Investigational Drug Substance(s)	Durvalumab (MEDI4736) and tremelimumab
Study Number	ESR-17-13142 / KGOG3046
Version Number	1.8
Date	12 Jan 2020

A phase II study of Neoadjuvant chemotherapy plus Durvalumab (MEDI4736) and Tremelimumab in Advanced-stage ovarian cancer (TRU-D)

Sponsor: Jung-Yun Lee

PROTOCOL SYNOPSIS

Clinical Protocol xxxxxxxx

Study Title: A phase II study of Neoadjuvant chemotherapy plus Durvalumab and Tremelimumab in Advanced-stage ovarian cancer
Protocol Number: ESR-17-13142
Clinical Phase: Phase II
Study Duration: 72 months
Investigational Product(s) and Reference Therapy: Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. Tremelimumab is supplied as a sterile solution for IV infusion, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL, accounting to 400 mg/vial or 25mg/vial) of tremelimumab, in an isotonic solution at pH 5.5. Chemotherapy regimen: Paclitaxel 175 mg/m^2 , Carboplatin AUC 5 or 6 (D1 every 3 weeks)
Research Hypothesis

Adding durvalumab and tremelimumab to chemotherapy in advanced-stage ovarian cancer can increase progression-free survival with minimal effects on safety.

Objectives:

Primary Objectives:

To evaluate the synergistic effects of durvalumab and tremelimumab plus chemotherapy in advanced-stage ovarian cancer

Primary endpoint : 12-months Progression-free survival (PFS) rate

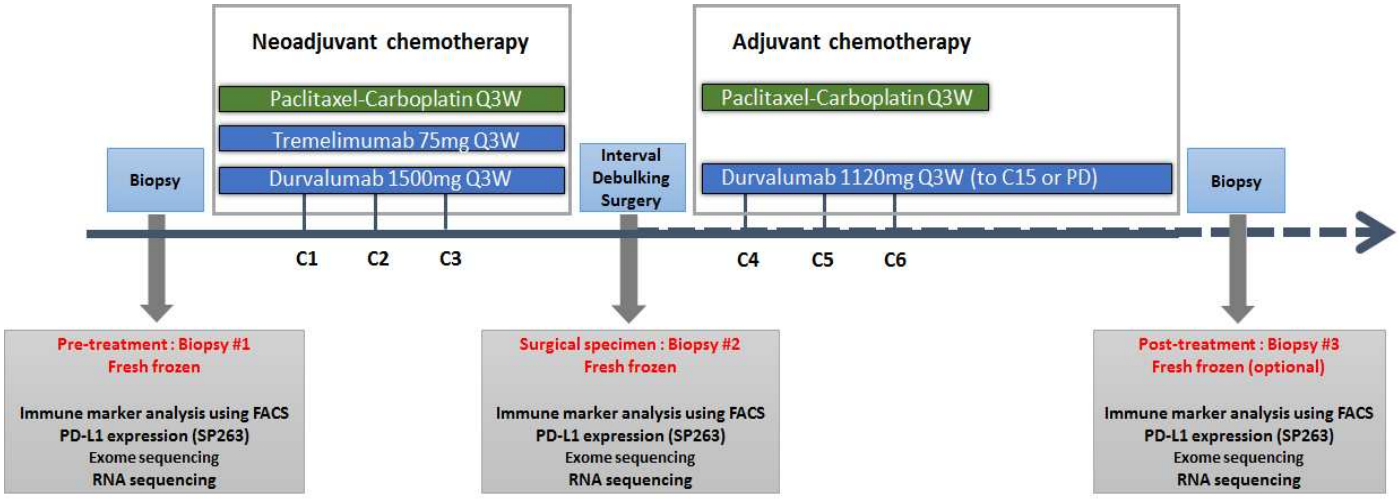
Secondary Objective(s):

To evaluate the safety of durvalumab and tremelimumab plus chemotherapy in advanced-stage ovarian cancer

Exploratory Objective(s):

To evaluate immune biomarker and immune dynamic change through serial biopsies.

Study Design:



Neoadjuvant treatment: Standard chemotherapy + Durvalumab + Tremelimumab Durvalumab : 1500mg q3 weeks (total 3 dosing) Tremelimumab : 75mg q 3 weeks (total 3 dosing) Chemotherapy regimen: Paclitaxel 175 mg/m2 , Carboplatin AUC 5-6 q3 weeks (total 3 dosing) Adjuvant treatment: Standard chemotherapy + Durvalumab Durvalumab; 1120mg q3 weeks (total 12 dosing) Chemotherapy regimen: Paclitaxel 175mg/m2, carboplatin AUC 5-6 q 3weeks (total3 dosing)
Number of Centers: 4
Number of Patients: Twenty four (24)
Study Population: Stage IIIC/IV ovarian cancer

Inclusion Criteria:

1. Histologically confirmed adenocarcinoma of ovary, fallopian tube, primary peritoneum(only up to 3 patients with clear cell carcinoma will be included and mucinous carcinoma will not be included)
2. Clinical stage IIIC/IV(according to revised FIGO staging in 2014)
3. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
4. Female aged 20 years older at the time of acquisition of informed consent
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 ~ 1
6. Must have life expectancy of at least 16 weeks
7. Body weight >30kg
8. Adequate normal organ and marrow function as defined below:
   - Haemoglobin ≥9.0 g/dL
   - Absolute neutrophil count (ANC ≥1.5 x 10^9/L
   - Platelet count ≥100 x 10^9/L

- Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). <<This will not apply to patients 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

- Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

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

Females:

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

9. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. 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).

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

Exclusion Criteria:

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

2. Participation in another clinical study with an investigational product during the last 60 days

3. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

4. Any previous treatment with anti-PD-1, PD-L1, CTLA-4 (including durvalumab and tremelimumab)

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

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

    – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

6. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable. <<amend as required based on any combination studies with other anticancer agents>>

7. Major surgical procedure (except diagnostic laparoscopy) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

8. History of allogenic organ transplantation.

9. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia
- Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients with celiac disease controlled by diet alone

10. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent

11. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1/2 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with a history of localised breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than two years prior to registration, and that the patient remains free of recurrent or metastatic disease

12. History of leptomeningeal carcinomatosis

13. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with IV contrast of the brain prior to study entry

14. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart) << For durvalumab ±tremelimumab in combination with an agent with pro-arrhythmic

potential or where effect of the combination on QT is not known if this criterion should be retained. Patient safety and the cardiac EKG should be consulted as needed>>.

15. History of active primary immunodeficiency

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

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

    – Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

    – Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent

    – Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

19. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or180 days after the last dose of durvalumab + tremelimumab combination therapy.

20. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

21. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment

Investigational Product(s), Dose, and Mode of Administration:

During neoadjuvant chemotherapy period:

Durvalumab + Tremelimumab + Standard chemotherapy

Durvalumab : 1500mg q3 weeks (total 3 dosing), intravenous

Tremelimumab : 75mg q3 weeks (total 3 dosing), intravenous

Chemotherapy regimen: (all intravenous)

Paclitaxel 175 mg/m2 , Carboplatin AUC 5-6 q3 weeks (total 3 dosing)

During adjuvant chemotherapy period:

Standard chemotherapy + Durvalumab

Durvalumab; 1120mg q3 weeks (total 12 dosing)

Chemotherapy regimen: (all intravenous)

Paclitaxel 175 mg/m2 , Carboplatin AUC 5-6 q3 weeks (total 3 dosing)

Study Assessments and Criteria for Evaluation:

Safety Assessments:

NCI-CTCAE (common toxicity criteria for adverse events) v5

Efficacy Assessments:

Chemotherapy response score, response rate via RECIST (Response evaluation criteria in solid tumor) v1.1 & immune-related Response Criteria, R0 rate at interval debulking surgery, progression free survival, overall survival

Pharmacodynamic/Pharmacokinetic Assessments :

We will find the immune dynamics change.
1. Analysis of immune marker using FACS
Examine the phenotypic characteristics of CD4 and CD8 T cells in terms of various immune check points (PD-1, CTLA4, TIM3, LAG3) and memory markers (CD45RO+/CCR7+) in fresh tissue and PBMC by FACS on pre-treatment, post-treatment(C1D8, blood sample only), at the time of surgery and at progression.
Examine the tumor infiltrating immune cells including Treg cells and MDSCs (CD11b+/Gr1+) on pre-treatment, post-treatment (C1D8, blood sample only), at the time of surgery and at progression.
Blood cytokine analysis will be performed at the time points with multi cytokine bead analysis on pre-treatment, post-treatment (C1D8, blood sample only), at the time of surgery and at progression..
2. Exome sequencing (tumor/normal pairs) of tumor tissues (fresh-frozen tumor tissues / FFPE) at pre-treatment, at the time of surgery and at progression to identify potential immune epitope and mechanisms of acquired resistance.
3. RNA sequencing or nanostring nCounter of available tissues (fresh-frozen tumor tissue / FFPE) at pre-treatment, at the time of surgery and at progression to identify potential immune-related gene signatures mRNA signature panel (IFN-r, extended, TCR, De novo)
4. PD-L1 testing at pre-treatment, at the time of surgery and at progression
5. Multiplex IHC at pre-treatment, at the time of surgery and at progression

Statistical Methods and Data Analysis:

The primary endpoint of the study is 12-months progression-free survival(PFS) rate.

