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Sponsor's Agreement to Protocol Version 1.0, 05-Jun-2017

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Date of Approval: _____
DD-MMM-YYYY

SYNOPSIS

Study Title:	Phase I (Safety Assessment) of Durvalumab (MEDI4736) with Focal Sensitizing Radiotherapy in Platinum Resistant Ovarian, Primary Peritoneal or Fallopian Tube Epithelial Carcinoma
Primary Objectives:	The primary objective of this study will be to assess the safety and tolerability of durvalumab and focal irradiation as defined by dose-limiting toxicities (DLTs) and define the maximum tolerated dose (MTD), and treatment schedule that can be safely used for future study of this therapeutic strategy.
Secondary Objectives:	The secondary objectives of this study are to evaluate the clinical activity of durvalumab and focal radiotherapy as measured by: 1) Objective Response rate as evaluated by a. RECIST (v 1.1) criteria b. GCIG CA-125 response criteria c. Immune-related response criteria 2) Progression free survival 3) Overall survival
Exploratory Objectives:	1) To collect blood and tissue samples for analysis of immune biomarkers 2) To investigate the relationship between the presence or absence and spatial distribution of lymphocyte subsets within the tumor microenvironment and clinical outcomes 3) To explore biomarkers of radiation and durvalumab efficacy 4) To analyze biomarkers (e.g. immune, tumor) in different cellular compartments (e.g. tumor, immune, serum, blood) which may influence and/or prospectively identify patients likely to respond to treatment
Study Design:	This is a phase I, open label, safety and tolerability assessment of the combination of PD-L1 blockade using the mAb, durvalumab, with focal irradiation of two selected cancer lesions in patients with recurrent, platinum-resistant ovarian cancer.
Duration:	Durvalumab will be continued as long as well tolerated, with no evidence of clinically significant disease progression, for up to 12 months duration.
Planned Total Sample Size:	The minimum number of patients required to complete this study will be 3. This would occur if all of the first 3 patients on dose level 1 experienced a DLT. The study would then stop accrual. The maximum number of patients required to complete this study will be 22. This would occur if at each dose level, the cohorts had to be fully expanded (n=9), and 2 patients at each dose level had to be replaced.
Test Drug, Administration and Dose-Escalation	Patients enrolled in the study will receive 1500 mg of durvalumab q 28 days, corresponding to one cycle. For the first 2 doses of durvalumab, focal radiation to the two selected target

Scheme:

lesions will be delivered 24-36 hours prior to the infusion of durvalumab (on Day -1 and 1 of Cycle 1 and Day 28 of Cycle 1 as well as Day 1 of Cycle 2).

Two radiation targets will be identified per patient. Target selection is described in Section 6.2. Each lesion will receive a total of 6Gy x 4 fractions. Radiation will be given 24-36 hours prior to durvalumab (e.g., both targets will receive 6Gy of radiation on days -1 & 1 and of cycle 1, and then on day 28 of Cycle 1, and day 1 of cycle 2). Where possible, radiation should precede administration of durvalumab on days when they are given together.

Subjects will be enrolled in cohorts of 3 each. Dose escalations for subsequent cohorts will be undertaken as per the dose modification tables below following a 3+3+3 design, to establish the MTD of the combination of durvalumab and focal radiation.

Dose Level	**Durvalumab dose**	**Total Radiation dose given per target lesion (2 targets per patient)**	**N**
1 (starting dose level)	1500 mg	24 Gy	3+3+3
2	1500 mg	32 Gy	3+3+3

Three subjects will be treated at an initial dose level of 1500 mg of durvalumab q28 days and 24 Gy of radiation (6Gy X 4) to both radiation targets (delivered as per the treatment schedule shown in Table 1). If 0, 1 or 2/3 subjects experience DLTs during cycle one (first 4 weeks of treatment), 3 additional subjects will be enrolled at the dose level 1. If at dose level 1, 2/6 experience DLTs, then 3 more subjects will be enrolled in the trial at the starting dose level. If 0 or 1/6, or <3/9 experience a DLT at dose level 1, then dose escalation to dose level 2 will be permitted (Table 2). Enrolment onto dose level 2 will follow the same rules as described for dose level 1, following a 3+3+3 design to define the MTD. If at any time on dose level 1, ≥3 subjects (3/3, 3/6, or 3/9) experience a DLT the trial will stop accrual and a MTD will not be defined due to excessive treatment toxicity. If at dose level 2, ≥3 subjects (3/3, >3/6, or 3/9) experience a DLT then accrual will stop and dose level 1 will be selected as the MTD. If at dose level 2, ≤ 1/6 or < 3/9 experience DLTs, then dose level 2 will

	represent the MTD.
	
