions at baseline.
- If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.

1.8 Lesions with Prior Local Treatment

- During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.).
- Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

1.9 No Disease at Baseline

- If a patient has no measurable and no non-measurable disease at baseline the radiologist will assign '***No Disease***' (irND) as the overall tumor assessment for any available follow-up time-points unless new measurable lesions are identified and contribute to the TMTB.

2.0 Follow-Up

2.1 Recording of Target and New Measurable Lesion Measurements

- The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axes of nodal target and new nodal measurable lesions will be recorded. Together they determine the ***Total Measured Tumor Burden (TMTB)*** at follow-up.

$$\textbf{TMTB \% change} = \frac{\textbf{Baseline Tumor Burden} - \textbf{Current Tumor Burden}}{\textbf{Baseline Tumor Burden}} \times \mathbf{100}$$

2.1 Definition of New Measurable Lesions

- In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time-point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

2.2 Non-Target Lesion Assessment

- The RECIST 1.1 definitions for the assessment of non-target lesions apply (i.e., measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation).
- The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN).
- Non-target lesions do not affect irPR and irSD assessments.
- Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD.

2.3 New Non-Measurable Lesions Definition and Assessment

- All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively.
- Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time-point.
- Persisting new non- measurable lesions prevent irCR.

2.4 irRECIST Overall Tumor Assessments

The irRECIST overall tumor assessment is based on the ***TMTB*** (total measured tumor burden) of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

Time point response assessments will be performed on Cycle 4 Day 1 (± 7 days) and then every 3 cycles.

Conventional RECIST 1.1 will also be documented during the trial however; RECIST 1.1 will not be used to determine disease progression. The irRECIST will be used for tumor response assessment at time of continuing review and will be used for IRB reporting and formal analysis.

- **irCR:** Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not mandatory.
- **irPR:** Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.
- **irSD:** Failure to meet criteria for irCR or irPR in the absence of irPD.

- **irNN:** No target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
- **irPD:** Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
- **irNE:** Used in exceptional cases where insufficient data exists.
- **irND:** In adjuvant setting when no disease is detected.

New Lesions: the presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements (the sum of the measurements = the sum of the longest diameters of all target lesions and new lesions, if any).

2.5 Confirmation Measurement

A confirmatory assessment is required no less than 6 weeks after a PR or CR is deemed by irRECIST

3.0 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans) however, conventional CT scan is the preferred modality to determine response to treatment.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the irRECIST or RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound

in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Tumor Markers:** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response.

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Appendix L Calculation for Creatinine Clearance

Cockroft-Gault Equation*

Men: CrCl = [(140-YR) x IBW] / (SCr x 72)

Women: CrCl = 0.85 x [(140-YR) x IBW] / (SCr x 72)

Note: At Roswell Park, clinical lab chemistries are performed with plasma.

Where:

CrCl is creatine clearance (mL/min)

IBW is ideal body weight (kg)

SCr is serum creatinine (mg/dL)

YR is age (years)

***Cockcroft D, W, Gault M, H, Prediction of Creatinine Clearance from Serum Creatinine. Nephron. 1976; 16 (1):31-41)**

Appendix M PAXgene® RNA Tube Freezing/Storage

1) Collect blood into PAX tube
2) Let tubes stand UPRIGHT for a minimum of 2 hours and a maximum of 72 hours at RT (18-25°C) Tubes should be placed in a wire or plastic rack. DO NOT USE Styrofoam.
3) Transfer specimens to -20°C freezer for 24 hours
4) After 24 hours move tubes to -70 to -80°C freezer for storage until batch shipment

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