PFS is defined as the time from treatment start until the first documented sign of disease progression or death from any cause; OS is defined as the time from first treatment until death from any cause. PFS and OS will be estimated using Kaplan-Meier techniques, and 95% confidence intervals (95% CIs) will be calculated. 12-months progression-free survival rates will be estimated, and 95% CIs will be calculated.

All the analyses will be based on the modified intent-to-treat (ITT) patient population, which including patients who received at least one dose of study drug.

Sample Size Determination:

This study is a single arm phase II trial with the primary endpoint of 12 month PFS rate. The 12 month PFS rate in the treatment arm is expected to be 70% against that of 50% in the historic control group. With 80% of statistical power, 5% of one-sided type I error, 21 patients are needed when patients are accrued for a period of 12 months and followed for a period of 30 months after the last patient is enrolled. The number of expected events would be 14. Considering 10% of drop-out, a total of 24 patients will be enrolled in this study.D, durvalumab; T, tremelimumab; SOC, standard of chemotherapy

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Screening**	**One cycle is considered 21 days. All assessments to be performed pre-infusion unless stated otherwise**				
		Neoadjuvant therapy		**Surgery**	**Adjuvant therapy**	**Follow-up**
		C1	**C2~C3**	**IDS**	**(C4 to C15 or PD)**	**From the first day of IP dose up to 5 years**
Day	**-28 to -1**	**D1**	**D1**		**D1**	**See Appendix 2 or 3**
Week	**-4 to -1**	**0**	**3, 6**		**Every 3 weeks**	
Window		**±1**	**±3**	**-3**	**±3**	
Written informed consent/assignment of screening number	X					
Demography	X					
Medical and surgical history	X					
Verification of eligibility criteria	X					
ECOG performance status	X	X	X		X	X[a]
Physical examination [b]	X	X	X		X	X[a]
Vital signs, body weight and height [c]	X	X	X		X	X[a]
Electrocardiogram [d]	X	Clinically indicated				
Hematology/chemistry [e]	X	X	X		X	X[a]
Hepatitis B and C; HIV	X					
Pregnancy test(urine or serum) [f]		Clinically indicated				
Thyroid function tests [g]	X	X	X		X	X[a]
Urinalysis [h]	X	Clinically indicated				
CA-125	X	X	X		X	X[a]
Tumor assessment (CT or MRI)[i]	X (AP-CT and PET-CT)		X (between C3 and IDS, AP-CT and PET-CT)		X (AP-CT every 3 cycles)	X[a]
Adverse event/serious adverse event assessment	X	X	X		X	X[a]

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Screening**	**One cycle is considered 21 days. All assessments to be performed pre-infusion unless stated otherwise**				
		Neoadjuvant therapy		**Surgery**	**Adjuvant therapy**	**Follow-up**
		C1	**C2~C3**	**IDS**	**(C4 to C15 or PD)**	**From the first day of IP dose up to 5 years**
Day	**-28 to -1**	**D1**	**D1**		**D1**	**See Appendix 2 or 3**
Week	**-4 to -1**	**0**	**3, 6**		**Every 3 weeks**	
Window		**±1**	**±3**	**-3**	**±3**	
Concomitant medications	X	X	X		X	X[a]
Blood sample for genomic analysis (optional on C1D8 and at the progression)	X	X(D8±2, optional)		X		
Tumor tissue sample for genomic analysis (optional at the progression)	X			X		
Chemotherapy		X	X		X(from C4 to C6)	
Durvalumab		X	X		X	
Tremelimumab		X	X			

a According to APPENDIX 2(Schedule of study procedures: follow-up for patients who have completed durvalumab and tremelimumab treatment and achieved disease control (until confirmed progression of disease) and patients who have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progression of disease) or APPENDIX 3(Schedule of study procedures: follow-up for patients who have discontinue durvalumab and tremelimumab treatment due to confirmed progression of disease at the investigator discretion)

b Full physical examination at baseline; targeted physical examination at other time points

c Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded at each visit along with vital signs. Height will be measured at Screening only.

d ECG during Screening and as clinically indicated. Screening and abnormal ECG at any time in triplicate others single. 1 ECG is needed as clinically indicated during treatment and should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion.

e If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Coagulation tests: aPTT and INR – only performed at Screening and as clinically indicated. Table 4 shows laboratory tests for Screening, Day1 and clinically indicated.

f Pre-menopausal female subjects of childbearing potential only

g If TSH is performed within 14 days prior to Day 1 they do not need to be repeated at Day 1. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

h Urinalysis performed at Screening and as clinically indicated.

i Tumor imaging window period : ±7

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ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report

Abbreviation or special term	Explanation
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E

Abbreviation or special term	Explanation
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease

Abbreviation or special term	Explanation
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine

Abbreviation or special term	Explanation
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

Clinical Study Protocol

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1. INTRODUCTION

1.1 Disease background

Ovarian cancer is the deadliest gynecologic cancer. The current standard therapy is surgical cytoreduction followed by taxane-platinum combination chemotherapy. However, most patients with advanced-stage ovarian cancer will experience a relapse of disease. Therefore, there is an urgent need to improve outcomes of patients with this aggressive cancer.

1.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn 2004).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al. 2012; Hirano et al. 2005; Iwai et al. 2002; Okudaira et al. 2009; Topalian et al. 2012; Zhang et al. 2008) with responses

that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al. 2014; Rizvi et al. 2015; Segal et al. 2015). In addition, high mutational burden e.g., in bladder carcinoma (Alexandrov et al. 2013) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. (Fife and Bluestone, 2008) Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, data from agents in the anti-PD-1/PD-L1class shows clinical activity in a wide range of tumor types.

1.1.2 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It 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.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 6.5. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.2 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (Tarhini and Kirkwood 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3 Durvalumab in combination with tremelimumab

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012); therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications 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 the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 3000 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Sections 1.4.2. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

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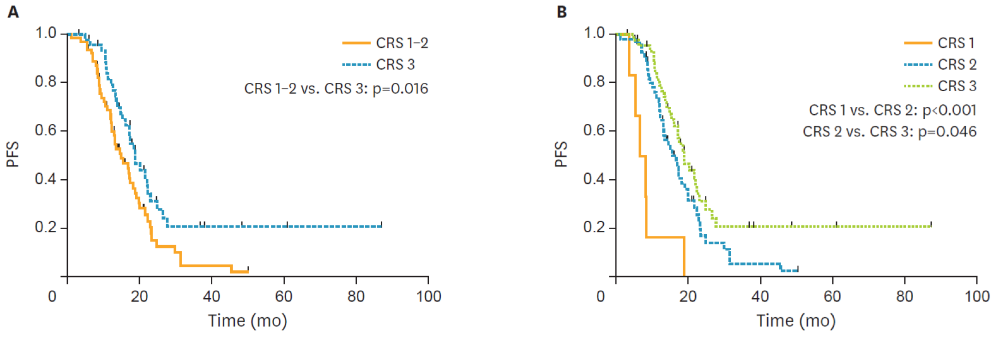
1.2 Research hypothesis

Adding durvalumab and tremelimumab to current neoadjuvant chemotherapy (front-line therapy) in advanced-stage ovarian cancer can increase response rate and improve patient's outcome such as progression-free survival and overall survival with minimal effects on safety.

1.3 Rationale for conducting this study

Recently, several phase 3 clinical trials have demonstrated that survival and the postoperative morbidity and mortality rates after receiving neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) are not inferior to those following PDS in women with stage III–IV ovarian cancer (Onda et al 2008; Vergote et al 2010; Kehoe et al 2015; Fagotti et al 2016). Therefore, NAC followed by IDS is an alternative approach for treating advanced-stage ovarian cancer. Moreover, the tumor response to NAC predicts survival and can be considered a surrogate prognostic marker. Recently, Bohm et al proposed a simple and reproducible scoring system for grading the response to NAC based on histopathological examination of IDS specimens (Bohm et al 2015). They reported that the three-tiered chemotherapy response score (CRS) of omental tissue sections showed a significant association with PFS and OS in their validation cohort. Our group performed validation of CRS system for assessing treatment response in an external cohort of ovarian cancer treated with NAC (Lee et al 2017).

External validation of CRS in a cohort from Yonsei Cancer Hospital



So far, emerging clinical data show limited clinical efficacy of check point inhibitors in ovarian cancer with objective response rate of 10-15% with some durable responses. To improve the efficacy of anti-PD-L1 inhibitor, combination with anti-CTLA-4 antibody and/or chemotherapy is suggested with promising results. In other solid cancer, several studies such

as POSEIDON are ongoing evaluating efficacy and safety of anti-PD-L1 inhibitor and anti-CTLA-4 antibody plus chemotherapy. Therefore, we proposed combination therapy of durvalumab, tremelimumab, and NAC to improve outcomes in advanced-stage ovarian cancer.

1.3.1.1 Durvalumab + 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.

Pharmacokinetics/Pharmacodynamics data

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. 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 maximum plasma concentration 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 ($C_{trough,ss}$) 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 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Clinical data

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the benefit-risk profile in an acceptable range of PK and pharmacodynamic values.

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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 patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

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. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response.