	Dose-limiting toxicity will be defined with the use of the Common Terminology Criteria for Adverse Events version 4.03 as any of the following as assessed by the investigator:
	• any grade ≥3 adverse event suspected to be related to the study agent or to the radiation
	  o radiation necrosis or radiation recall reactions at previously irradiated sites
	  o if the radiation field includes bowel, then radiation induced bowel perforation
	  o any unexpected grade 3 or greater toxicity at the site of irradiation
	• any grade ≥2 allergic or autoimmune event that involves vital organ functions
	• any other grade 3 allergic or autoimmune events that does not resolve to grade 1 toxicity before the next scheduled dose of antibody.

Inclusion/Exclusion Criteria:	**Inclusion Criteria** 1. Provision of written informed consent prior to any study specific procedures 2. Female patients aged 19 years and older 3. Platinum-resistant (progression within 6 months of platinum based regimen) or platinum-refractory ovarian/fallopian tube/peritoneal origin. • High grade serous, endometrioid, clear cell, mucinous, malignant mixed Mullerian tumor, and low grade serous histotypes are permitted. Non-epithelial tumours will not be permitted. 4. ECOG performance status 0-1. 5. No more than 2 lines of therapy in the platinum-resistant setting. 6. No bowel obstructions within the preceding 6 months. 7. Last radiation therapy treatment ≥3 months prior to enrollment. 8. Expected survival >3 months. 9. All patients much have at least one site of measurable disease as defined by RECIST criteria (v.1.1). 10. All patients must have disease suitable for core biopsy and agree to study related biopsies. Disease suitable for biopsy can serve as radiation targets, but cannot be used for response assessment. 11. All patients must have at least 2 additional sites of disease that serve are suitable radiation targets (see section 6.2.1).

- Lesions suitable for radiation targeting must meet all of the following criteria:
  - each target must be > 4 cc in volume by standard imaging techniques, such as CT scan, MRI, or radiograph
  - for each lesion, partial treatment of a tumour mass is permitted, but the treatment volume cannot be less than the equivalent of a 2cm sphere (4cc) and the two targets cannot be part of the same contiguous mass
  - must be outside of previously irradiated fields

12. Adequate organ and marrow function as defined below within 14 days of cycle 1 day 1 and prior to first dose of focal radiotherapy:
    - Absolute neutrophil count >1.5 x 10^9/L (1500 per mm^3)
    - Platelets >100 x 10^9/L (100,000 per mm^3)
    - Hemoglobin ≥9.0 g/dL (5.59 mmol/L)
    - Serum creatinine CL >40 mL/min by the Cockcroft-Gault formula [82] or by 24-hour urine collection for determination of creatinine clearance:

      Females: Creatinine CL as calculated by Cockcroft-Gault Formula

      $$GFR = \frac{1.04 \times (140 - \text{age in years}) \times \text{weight (kg)}}{\text{serum creatinine (micromol/L)}}$$

    - Serum bilirubin ≤1.5 x upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinaemia that is predominantly unconjugated in the absence of evidence of haemolysis or hepatic pathology) who will be allowed in consultation with their physician.
    - AST and ALT ≤2.5 x ULN.

Exclusion Criteria

1. Participation in another clinical study with an investigational agent during the last 4 weeks.
2. Concurrent enrolment in another clinical study, the only exception being observational (non-interventional) clinical studies.
3. History of pneumonitis requiring treatment with steroids, or has a history of interstitial lung disease.
4. Patients who have contraindications to receiving radiation therapy, such as: Rheumatoid Arthritis, connective tissue disorders, Lupus, scleroderma, CREST syndrome, Crohn's syndrome, Ulcerative colitis, or other conditions identified by