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

1.3.2 Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I 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 the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PKexposures (AUC_{ss},0-28, $Cmax_{,ss}$, and $Cmin_{,ss}$) using the population PK model. A fixed dose of 750 mg Q2Wwas selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (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 (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady state Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W .
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 kg 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-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al. 2006; Wang et al. 2009; Zhang et al. 2012; Narwal et al. 2013). Wang and colleagues 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 (Wang et al. 2009). 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-patient variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al. 2012).

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 1500 mg (neoadjuvant chemotherapy period)/ 1120mg (adjuvant chemotherapy period) Q3W durvalumab (equivalent to 20 mg/kg or 15mg/kg Q3W) and a fixed dose of 75 mg Q3W tremelimumab (equivalent to 1mg/kg Q3W) is included in the current study.

1.4 Benefit-risk and ethical assessment

1.4.1 Potential benefits

1.4.1.1 Durvalumab + tremelimumab

Promising evidence of clinical activity has been observed for durvalumab, and tremelimumab in ovarian cancer as well as in other solid tumors. The experience to date with the abovementioned targeted agents suggests that adding durvalumab and tremelimumab to current neoadjuvant chemotherapy can provide significant clinical activity with a manageable safety profile that is superior to that of standard care of chemotherapy.

1.4.1.2 Overall risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects, can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

1.4.1.3 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus.

Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Appendix 1)

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

1.4.1.4 Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia.

For information on all identified and potential risks with tremelimumab please always refer to the current version of the tremelimumab IB.

Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnoea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

Further information on these risks can be found in the current version of the tremelimumab IB.

A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

1.4.2 Durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being

studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20m/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities.

For information on all identified and potential risks with the durvalumab+tremelimumab combination please always refer to the current version of the durvalumab IB

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥ 10% of patients) are fatigue, diarrhoea,nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, oedema peripheral, weight, decreased hyponatraemia and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 15% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

1.4.3 Overall benefit-risk

Refer to the Investigator' Brochure (IB) for each agent used for information on the potential benefits of each agent and an assessment of the potential and known risks.

Ovarian cancer is not considered as immune-flamed tumor. Therefore, previous studies show limited clinical efficacy of immune check point inhibitors in ovarian cancer with objective response rate of 10-15% with some durable responses. To improve the efficacy of anti-PD-L1 inhibitor, combination with anti-CTLA-4 antibody and/or chemotherapy is suggested with promising results. Chemotherapy is known to increase release of tumor antigens and induce neoantigen through immunogenic cell death. From this study, we expect increasing response rates from neoadjuvant chemotherapy, durvalumab, and tremelimumab. In addition, we expect durable responses from adjuvant chemotherapy and durvalumab maintanence.

However, some toxicity from combination therapy are anticipated. Previous clinical trials investigated the safety of combination therapy (chemotherapy, immune check point inhibitors) Q3W regimen.

PK modelling has been carried out to predict the effect of switching from a Q4W regimen to a Q3W regimen for both durvalumab (1500 mg; 4 doses) and tremelimumab (75 mg; 4 doses)

exposures. Results suggest that a Q3W regimen would yield similar exposures to Q4W; both durvalumab and tremelimumab are expected to yield a slightly higher Cmax and Cmin on a 3 week schedule, but a lower AUC. For durvalumab, Cmax values were 660 vs. 596 (μg/mL), Cmin, were 144 vs. 94 (μg/mL), and AUC was 5879 vs.6061 (μg/mL) for Q3W and Q4W schedule, respectively. For tremelimumab, Cmax is 26.1 vs. 25.1 (μg/mL), Cmin is 7.2 vs. 5.7 (μg/mL), and AUC is 267 vs. 289 (μg/mL), respectively for the Q3W vs. Q4W regimen. Therefore, PK modeling suggests that a Q3W schedule does not impose a significant increased safety risk based on expected durvalumab and tremelimumab exposures. Taken together, the totality of data provides sufficient safety data to support the combination of 1500mg durvalumab plus 75mg tremelimumab with chemotherapy. There is supportive safety data for the combination of 1120 mg durvalumab plus 75 mg tremelimumab Q3W x 4 doses followed by 1120 mg durvalumab Q3W from Study D419SC00001. The safety of the combination of 1125 mg durvalumab (Q3W) plus tremelimumab 75mg (multiple doses, Q6W) or 225mg (3 doses, Q6W) or 56mg (multiple doses, Q3W) with chemotherapy has been assessed in more than 100 patients in the CCTG Phase I trial. Clinical data from NSCLC patients in Study D4190C00006 suggest that increasing the dose of durvalumab has no significant impact on the safety and tolerability of the durvalumab and tremelimumab combination. In addition, PK modelling data suggest there will be a minimal impact on IP exposure if the standard doses (1500/75) are given on a Q3W regimen.

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2. STUDY OBJECTIVE

2.1.1 Primary objective(s)

To evaluate the synergistic effects of durvalumab and tremelimumab plus chemotherapy in advanced-stage ovarian cancer

Primary outcome is 12-months PFS rate.

Secondary outcome is response rate by RECIST version 1.1 after neoadjuvant chemotherapy, immune-related response criteria after neoadjuvant chemotherapy, response rate by PERCIST after neoadjuvant chemotherapy, R0 rate at interval debulking surgery, the rate of Chemotherapy Response Score 3, overall survival, and safety

Followings are details how Chemotherapy Response Score (CRS) will be analyzed.
Resected specimens from interval debulking surgery will be formalin-fixed and paraffin-embedded according to standard procedures and stained with H&E. The slides will be collected at Yonsei Cancer Center. All slides will be reviewed by an experienced gynecologic pathologist (Prof. Hyun Soo Kim). The slide with the most viable tumor and/or the least chemotherapy response was selected from omentum.
A Pathologist will independently score each slide according to the 3-tiered CRS system proposed by Bohm et al. In brief, CRS 1 indicases no or minimal tumor responses; mainly viable tumor with no or minimal regression-assocaited fibroinflammatory changes, limited to a few foci and cases in which it is difficult to decide between regression and tumor-associated desmoplasia or inflammatory cell infiltration. CRS 2 indicates appreciable tumor response amid viable tumor that is readily identifiable; multifocal or diffuse regression-associated fibroinflammatory changes with viable tumor in sheets, streaks, or nodules; and extensive regression-associated fibroinflammatory changes with multifocal residual tumor, which is easily identifiable. CRS 3 indicates complete or near-complete response with no residual tumor; minimal irregularly scattered tumor foci seen as individual cells, cell groups, or nodules up to 2 mm maximum size; mainly regression-associated fibroinflammatory changes; and no or very little residual tumor in the complete absence of any inflammatory response.

Examples of histopathological features of tumor regression after NAC corresponding to CRS 1 to 3

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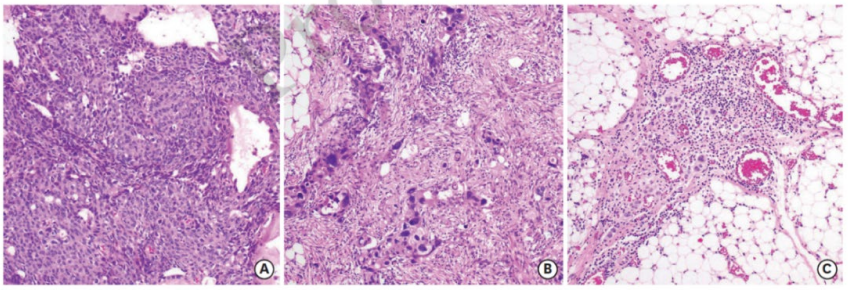

Fig. 1. Examples of histopathological features of tumor regression after NAC corresponding to CRS 1 to 3. CRS 1: no or minimal tumor response (A). CRS 2: appreciable tumor response amid viable, readily identifiable tumor (B). CRS 3: complete or near-complete response with no or minimally residual tumor (C). CRS, chemotherapy response score; NAC, neoadjuvant chemotherapy.

2.1.2 Secondary objective(s)

To evaluate the safety of durvalumab and tremelimumab plus chemotherapy in advanced-stage ovarian cancer

2.1.3 Exploratory objective(s)

To explore immune biomarker and immune dynamic change through serial biopsies by comparing immune signature before and after treatment

3. STUDY DESIGN

3.1 Overview of study design

This study is single arm phase II study to evaluate efficacy and safety of durvalumab and tremelimumab and chemotherapy in treatment-naïve clinical stage IIIC/IV ovarian cancer

3.2 Study schema

Specific study flow will be presented in figure 1.

- During neoadjuvant period

Durvalumab : 1500mg q3 weeks (Total 3 dosing)

Tremelimumab : 75mg q3 weeks (Total 3 dosing)

Paclitaxel 175 mg/m2 (Total 3 dosing)

Carboplatin AUC 5-6 (Total 3 dosing)

- Surgery

At the time of surgery, chemotherapy response score and other immune marker analysis will be performed.

- During adjuvant period

Durvalumab : 1120mg q3 weeks (Total 12 dosing)

Paclitaxel 175 mg/m2 (Total 3 dosing)

Carboplatin AUC 5-6 (Total 3 dosing)

After treatment,

Post-operative follow-up will be done until maximum 5 year.

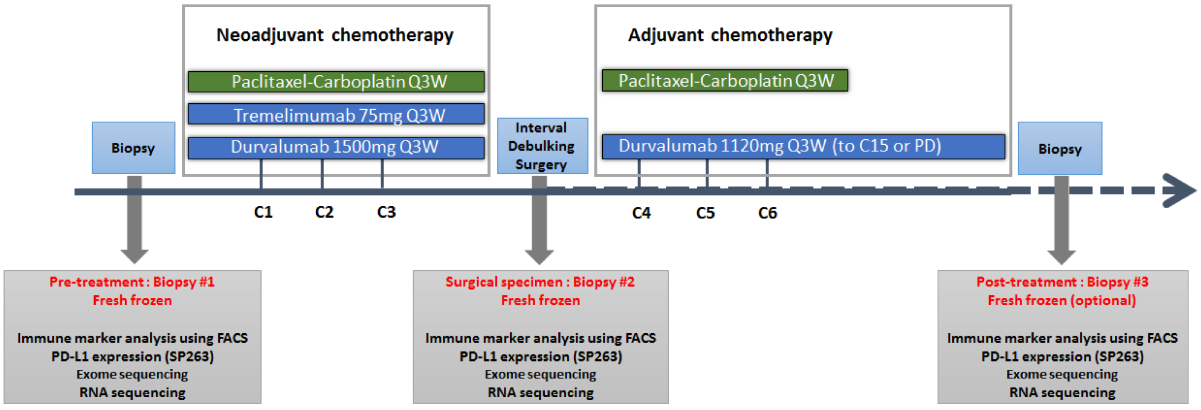

Figure 1. Study flow chart

3.3 Study oversight for safety evaluation

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, *laboratory data, vital signs, ECGs, and exposure*. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. "On treatment" will be defined as assessments between date of *start dose* and 90 days following discontinuation of IP (ie, the last dose of durvalumab ± tremelimumab therapy). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

AEs will be listed individually by patient, and the number of patients experiencing each AE will be summarized by CTCAE grade. Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. *Exposure to Durvalumab*

± *tremelimumab* ± *Chemotherapy will be summarized*. Time on study, dose delays and dose reductions, where necessary will also be summarized.

A separate data listing of AEs occurring more than 90 days after discontinuation of IP will be produced. These events will not be included in AE summaries.

The study may be stopped if, in the judgment of principal investigator, study patients are placed at undue risk because of clinically significant findings that meet any of the following criteria:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study drug
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the patients at the time of discontinuation of follow-up must be recorded in the eCRFs. All reasons for discontinuation of treatment must be documented.

In terminating the study, AstraZeneca will ensure that adequate consideration is given to the protection of the patients' interests. If this study is discontinued, all other studies involving durvalumab or tremelimumab will remain open to enrolment and screening, if deemed appropriate by AstraZeneca.

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Under no circumstances will there be exceptions to this rule.

4.1 Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

11. Histologically confirmed adenocarcinoma of ovary, fallopian tube, primary peritoneum(only up to 3 patients with clear cell carcinoma will be included and mucinous carcinoma will not be included)

12. Clinical stage IIIC/IV(according to revised FIGO staging in 2014)

13. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and any locally required authorization (eg, Health Insurance Portability and Accountability Act in the US, European Union [EU] Data Privacy Directive in the EU) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

14. Female aged 20 years older at the time of acquisition of informed consent

15. Eastern Cooperative Oncology Group (ECOG) performance status of 0 ~ 1

16. Must have life expectancy of at least 16 weeks

17. Body weight >30kg

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

- Haemoglobin ≥9.0 g/dL
- Absolute neutrophil count (ANC ≥1.5 x 10^9/L
- Platelet count ≥100 x 10^9/L
- Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). <<This will not apply to patients 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

- Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

  Males:

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

  Females:

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

19. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. 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).

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

4.2 Exclusion criteria

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

5. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)

6. Participation in another clinical study with an investigational product during the last 60 days

7. Concurrent enrolment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

8. Any previous treatment with anti-PD-1, PD-L1, CTLA-4 (including durvalumab and tremelimumab)

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

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

    – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

23. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable. <<amend as required based on any combination studies with other anticancer agents>>

24. Major surgical procedure (except diagnostic laparoscopy) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

25. History of allogenic organ transplantation.

26. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease,

rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia
- Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients with celiac disease controlled by diet alone

27. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent

28. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ (DCIS), Stage 1, grade 1/2 endometrial carcinoma, or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years. Patients with a history of localised breast cancer may be eligible, provided they completed their adjuvant chemotherapy more than two years prior to registration, and that the patient remains free of recurrent or metastatic disease

29. History of leptomeningeal carcinomatosis

30. Brain metastases or spinal cord compression. Patients with suspected brain metastases at screening should have an MRI (preferred) or CT each preferably with IV contrast of the brain prior to study entry

31. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart) << For durvalumab ±tremelimumab in combination with an agent with pro-arrhythmic potential or where effect of the combination on QT is not known if this criterion should be retained. Patient safety and the cardiac EKG should be consulted as needed>>.

32. History of active primary immunodeficiency

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

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

    – Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

    – Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent

    – Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

35. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

36. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or180 days after the last dose of durvalumab + tremelimumab combination therapy.

37. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

38. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3

If a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

4.3 Withdrawal of patients from study treatment and/or study

Permanent discontinuation of investigational product

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

1. An individual patient will not receive any further durvalumab ± tremelimumab therapy or if their weight falls to 30kg or less
2. Withdrawal of consent or lost to follow-up
3. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
4. Patient 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
5. Pregnancy or intent to become pregnant
6. Any AE that meets criteria for discontinuation as defined in Section 0.
7. Grade ≥3 infusion reaction
8. Patient 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 patient is no longer benefiting from treatment with durvalumab ± tremelimumab. Patients 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
11. Patients who are permanently discontinued from receiving investigational product will be followed for safety per Section 10 and Appendix 2 or Appendix 3, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the patient is lost to follow-up or enrolled another clinical study. All

patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Withdrawal of consent

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

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

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

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

- all further participation in the study including any further follow up (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

4.4 Replacement of patients

If a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab and tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the investigator as a solution for infusion after dilution.

5.1.1 Formulation/packaging/storage

Durvalumab

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial or 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. The nominal fill volume is 20.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in secondary container until use to prevent excessive light exposure.

5.2 Dose and treatment regimens

5.2.1 Treatment regimens

Durvalumab ± tremelimumab combination therapy

Patients in the durvalumab + tremelimumab combination therapy will receive durvalumab (1500mg Q3W) in combination with tremelimumab (75 mg IV Q3W) for up to 3 doses/cycles each, followed by durvalumab 1120mg Q3W for up to a maximum of 9 months (12 additional doses/cycles) until disease progression unless there is unacceptable toxicity, withdrwal of consent, or another discontinuation criterion is met

Tremelimumab will be administered first; the durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Standard infusion time for each is 1 hour. In the event that there are interruptions during infusion, the total allowed

time should not exceed 8 hours at room temperature per infusion. If there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab can be given immediately after the tremelimumab infusion has finished.

Figure 1. Durvalumab (MEDI4736) ± tremelimumab combination therapy dosing schedule

Neoadjuvant chemotherapy															
Cycle	1	2	3	IDS											
Week	0	3	6	9											
Durvalumab	O	O	O	X	Q3W (3 doses)										
Tremelimumab	O	O	O	X	Q3W (3 doses)										
Adjuvant chemotherapy															
Cycle	4	5	6	7	8	9	10	11	12	13	14	15			
Week	12	15	18	21	24	27	30	33	36	39	42	45			
Durvalumab	O	O	O	O	O	O	O	O	O	O	O	O	Q3W (12 doses)		

5.2.2 Duration of treatment and criteria for retreatment

Not applicable in this study

5.2.3 Study drug preparation of durvalumab and tremelimumab

Based on average body WT of 75 kg, 1500 mg Q3W durvalumab (equivalent to 20 mg/kg Q3W) for neoadjuvant chemotheray/ 1120 mg Q3W durvalumab (equivalent to 15mg/kg Q3W) for adjuvant therapy and 75 mg Q3W tremelimumab (equivalent to 1 mg/kg Q3W) is included in the current study.

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

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

A dose of 1500mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (ie, 1500mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

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

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

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

A dose of 75 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 3.8 mL (ie,75 mg of tremelimumab, with the dose volume rounded to the nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

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

5.2.4 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. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix 1.

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

5.2.5 Accountability and dispensation

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

5.2.6 Disposition of unused investigational study drug

The investigator is responsible for keeping accurate records of the clinical supplies received from AstraZeneca, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

5.3 Paclitaxel, Carboplatin

Paclitaxel will be administered at a 175mg/m2 day 1 of every 3 weeks for 3 doses during treatment period. There should be an interval of at least 18 days between the doses of paclitaxel. To calculate the first dose of paclitaxel, the body weight measured at study enrollment can be used instead of that on the day of administration (predose). The dose on Day 1 of each cycle should be continued throughout the cycle as a rule. If the subject has had a ≥10% change in body weight from that measured at the initial dose, the dose should be adjusted. If the change is observed on the day of administration from the initial dose, the dose can be adjusted from the next administration onwards. Each dose should be similarly adjusted if a further body weight change of ≥10% is observed after the previous change. The dose (mg) will be rounded to one decimal place. Although administration should be performed per procedure of the study site, recommended procedure is as follows:

Paclitaxel will be administered intravenously through an in-line filter using a membrane filter of ≤0.22 μm over 30 minutes in accordance with the package insert. Pretreatment and adverse reactions to paclitaxel must be treated appropriately with reference to local standards, such as the package insert and treatment guidelines.