	the Radiation Oncologist as unsuitable for radiation therapy. 5. Current or prior use of immunosupressive medication within 28 days before the first dose of the study drug, with the exception of intra-nasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses, which must not exceed 10 mg/day of prednisone, or an equivalent corticosteroid. 6. Prior exposure to an anti-PD-1 or anti-PD-L1 antibody (including durvalumab). 7. History of acute diverticulitis, intra-abdominal abscess, or GI obstruction. 8. Previous severe hypersensitivity reaction to another monoclonal antibody (mAb). 9. Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with Vitiligo, Grave's disease or psoriasis not requiring systemic treatment (within the past 2 years) or those with resolved childhood asthma/atopy are <u>not</u> excluded. 10. Uncontrolled intercurrent illness including: infection requiring therapy, symptomatic congestive heart failure, uncontrolled hypertension (systolic blood pressure > 150 and diastolic blood pressure >100), unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses. 11. Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from using Fredericia's Correction. 12. Positive for Human Immunodeficiency Virus (HIV), Hepatitis B (Hepatitis B Surface Antigen [HBsAg] reactive), or Hepatitis C virus (Hepatitis C Virus Ribonucleic Acid [HCV RNA] (qualitative) is detected). 13. Previous clinical diagnosis of active tuberculosis. 14. Receipt of a live attenuated vaccination within 30 days of study entry or within 30 days or receiving the study drug. 15. History of another malignancy, with the exception of: • Malignancy treated with curative intent without evidence of recurrence for ≥ 5 years • Adequately treated non –melanoma skin cancer or lentigo maligna without evidence of disease • Adequately treated carcinoma in situ without evidence of disease e.g. cervical carcinoma in situ 16. Female patients who are pregnant, breast-feeding or of childbearing potential who are not employing an effective method of birth control (see Table 3). 17. Any condition that, in the opinion of the investigator, would

	interfere with evaluation of the study drug or interpretation of patient safety or study.
Screening Assessments:	• Complete medical history • Concomitant medication assessment • Physical examination and ECOG Performance Status • Vital signs • Hematology • Coagulation • Chemistry • Urinalysis • 12-lead ECG • HIV test • Hepatitis B & C test • Serum pregnancy test (for non-sterile women of childbearing potential) • Tumour measurement • Core needle biopsy • Peripheral blood for immune marker analysis • Baseline symptoms
Treatment and Post-Treatment Assessments:	<u>Treatment Assessments:</u> • Physical examination and ECOG Performance Status • Concomitant medication assessment • Vital signs • Hematology • Coagulation • Chemistry • Urinalysis • 12-lead ECG • Tumour measurement • Core needle biopsy • Peripheral blood for immune marker analysis • Adverse event assessment <u>End of Treatment Visit:</u> • Physical examination and ECOG Performance Status • Concomitant medication assessment • Vital signs • Hematology • Coagulation • Chemistry • Urinalysis • 12-lead ECG • Tumour measurement

<table>
<tr><td></td><td>• Core needle biopsy
• Peripheral blood for immune marker analysis
• Adverse event assessment

<u>Follow up Assessments:</u>
• Tumor measurement
• Adverse event assessment
• Survival status</td></tr>
<tr><td>Response:</td><td>RECIST 1.1 criteria will be used to assess patient response to treatment by determining PFS, ORR, and DoR.</td></tr>
<tr><td>Safety Variables & Analysis:</td><td>The primary objective of this trial is to assess the safety and tolerability of durvalumab combined with focal radiotherapy, and hence determine the MTD of this combination. Safety endpoints will include DLTs, AEs, SAEs and deaths.

Secondary endpoints will include clinical measures of treatment outcome: ORR (as measured by RECIST v 1.1, GCIG CA125 response, and immune related response criteria), PFS and OS.</td></tr>
<tr><td>Exploratory Samples:</td><td>Core needle biopsy and peripheral blood will be collected at the protocol-specified timepoints and analyzed for immune markers as outlined below:

<table>
<tr><th>Exploratory objectives</th><th>Outcome measures</th></tr>
<tr><td>To collect blood and tissue samples for analysis of immune biomarkers</td><td>Biomarker analysis to assess exploratory markers include but are not limited to: immune cell gene expression profiles in the peripheral blood and tumor, frequency of lymphocyte subsets as defined by cell surface markers, presence of functional markers of immune activity, tumor associated antibodies</td></tr>
<tr><td>To investigate the relationship between the presence or absence and spatial distribution of lymphocyte subsets within the tumor microenvironment and outcomes</td><td>Tumor and tumor associated expression of immune checkpoints and their spatial distribution within the tumor microenvironment relative to OS, PFS, ORR</td></tr>
<tr><td>To explore biomarkers of radiation and durvalumab and efficacy</td><td>Biomarkers in the serum and tumor before and after treatment will be assessed and correlated with response to</td></tr>
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</td></tr>
</table>

		treatment and/or tumor progression
	To analyze biomarkers (e.g. immune, tumor) in different cellular compartments (e.g. tumor, immune, serum, blood) which may influence and/or prospectively identify patients likely to respond to treatment	Correlate expression of biomarkers with response to treatment and/or progression
Statistical Analysis:	**Evaluable for Adverse Events** For the primary objectives of this study (i.e. safety and MTD), the evaluable population will consist of patients who completed Cycle 1 of planned therapy, unless a DLT was encountered. Patients who did not complete Cycle 1 and did not experience a DLT will be replaced. All patients registered to the study who receive at least one dose of durvalumab will be assessed of safety and toxicity, but may not necessarily be included in the evaluable population for the primary endpoints (see definition above). For example, if a patient received one dose of durvalumab, and then declined further treatment, or had rapid disease progression, then they would be assessed for treatment toxicity at the time of the end treatment visit. If DLTs were not encountered the patient would be replaced in the study. Subjects who receive radiation without receiving durvalumab will not be included in the safety analysis. **Evaluable for Response** The efficacy analysis set will include all evaluable patients registered to the study. The evaluable population will consist of patients completing planned Cycle 1 of therapy, unless a DLT was encountered. Patients who did not complete Cycle 1 and came off treatment due to disease progression will not be included in the efficacy analysis. **Methods of Statistical Analysis** All safety analyses will be performed on the safety population. The incidence of events that are new or worsening from the time of the first dose of treatment with durvalumab will be summarized by dose level, organ system, severity and relationship to the study treatment and reported by CTCAE grade. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by primary system/organ and type of adverse event. The analysis of secondary endpoints will be	

	descriptive. Time-to-event endpoints (i.e., PFS, OS) will be summarized for the aggregated sample. The final analysis for the primary objectives will occur after the last patient to enroll in the study has completed Cycle 1 of therapy. The final analysis for secondary endpoints will occur when data are mature or within 6 months of study completion.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADCC	antibody-dependent cell mediated cytotoxicity
AEs	Adverse events
AESI	Adverse event of special interest
APCs	antigen presenting cells
B7-H1	B7 homolog 1
B-cells	B lymphocytes
cc	cubic centimeter
CD	cluster of differentiation
CR	Complete response
CSR	Clinical study report
CT	computed tomography
CTCAE	Common terminology criteria for adverse events
CTL	cytotoxic T lymphocytes
CTLA-4	cytotoxic T-lymphocyte antigen 4
DLT	Dose limiting toxicity
Dmax	maximum dose
DoR	Duration of response
DSMC	Data and Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GFR	Glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
GTV	Gross tumour volume
HBsAg	Hepatitis B Surface Antigen
HGSC	high grade serous cancer
HR	Hazard ratio
IGTV	Internal gross tumour volume
IMRT	intensity modulated radiotherapy

IV	intravenously
Kg	Kilogram
L	Liter
mAb	Monoclonal antibody
mCRPC	Castration resistant prostate cancer (mCRPC)
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
NED	No evidence of disease
NSCLC	non-small cell lung cancer
OAE	Other adverse event
OAR	organs at risk
ORR	Objective response rate
OS	Overall survival
PARP	poly ADP ribose polymerase
PD	Progressive disease
PD-1	programmed death -1
PD-L1	programmed death ligand 1
PFS	Progression free survival
PK	pharmacokinetics
PR	Partial Response
PTV	planning target volume
q 28 days	every 28 days
SAE	Serious adverse event
SD	Stable disease
TIL	tumour infiltrating lymphocytes
V	Volume
VMAT	volumetric modulated arc therapy

1. INTRODUCTION

Investigators should be familiar with the urvalumab Investigator's Brochure (IB).