Carboplatin AUC 5 or 6 will be administered as an IV infusion over 30 minutes every 3 weeks following paclitaxel infusions. To calculate the first dose of carboplatin, Calvert formula can be used.

Calvert formula : Dose (mg) = Target AUC (mg/mL per min) X [CrCl (mL/min) + 25]

6. TREATMENT PLAN

6.1 Patient enrollment

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

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations. All patients will be required to provide consent to supply a sample of their tumor (archived or newly acquired biopsy) for entry into this study. This consent is included in the main patient informed consent form (ICF). Screening/baseline evaluations may be performed over more than 1 visit.

6.1.1 Procedures for randomization

Not applicable

6.1.2 Procedures for handling patients incorrectly enrolled

Patients who fail to meet the eligibility criteria should not, under any circumstances, receive study medication. There can be no exceptions to this rule. Patients who are enrolled but found to not meet all the eligibility criteria must not be initiated on treatment and must be withdrawn from the study as a screen failure. When a patient does not meet all the eligibility criteria but incorrectly starte on treatment, the Investigator should inform the Study Physician immediately, and the Study Physician and the Investigator should discuss whether to continue or discontinue the patient from treatment. The Study Physician must ensure that all decisions are appropriately documented.

6.2 Blinding and procedures for unblinding the study

6.2.1 Methods for ensuring blinding

Not applicable

6.2.2 Methods for unblinding the study

Not applicable

6.3 Dosage and administration

Neoadjuvant chemotherapy Regimen: Durvalumab + Tremelimumab + Standard of care platinum-based combination chemotherapy

Durvalumab (1500mg IV every 3 weeks for up to 3 doses)

Tremelimumab (75mg IV every 3 week for up to 3 doses)

Chemotherapy regimen:

Paclitaxel 175mg/m^2 IV every 3 weeks for up to 3 doses

Carboplatin AUC 5 or 6 IV every 3 weeks for up to 3 doses

Adjuvant chemotherapy regimen: Durvalumab + Standard of care platinum-based combination chemotherapy

Durvalumab (1120mg IV every 3 weeks for up to 12 doses)

Chemotherapy regimen:

Paclitaxel 175mg/m^2 IV every 3 weeks for up to 3 doses

Carboplatin AUC 5 or 6 IV every 3 weeks for up to 3 doses

To avoid toxicity, FDA recommends capping the carboplatin dose for a desired AUC. The maximum dose is based on a GFR estimate that is capped at 125 mL/min for patients with normal renal function:
Maximum Carboplatin Dose (mg) = target AUC (mg/mL per min) x (125 mL/min + 25)
Based on AUC 6, maximum dose of carboplatin is 900mg.

6.4 Dose escalation decision rules

Not applicable

6.5 Definition of DLT

Not applicable

6.6 Dose modification and toxicity management

6.6.1 Durvalumab and tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab and durvalumab + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines in Appendix 1.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 4.3 of this protocol and the Dosing Modification and Toxicity Management Guidelines in Appendix 1).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Appendix 1. These guidelines have been prepared to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting investigator.

All toxicities will be graded according to NCI CTCAE, Version 5.

6.6.2 Paclitaxel / Carboplatin

The dosing regimens of carboplatin and paclitaxel that will be used in this study are reflective of current clinical practice. Carboplatin and paclitaxel may be reduced, interrupted, or discontinued at the investigator's discretion per the approved product labels and local regulations. The following is an example of dose reduction.

Dose modification for hematologic toxicity (1DL=25% dose reduction)

Event		**Action**
Grade 1-3	1st occurrence	Hold until recovery to ≤ grade 1 or baseline. Resume without reduction Consider G-CSF support

	2nd occurrence	Reduce by 1 dose level (DL). Consider G-CSF support
	3rd occurrence	Reduce by 2DL Consider G-CSF support
Grade 3 Febrile neutropenia	1st occurrence	Hold until recovery to ≤ grade 1 or baseline. Reduce by 1DL Consider G-CSF support
	2nd occurrence	Reduce by 2DL Consider G-CSF support
	3rd occurrence	Discontinue
Grade 4 Febrile neutropenia	1st occurrence	Reduce by 2DL Consider G-CSF support
	2nd occurrence	Discontinue

Dose modification for non-hematologic toxicity

Event		**Action**
Grade 3-4 non-hematologic toxicities	1st occurrence	Hold until recovery to ≤ grade 1 or baseline. Reduce by 1 DL
	2nd occurrence	Reduce by 2 DL.

	3rd occurrence	Discontinue
Grade 4 Laboratory Adverse Events	1st occurrence	Hold until recovery to ≤ grade 1 or baseline. Reduce by 1DL
	2nd occurrence	Reduce by 2DL

6.6.3 Toxicity management guidelines for combination treatment regimen

Reduction or holding of one agent and not the other agents is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the study drugs. If, in the opinion of the Investigator, the toxicity is related to the combination of two agents, both drugs should be reduced or held according to recommended dose modifications. If the toxicity is related to the combination of three agents, all three agents should be reduced or held according to the recommended dose modifications. If one or more study agent(s) are held for toxicity, the schedule for restarting the agent(s) should correspond with the next treatment cycle once the toxicity has resolved according to the recommended guidelines.

If any of the individual study drugs must be delayed for a day or more, all agents should be delayed for the same timeframe. If a patient requires a dose delay of paclitaxel/carboplatin components of study treatment for > 3 weeks due to toxicity, the treatment regimen will be permanently discontinued for unacceptable toxicity.

6.7 Surgery

AP-CT and/or PET-CT with appropriate other diagnostic method will be performed before interval debulking surgery and type of surgery (ex. Laparotomy or laparoscopy) will depend ont the surgeon’s best decision.

6.8 Follow-up period

AP-CT and serum CA-125 will be performedup to 5 years from first administration according to Appendix 1 or 2. Other diagnostic method can be performed if indicated.

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

7.1 Restrictions during the study

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

> Female patients of childbearing potential who are not abstinent and intend to be sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 1) from the time of screening throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy). Non-sterilised male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. 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 (ie, bilateral salpingectomy, 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.

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.

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 1. 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 1. Highly effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

Blood donation

Patients should not donate blood while participating in this study and for at least 90 days following the last infusion of durvalumab or tremelimumab or 90 days.

7.2 Concomitant treatment(s)

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.6 for guidance on management of IP-related toxicities.

7.2.1 Permitted concomitant medications

Table 2. Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

7.2.2 Excluded concomitant medications

Table 3. Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])

Prohibited medication/class of drug:	**Usage:**
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *<<short-term premedication for patients receiving combination agent paclitaxel where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions>>* • *Use in patients with contrast allergies.* • *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of* non-immunotherapy related events experienced by *the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).*
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs <<unless the study is assessing the combination of an EGFR TKI and durvalumab>>	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

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8. STUDY PROCEDURES

8.1 Schedule of 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 following the Protocol Synopsis

For all treatments

- Tumor efficacy (RECIST) assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the start of the treatment
- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc required for dosing should be performed within 3 days prior to dosing.

For durvalumab ± tremelimumab combination therapy

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
  - Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST). Subsequent time between 2 consecutive doses cannot be less than 18 days, based on the half-lives of durvalumab and tremelimumab (see current Investigator Brochures for durvalumab and tremelimumab.

Standard of Care:

- Patients may delay and subsequently resume dosing per local standard clinical practice.

- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible.

8.1.1 Screening phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All patients 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, patients will be enrolled in the study. All patients must submit available tissue (fresh-frozen tumor tissues or FFPE) and undergo IHC for PD-L1. 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:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG
- Tumor biopsy
- Review of prior/concomitant medications
- Imaging by CT or MRI
- Clinical laboratory tests for:
  - Clinical chemistry (see Table 4)
  - Hematology (see Table 5)
  - TSH
  - Coagulation (PTT, INR)
  - Creatinine Clearance
  - Serum pregnancy test (for women of childbearing potential only)
  - Hepatitis serologies
  - Urinalysis (see Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

- Table 6)
- CA-125

8.1.2 Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 4 weeks of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

1) Safety run-in phase

There will be a safety run-in phase with 7 patients. After then, a phase II expansion phase will be conducted with dose level considered to be safe.

Based on historial data, the proportion of patients who experience G3 or more TRAEs in the neoadjuvant chemotherapy is approximately 30~50% even without durvalumab and tremelimumab (Becker et al 2016, Garcia et al 2017, Yoshihama et al 2017).

There will be the first DSMB meeting after 7 patients completed neoadjuvant chemotherapy period and 4 patients underwent interval debulking gurgery. In the event of severe toxicity related to IP, DSMB will be held ahead of schedule. . DSMB will review the safety of this trial and suggest recommendation considering criteria as like as examples below:

If patients who experience grade 3 or more TRAEs (except hematologic toxicity) are ≥ 4, then stop the trial.
If patients who experience grade 3 or more TRAEs (except hematologic toxicity) are ≤ 3, then go to the phase II. (3/7, 42.9%)

According to the recommendation, it will be decided whether to stop the trial or go to the phase II.

2) A single-arm phase II study

Durvalumab 1500mg iv , Tremelimumab 75mg iv, Paclitaxel 175mg/m^2, and carboplatin AUC 5 or 6 will be administered every 3 week. Total 3 cycles of neoadjuvant chemotherapy will be performed before interval debulking surgery. After surgery, Durvalumab 1120mg iv, Paclitaxel 175mg/m^2, and carboplatin AUC 5 or 6 will be administered every 3 week. Total 3 cycles of

adjuvant chemotherapy and Total 12 cycles of Durvalumab will be performed after interval debulking surgery.

8.1.3 End of treatment

End of treatment is defined as the last dose of Durvalumab or disease progression in this study.

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

8.2 Description of study procedures

8.2.1 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.

8.2.2 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. 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.

8.2.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening 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.

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 (within 15 minutes at 5 minutes apart) to confirm the finding.

8.2.4 Vital signs, body weight and height

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules. Body weight is also recorded at each visit along with vital signs. Height will be measured at Screening only.

First infusion

On the first infusion day, patients in the durvalumab ± tremelimumab combination therapy will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected from patients in the I-O therapy 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)

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab.

Subsequent infusions

BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

8.2.5 Clinical laboratory tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 24 through Table 5).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal

clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in Table 4 (clinical chemistry), Table 5 (hematology), and Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Table 6 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies and HIV antibodies.

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Table 4. Clinical chemistry

Albumin	Total bilirubin [a]
Alkaline phosphatase	Magnesium [d]
ALT[a]	
Amylase[b]	
AST[a]	
Bicarbonate[c]	
Calcium	
Chloride[c]	
Creatinine clearance[d]	
Creatinine	
Gamma glutamyltransferase[c]	
Glucose	
Lactate dehydrogenase	
TSH[e]	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable.

[c] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight) or measured by 24-hour urine collection.

[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at day Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

ALT Alanine aminotransferase; AST Aspartate aminotransferase, TSH Thyroid Stimulating Hormone

Table 5. Hematology

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils

Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count[a]
Mean corpuscular hemoglobin concentration	

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 0 (unless all screening laboratory haematology assessments are performed within 3 days prior to Day 1), and as clinically indicated.

[a] Can be recorded as absolute counts or as percentages. Absolute counts will be calculated by DM if entered as percentage. Total white cell count therefore has to be provided.

Table 6. Urinalysis

Urinalysis should be done at baseline (screening) and then as clinically indicated	
Bilirubin	Ketones
Blood	pH
Color and appearance	Protein
Glucose	Specific gravity

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

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, refer to Appendix 1 for further instructions on cases of increases in liver biochemistry and evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry and hematology profiles performed at 30 days (±3 days) and 3 months (±1 week) after permanent discontinuation of IP (see Table 4 and Table 5).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 10.3.5.

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

8.2.6 Patient reported outcomes (PRO)

Not applicable

8.3 Biological sampling procedures

8.3.1 Pharmacokinetic sampling and evaluation methods

Not applicable

8.3.2 Immunogenicity sampling and evaluation methods

Not applicable

8.3.3 Biomarker/pharmacodynamic sampling and evaluation methods

PD-L1 Testing

To ensure comparability of data across all studies of durvalumab and/or tremelimumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the 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.

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

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

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

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

Sample data collection for PD-L1 testing

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

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

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

- Are the negative and positive controls stained correctly

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

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background. PD-L1 status is considered high if ≥ 25% of tumor cells exhibit membrane staining. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

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

Preparing Stored samples for testing

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

Preparing newly acquired samples for PD-L1 testing

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

- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

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

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

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended

Storage of tumor blocks for PD-L1 testing

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

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

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

- Each sample should be reviewed for:

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

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

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

Sectioning instructions

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

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

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

8.3.4 Estimate of volume of blood to be collected

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

Table 7. Volume of blood to be drawn from each patient

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
<<*Biomarker*>>	10	4	40
Total	10	4	40

<<>>

Examine the phenotypic characteristics of CD4 and CD8 T cells in terms of various immune check points (PD-1, CTLA4, TIM3, LAG3) and memory markers (CD45RO+/CCR7+) in fresh tissue and PBMC by FACS on pre-treatment, post-treatment(C1D8, blood sample only) and at the time of surgery and progression.

Examine the tumor infiltrating immune cells including Treg cells and MDSCs (CD11b+/Gr1+) on pre-treatment, post-treatment(C1D8, blood sample only) and at the time of surgery and progression.

Blood cytokine analysis will be performed at the time points with multi cytokine bead analysis on pre-treatment, post-treatment(C1D8, blood sample only) and at the time of surgery and progression.

8.3.5 Archival tumor samples and fresh tumor biopsies use beyond PD-L1

8.3.5.1 Archival tumor samples

Not applicable

8.3.5.2 Fresh tumor biopsies

There are three time points of getting tumor samples – pretreatment biopsy from diagnostic laparoscopy (biopsy #1), at the time of interval debulking surgery (biopsy #2) and at the disease progression after treatment(biopsy #3, optional). Pretreatment and IDS biopsies are mandated for all patients. FFPE should be available at both biopsy and biopsy#1 & #2 should be also available as a fresh-frozen tumor sample if possible. HRR gene panel /Exome sequencing, RNA sequencing, PD-L1 expression will be checked.

Lynparza HRR Gene Panel and Classification Algorithm

Table 8 outlines the 15 HRR genes with their priority. For three specific HRR genes, i.e. ***BRCA1***, ***BRCA2***, and ***ATM***.

Table 8. List of 15 HRR genes

Number	Gene Symbol	EntrezID	Refseq	Tier
1	***BRCA1***	672	NM_007294	1
2	***BRCA2***	675	NM_000059	1
3	***ATM***	472	NM_000051	1
4	***BRIP1***	83990	NM_032043	2
5	***PALB2***	79728	NM_024675	2
6	***RAD51C***	5889	NM_058216	2
7	***BARD1***	580	NM_000465	2
8	***CDK12***	51755	NM_016507	2
9	***CHEK1***	1111	NM_001274	2
10	***CHEK2***	11200	NM_007194	2
11	***FANCL***	55120	NM_018062	2
12	***PPP2R2A***	5520	NM_002717	2
13	***RAD51B***	5890	NM_133509	2
14	***RAD51D***	5892	NM_002878	2
15	***RAD54L***	8438	NM_003579	2

Exome sequencing

Exome sequencing (tumor/normal pairs) of FFPE or fresh-frozen tumor tissues (if possible) at pre-treatment, at the time of surgery and progression to identify potential immune epitope and mechanisms of acquired resistance.

RNA sequencing or nanostring nCounter

RNA sequencing or nanostring nCounter of FFPE or fresh-frozen tumor tissues (if possible) at pre-treatment, at the time of surgery and progression to identify potential immune-related gene signatures such as mRNA signature panel (IFN-r, extended, TCR, De novo)

Immunohistochemistry

PD-L1 expression level at pre-treatment, at the time of surgery and progression to identify changes in PD-L1 expression level through neoadjuvant chemotherapy treatment.

Tumor infiltrating lymphocyte at pre-treatment, at the time of surgery and progression to identify changes in microenvironment through neoadjuvant chemotherapy treatment.

PD-L1 expression testing for the in-house historical data (specimens which were treated with standard neoadjuvant chemotherapy followed by surgery)

8.3.6 Withdrawal of informed consent for donated biological samples

<<If a patient 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 patient is withdrawn from further study participation.>>

The Principal Investigator:

- Ensures that biological samples from that patient, 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 patient is informed about the sample disposal.

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9. DISEASE EVALUATION AND METHODS

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

- 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 anticancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- 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 would continue between the initial assessment of progression and confirmation for progression.

- In addition, patients may continue to receive durvalumab ± tremelimumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab ± tremelimumab and provide a more complete evaluation of its antitumor 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 anticancer therapy other than durvalumab ± tremelimumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).>>

9.1.1 Efficacy variable

Primary outcome is Progression-free survival.

12-months progression-free survival rate will be estimated, and 95% confidence intervals will be calculated.

Secondary outcome is response rate by RECIST version 1.1 after neoadjuvant chemotherapy, immune-related response criteria after neoadjuvant chemotherapy, response rate by PERCIST after neoadjuvant chemotherapy, R0 rate at interval debulking surgery, the rate of chemotherapy response score 3, overall survival, and safety

Resected specimens will be formalin-fixed and paraffin-embedded according to standard procedures and stained with H&E. The slides will be collected at Yonsei Cancer Center. All slides will be reviewed by an experienced gynecologic pathologist (Prof. Hyun Soo Kim). The slide with the most viable tumor and/or the least chemotherapy response was selected from omentum. A Pathologist will independently score each slide according to the 3-tiered CRS system proposed by Bohm et al.

Patients who have disease control following completion of 12 months of treatment or patients who are withdrawn from durvalumab ± tremelimumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix 2).

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,

- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),

- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive assessments meeting the PD definition: the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first assessment fulfilling the PD definition by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

Following confirmed progression, patients should continue to be followed up for survival every 2 months (8 weeks) as outlined in the follow-up schedules of assessments.