1.1 Background

1.1.1 Ovarian cancer

Approximately 27000 women are diagnosed with ovarian/primary peritoneal/fallopian tube cancer (henceforth called ovarian cancer) in the US annually. Of these, nearly 60% will have high grade serous cancer (HGSC), the most common subtype of this disease. Given the absence of effective screening strategies, cancer of the ovary is typically diagnosed in advanced stages (stages III and IV). Survival rates have improved; however, cures remain elusive for the majority of patients with stage III and IV disease [1]. The standard of care remains de-bulking surgery and successive rounds of cytotoxic therapy. Clinical trials of first-line sequential therapies, maintenance treatments, targeted therapies, amongst other strategies have not lead to cures, although modest improvements in survival can be achieved. Other emerging treatment options include angiogenesis inhibitors such as bevacizumab [2] and poly ADP ribose polymerase (PARP) inhibitors, particularly in tumours deficient in homologous repair [3].

All cases of recurrent ovarian cancer progress to the penultimate state of platinum resistance. Patients with platinum resistant disease, defined by disease progression within 6 months of the last line of platinum based therapy, have a poor prognosis (medial survival 12-18 mo), with standard therapies having minimal activity (10-15% response rate) and none demonstrating an improvement in overall survival [4]. The AURELIA trial is the first advance in the treatment of platinum refractory carcinoma of the ovary. Bevacizumab added to standard single agent chemotherapy improved progression free survival by 4 months, however, overall survival was not improved, potentially because of the 40% crossover observed from the standard arm to bevacizumab [5]. Radiotherapy in recurrent ovarian cancer is routinely used for palliation, for example, in the case of a painful retroperitoneal lymph node, or uncomfortable pelvic mass, but does not lead to improved survival due to the systemic nature of advanced disease. Therefore, new approaches are urgently needed for the treatment of this highly lethal cancer.

1.1.2 Immunotherapy: checkpoint blockade

The immune system can identify tumour-associated antigens and eliminate cancerous cells. The observed co-evolution of the tumour and the immune response is termed immunoediting, which is purported to have 3 stages [6]: elimination, during which the innate and adaptive immune systems detect and eliminate tumour cells; equilibrium, during which the immune system eliminates susceptible tumour cells, however, some tumours may evolve mechanisms to avoid or attenuate the immune response, and; escape, during which many factors may contribute to the failure of the immune system to control tumour growth including the expression of immune-inhibitory molecules, presence of immunosuppressive regulatory T lymphocytes (T-regs) or immunosuppressive cytokines within the tumour microenvironment,

and down-regulation of major histocompatibility molecules and tumour antigens leading to reduced antigen presentation and recognition.

Blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed death -1 (PD-1) and programmed death ligand 1 (PD-L1) have shown promising clinical activity in activating immune recognition and elimination of cancers. Ipilimumab binds to CTLA-4 and prevents the interaction of CTLA-4 with cluster of differentiation (CD) 80 and CD86, resulting in enhanced T-cell activation and proliferation [7]. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval in 2011 for the treatment of metastatic melanoma and is currently under investigation for several other malignancies. Nivolumab and pembrolizumab are IgG4 (fully human and humanized respectively) antibodies targeting PD-1. These agents are approved by the FDA for treatment of advanced melanoma and squamous non-small cell lung cancer (NSCLC). Increased PD-L1 expression was shown to be predictive of response in patients with melanoma and NSCLC treated with pembrolizumab [8,9]. However, PD-L1 status was not predictive in patients with squamous NSCLC treated with nivolumab [10].

PD-L1 (B7 homolog 1 [B7-H1], CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 is normally expressed on T-cells, B lymphocytes (B-cells), dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various non-haematopoietic cells [11]. The normal tissues, PD-L1 acts to repress T-cell activation and induce tolerance through interaction with 2 receptors, programmed death 1 (PD-1, CD279) and CD80 (B7-1). The expression of PD-1 is induced on lymphocytes and regarded as an activation marker. However, chronic antigen stimulation can cause T cells to retain high levels of PD-1 expression and thereby lose the capacity to respond to activation signals, a state known as T cell exhaustion. This physiological feedback mechanism limits the potential for hyper-lymphocyte activation and tissue damage. Tumours have co-opted the PD-L1/PD-1 axis at multiple sites to help tumours evade detection and elimination by the host immune system. For example, PD-L1 expression can be innate to cancers (innate immune resistance) or it can be induced by selective pressure from the immune system (adaptive immune resistance) [12]. PD-L1 on antigen presenting cells (APCs), found in lymph nodes, binds to PD-1 (CD279) or CD80 (B7-1) on activated T-cells, inhibiting their function [11,13]. Likewise, APCs that express CD80 can bind to PD-L1 on T-cells, also leading to T-cell inhibition. These interactions reduce T-cell activation and lower activated T-cells in the circulation. T-cell inhibition also occurs in the the tumour microenvironment, where PD-L1 expressed on tumour cells binds to PD-1 on activated T-cells [14].