10. ASSESSMENT OF SAFETY

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

10.1.1 Safety parameters

10.1.1.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

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

10.1.2 Definition of serious adverse events

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

Results in death

Is immediately life-threatening

Requires in-patient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability or incapacity

Is a congenital abnormality or birth defect in offspring of the patient

Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above:

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

10.1.3 Durvalumab ± tremelimumab adverse events of special interest

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

AESIs for durvalumab ±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 may require close monitoring in clinical studies with durvalumab monotherapy and durvalumab combination therapy." An immune-mediated adverse event (imAE) is defined as an AESI 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 imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab ±tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator's Brochures. More specific guidelines for their

evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix F) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    - (ii) Tumour markers: Particular tumour markers which are related to disease progression.

Additional Clinical chemistry: CRP, LDH

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to <<the NCI CTCAE v5.
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 patient.

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 patient.

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 patient 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 10.2.1. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

The Investigator will assess the causal relationship between the IPs and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

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

10.3 Recording of adverse events and serious adverse events

AEs and SAEs will be collected from the time of the patient signing the informed consent form until the follow-up period is completed (90 days after the last dose of durvalumab ±tremelimumab). If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient'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. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE

- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 6.3.4
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

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

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

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

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

If a patient 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 90 days after the last dose of IP.

The investigator is responsible for following all SAEs until resolution, until the patient 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.

10.3.2 Causality collection

The Investigator will assess causal relationship between the IPs and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

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

A guide to the interpretation of the causality question is found in Appendix 1.

10.3.3 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

10.3.4 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit/you were last asked?" or revealed by observation will be collected and recorded in the eCRF. When collecting

AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

10.3.5 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs measurements will be summarized in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IPs.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value that is unequivocally due to disease progression should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

10.3.6 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.3.7 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study.

10.3.8 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

10.3.9 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It 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 the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

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

10.3.10 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

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

A cover page and a copy of the SAE report written in English must be sent to AstraZeneca at the time the event is reported to the Regulatory Authority. To meet data privacy and confidentiality

requirements AE information (both individual case reports and listings) must be sent from the investigator and/or Coordinating Investigator to AstraZeneca by secure e-mail, if secure email is not available AE information must be sent by fax. For methods of achieving secure email data exchange, via encrypted email or password protected attachment.

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

- "Notification from an Investigator Sponsored Study"
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-##-#####)

***** 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 Regulatory Authority.

Serious adverse events that do not require expedited reporting to the Regulatory Authority 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.

10.3.10.1 Reporting of deaths to AstraZeneca

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab + tremelimumab safety follow-up period must be reported to AstraZeneca 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 AstraZeneca as a SAE within **24 hours** (see Section 10.3.2 for further details). The

report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

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

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

10.3.11 Other events requiring reporting

10.3.11.1 Overdose

Use of durvalumab or tremelimumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab or tremelimumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

If an overdose of an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel will inform appropriate AstraZeneca representatives immediately, or **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.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 10.3.10. For other overdoses, reporting must occur within 30 days.

10.3.11.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- Pregnancy discovered before the study patient has received any study drugs.

10.3.12 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.

10.4 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the patient received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature

- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs 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 works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 10.3.10) and within 30 days for all other medication errors.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Safety analysis set

Safety analyses are based on modified intent-to-treat (ITT) approach (patients should receive at least one treatment dose).

11.1.2 Efficacy analysis set

Efficacy analyses are based on modified intent-to-treat (ITT) approach (patients should receive at least one treatment dose).

11.2 Methods of statistical analyses

11.2.1 Efficacy analyses

Response rate is evaluated by RECIST version 1.1.
PFS is defined as the time from treatment start until the first documented sign of disease progression or death from any cause; OS is defined as the time from first treatment until death from any cause. PFS and OS will be estimated using the Kaplan-Meier(K-M) method, and 95% confidence intervals (95% CIs) will be calculated. The rate of Chemotherapy response score 3 will be estimated, and 95% CIs will be calculated.

12 months PFS rate will be estimated using the K-M method, and 95% CIs will be calculated.

A one-sample log-rank test will be performed to examine whether the 12 month PFS rate in the treatment group is greater than 50% at a 5% significance level.

11.2.2 Safety analyses

Adverse events are graded according to CTCAE version 5.

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, *laboratory data, vital signs, ECGs, and exposure*. These will be collected for all patients. Data from all cycles of treatment will be combined in the presentation of safety data. “On treatment” will be defined as assessments between date of *start dose* and 90 days following discontinuation of IP (ie, the last dose of durvalumab ± tremelimumab combination therapy). For AEs, on treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

AEs will be listed individually by patient, and the number of patients experiencing each AE will be summarized by CTCAE grade. Other safety data will be assessed in terms of physical examination, clinical chemistry, hematology, vital signs, and ECGs. *Exposure to Durvalumab ± tremelimumab± Chemotherapy will be summarized*. Time on study, dose delays and dose reductions, where necessary will also be summarized.

A separate data listing of AEs occurring more than 90 days after discontinuation of IP will be produced. These events will not be included in AE summaries.

11.2.3 Exploratory analyses

The aim of this study was to evaluate the immune biomarker and resistance mechanism through serial biopsies in patients with advanced-stage ovarian cancer undergoing Durvalumab + Tremelimumab + chemotherapy. Immune-biomarkers will be explored to find responders.

The immune dynamic changes are identified through serial tumor tissue analysis and surgical specimen by comparing pre-treatment, at the time of surgery, and at progression.

1. Analysis of immune marker using FACS

Examine the phenotypic characteristics of CD4 and CD8 T cells in terms of various immune check points (PD-1, CTLA4, TIM3, LAG3) and memory markers (CD45RO+/CCR7+) in fresh tissue and PBMC by FACS on pre-treatment, post-treatment(C1D8, blood sample only), at the time of surgery, and at progression.

Examine the tumor infiltrating immune cells including Treg cells and MDSCs (CD11b+/Gr1+) on pre-treatment, post-treatment(C1D8, blood sample only), at the time of surgery, and at progression.

Blood cytokine analysis will be performed at the time points with multi cytokine bead analysis on pre-treatment, post-treatment(C1D8, blood sample only), at the time of surgery and progression.

In particular, ovarian cancer is known as cold tumor, we will characterize mmune-suppressive environment as well as T cell characterization.

In particular, **blood-based biomarker** for immune checkpoint inhibitors will be explored using FACS. Peripheral blood was collected from patients on days 0, 7, 21 and PBMCs were isolated. Multi-color flow cytometry will be performed to identify dynamic blood-based biomarkers that predict responses to immune check point inhibitors. Fold changes of T cell activation of proliferation markers (eg. Ki-67) among PD-1+CD8+ T cells after the first dose of anti-PD-L1 and ant-CTLA-4.

2. Exome sequencing (tumor/normal pairs) of fresh-frozen tumor tissues at pre-treatment, at the time of surgery, and at progression to identify potential immune epitope and mechanisms of acquired resistance (loss of mutation-associated neoantigens in tumors). Tumor mutation burden will be calculated and correlated with treatment response

3. RNA sequencing of available tissue (fresh-frozen tumor) tissues at pre-treatment, at the time of surgery and at progression to identify potential immune-related gene signatures mRNA signature panel (IFN-r, extended, TCR, De novo). CIBERSORT will be performed to identify cell composition including fibroblast, T-cell, and macrophage. By doing so, we will characterize for ovarian cancer tumor microenvironment.

Neoantigen can be used as a biomarker predicting patient response to cancer immunotherapy. A machine-learning based neoantien prediction program was developed for next-generation sequencing data (Kim S et al 2018). Using this platform, we will validate Neopepsee algorithms to predict immunotherapy response.

4. PD-L1 testing (Ventana SP 263 assay) and immunohistochemistry for immune markers at pre-treatment, at the time of surgery, and at progression

5. Multiplex IHC at pre-treatment and at the time of surgery

Using established platform of Vectra, multispectral imaging will be performed to identify tumor microenvironement comprehensively.

11.2.4 Interim analyses

No interim efficacy analyses are preplanned.

11.3 Determination of sample size

This study is a single arm phase II trial with the primary endpoint of 12 month PFS rate. The 12 month PFS rate in the treatment arm is expected to be 70% against that of 50% in the historic control group (Hazard Ratio=0.515). With 80% of statistical power, 5% of one-sided type I error, 21 patients are needed when patients are accrued for a period of 12 months and followed for a period of 30 months after the last patient is enrolled. The number of expected events would be 14. Considering 10% of drop-out, a total of 24 patients will be enrolled in this study.
The sample size was calculated using the PASS software(Version 15) based on the one-sample log-rank test. Below is the list of reference(Wu Jianrong, 2014; Wu Jianrong 2015; Finkelstein D et al., 2003; Sun X et al., 2011; Schmidt R et al., 2015).

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Patient data protection.

12.2 Ethics and regulatory review

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

The opinion of the EC/IRB should be given in writing. The local Investigator should submit the written approval to Principal Investigator before enrolment of any patient into the study.

The Principal Investigator should approve all advertising used to recruit patients for the study.

The Principal Investigator should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the EC/IRB annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority should be approved, according to local regulations.

The Principal Investigator will handle the distribution of these documents to the national regulatory authorities.

The Principal Investigator will provide regulatory authorities, ECs/IRBs, and Principal Investigators safety updates or reports according to local requirements.

Each Principal Investigator is responsible for providing the EC/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP.

12.3 Informed consent

The Principal Investigator at each center will:

Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study

Ensure that each patient is notified that he or she is free to discontinue from the study at any time

Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided

Ensure that each patient provides a signed and dated informed consent before

conducting any procedure specifically for the study

- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure that a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any

provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

12.4 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised clinical study protocol).

The amendment is to be approved by the relevant EC/IRB and, if applicable, the national regulatory authority, before implementation. Local requirements are to be followed for revised protocols.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's EC/IRB are to approve the revised ICF before the revised form is used.

If required by local regulations, any administrative change will be communicated to or approved by each EC/IRB.

12.5 Audits and inspections

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

Clinical Study Protocol

Drug Substance

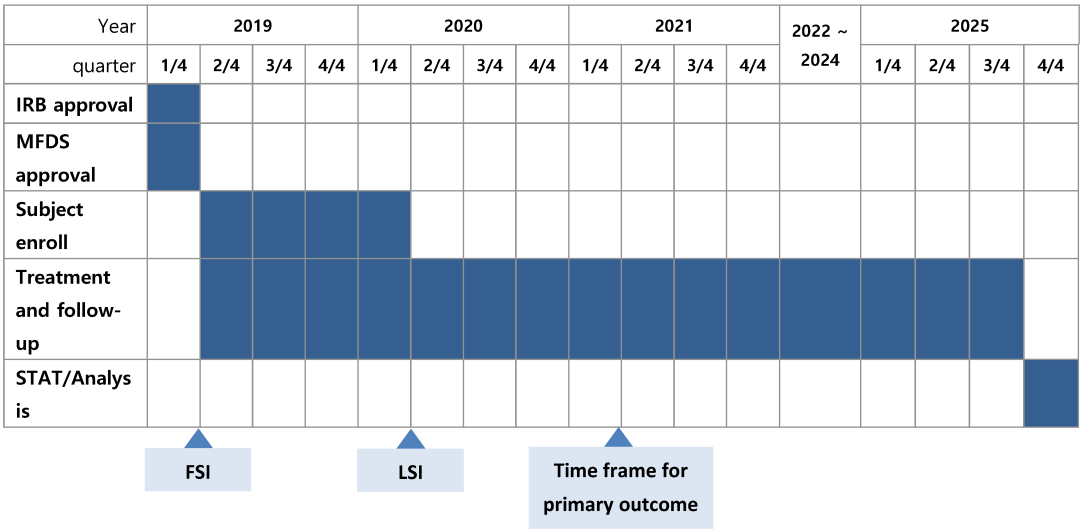
Study Code ESR-17-13142 / KGOG3046

Edition Number 1.8

Date 12 Jan 2020

13. STUDY MANAGEMENT

13.1 Study timetable and end of study



14. DATA MANAGEMENT

14.1 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.

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1 Identity of investigational product(s)

Table 9. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	*50 mg/mL solution for infusion after dilution*	MedImmune
Tremelimumab	*20 mg/mL solution for infusion after dilution*	MedImmune
Paclitaxel		
Carboplatin		

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APPENDIX 1.

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 (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

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 v5.0. 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 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.	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 such events should be managed as if they were 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

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General Considerations regarding Immune-Mediated Reactions

	Dose Modifications	Toxicity Management
Grade 3	Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	– 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.
Grade 4	Permanently discontinue study drug/study regimen.	– With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.		– 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 drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.
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		
Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).		

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.

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Pediatric Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** of the start of the immune-mediated event	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

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Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease 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 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 – 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 patient is improving, gradually taper steroids over ≥28 days and consider

			prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – 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	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.

observations only)		
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (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.
Grade 3 or 4	**Grade 3** Permanently discontinue	**For Grade 3 or 4:**

	(Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: life-threatening consequences; urgent interventnion indicated)	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** Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (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
Hepatitis (elevated LFTs)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis,

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**			disease progression, concomitant medications).
	Grade 1 **(**AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	• No dose modifications. • If it worsens, then treat as Grade 2 .	– Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	• Hold study drug/study regimen dose until resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – 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 Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional 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 (i.e., 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
	Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal) **Grade 4** (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)	For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 • Resume study drug/study regimen if elevations downgrade to Grade ≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis [i.e., elevated alkaline P04] and in the absence of any alternative cause).[b]	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., 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 treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] **For Grade 4:**

		Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** 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**	**Any Elevations of 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 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 to AST or ALT ≤5.0×ULN • If toxicity worsens, then treat as described 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. – 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×	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN.	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved.

	ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• 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]	– 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 NCCN guidelines for treatment of cancer-related infections).[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**			

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			- **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 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 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup

			should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-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 5 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. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, 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. If > 30% body surface area is involved, consider initiation of systemic steroids promptly – 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-PJP 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 v5.0 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 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/hypopituitarism, 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 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 endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 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 1 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 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 1 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 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 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 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 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 1 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]
Neurotoxicity	**Any Grade**	**General Guidance**	**For Any Grade:**

(to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	(depending on the type of neurotoxicity, refer to NCI CTCAE v5 for defining the CTC grade/severity)		– 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.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization.

		Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **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 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 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	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 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate	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:* o Steroids may be successfully used to

	instrumental ADL)		treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:**	**For Grade 3 or 4 (severe or life-threatening events):**

	(Grade 3 GB: severe symptoms; limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	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.	– Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o 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:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in

	proven immune-mediated myocarditis.	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. – 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,	**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.

		resume after complete resolution to Grade 0.	
	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))	- If 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. If 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 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 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 modifications.	**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 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 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; CT 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.

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Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	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.

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Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	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.

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Appendix 2. Schedule of study procedures: follow-up for patients who have completed durvalumab and tremelimumab treatment and achieved disease control (until confirmed progression of disease) and patients who have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progression of disease

Evaluation	Time Since Last Dose of IP				
	Day (±3)	Months (±1 week)			12 Months and Every 6 Months (±2 weeks), up to 5 years from first dose of IP
	30	3	6	9	
Physical examination[a]	X				
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X				
Weight	X				
Urine hCG or serum βhCG	X				
AE/SAE assessment	X	X			
Concomitant medications	X	X			
Palliative radiotherapy	As clinically indicated →				
ECOG performance status	X	X	X	X	X
Subsequent anticancer therapy	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X (every 3 months)
Hematology	X	X			
Serum chemistry	X	X			
Thyroid function tests (TSH, and fT3 and fT4)[b]	X				
Tumour assessment (CT or MRI) and ca-125	For patients who **achieve disease control following 12 months of treatment**, tumour assessments should be performed relative to the date of **first infusion as follows:** every 12 weeks for the first 2 years, then every 24 weeks thereafter until confirmed PD by RECIST 1.1 by investigational site review. For patients who **discontinue durvalumab due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the date of **first infusion** every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review. Upon confirmed PD, scans should be conducted according to local standard clinical practice.				

[a] Full physical exam

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

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Appendix 3. Schedule of study procedures: follow-up for patients who have discontinue durvalumab and tremelimumab treatment due to confirmed progression of disease at the investigator discretion

Evaluation	Time Since Last Dose of IP				
	Day (±3)	Months (±1 week)			12 Months and Every 6 Months (±2 weeks), up to 5 years from first dose of IP
	30	3	6	9	
Physical examination[a]	X				
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X				
Weight	X				
Urine hCG or serum βhCG	X				
AE/SAE assessment	X	X			
Concomitant medications	X	X			
Palliative radiotherapy	As clinically indicated →				
ECOG performance status	X	X	X	X	X
Subsequent anticancer therapy	X	X	X	X	X
Survival status: phone contact with patients who refuse to return for evaluations and agree to be contacted		X	X	X	X (every 3 months)
Hematology	X	X			
Serum chemistry	X	X			
Thyroid function tests (TSH, and fT3 and fT4)[b]	X				
Tumour assessment (CT or MRI) and CA-125	For patients who **continue on MEDI4736 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 until MEDI4736 is stopped. For patients who **discontinue MEDI4736 following confirmed progression**, **scans should be conducted according to local clinical practice**.				

[a] Full physical exam
[b] PS to be collected if available at the 3 monthly calls to obtain subsequent anticancer therapy and survival status
[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.

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Appendix 4. Recommendation of study procedures: management of patients who have skin rash (≥ grade 2) at previous cycles

In the DSMB meeting that followed the safety run-in period, DSMB committee expressed concerns about frequent skin rashes and repeated occurrence in the next cycles in same participants. Therefore, DSMB recommended early treatment of skin rash and prophylaxis for skin rash for the next cycle. The following prophylaxis are recommended in the event of a skin rash in a previous cycle.

1. (-D1) Midnight dexamethasone 20mg iv
2. (D1) H1 blocker antihistamine and H2 blocker , 30 minutes before administration
3. (D1) dexamethasone 20mg iv , 30 minutes before administration
4. (D1) desensitization protocol needs to be considered

   (for examples, 2mg in 100ml NS over 30 mins → if no reaction → 10mg in 100 mL NS over 30 mins → if no reaction → remaining full dose in 500 mL NS over 3 hours
5. If skin rash recurs, consult to allergist or specialist