In vitro, antibody blockade of PD-L1: PDL-1 receptor interaction can relieve PD-L1-dependent immunosuppressive effects, leading to enhanced cytotoxic activity of anti-tumour T-cells [15]. Several preclinical studies in mouse tumour models also demonstrate that antibodies directed against PD-L1, or its receptor PD-1, improves anti-tumour activity [16-19].

1.1.3 Immune system in ovarian cancer

There is strong evidence to suggest that the immune system plays a key role in the progression of HGSC ovarian cancer. An immune response signature (defined by a set of 49 genes) has been associated with improved ovarian cancer survival in a large analysis conducted on samples of The Cancer Genome Atlas Repository [20]. Likewise, intra-tumoural infiltration by CD8+ and CD3+ T cells (cytotoxic T lymphocytes - CTL) is associated with better prognosis in advanced HGSC of the ovary [21-23] and many factors associated with cytolytic T cells (CTLs) are also associated with better survival (e.g. IFN-gamma, IFN-gamma receptor, interferon regulatory factor-1, IL-18, TNF-α, MHC class I, MHC class I antigen processing machinery) (reviewed in Milne et al. [24]). On the other hand, worse survival has been associated with infiltrating regulatory T cells (Tregs) [25,26]. Tregs act to suppress the immune response of CTLs by inhibiting proliferation, cytokine production and cytolytic activity. Tregs also induce immunosuppressive phenotypes in cells such as macrophages.

Up to 50% of ovarian HGSCs have CD8+ and CD3+ tumour infiltrating lymphocytes (TIL), suggesting that appropriate tumor-derived antigens lead to T-cell priming and immune activation. Immune activation is a key step in triggering an immune response; however, the presence of TIL is insufficient to eliminate the cancer. This suggests that the TIL are hypo-reactive. Several immune suppressive pathways have been identified. These include inhibitory receptors, e.g. CTLA-4 and PD-1, which, when engaged by their ligands (B7 and PD-L1 respectively) expressed on an antigen presenting cells or tumor cells, block T -cell activation. In many cases, tumors up-regulate the expression of inhibitory ligands, resulting in a state of immune tolerance/immune exhaustion.

1.1.4 PD-1/PD-L1 expression in ovarian cancer

PD-L1 is expressed in a broad range of cancers [11,14]. In a number of these cancers, including lung [27], renal [28-30], pancreatic [31-33], and ovarian cancers [34], the expression of PD-L1 is associated with reduced survival and an unfavourable prognosis. In ovarian cancer, for example, the 5-year survival rate in patients with low levels of PD-L1 was 80.2%, compared with 52.6% in patients with high levels of PDL-1.

PD-L1 expression is observed in the ascites of ovarian cancer patients and is also associated with shorter overall survival [35]. A series of pre-clinical studies have demonstrated that PD-1 blockade, alone or in combination with other immune modulators (e.g. OX40, CTLA-4) impairs ovarian cancer growth in model systems and restores T cell function [36-40]. PD-1 is expressed by TILs of ovarian cancers.

1.1.5 Clinical trials of checkpoint inhibitors in metastatic cancers

Since the first reports of activity of checkpoint inhibitors in metastatic cancers [41,42] progress in clinical immunotherapy research has been rapid. Numerous phase III trials have demonstrated the efficacy of anti-CTLA4 therapy [43-45], and anti-PD-1 therapy [46-48] in improving progression free survival and overall survival for metastatic melanoma. A comparative trial suggests that anti-PD-1 blockade may have superior clinical outcomes and better toxicity profiles than anti-CTLA4 therapy for melanoma patients [47]. However,

combined anti-PD-1 (nivolumab) and anti-CTLA4 (ipilimumab) therapy showed better clinical outcomes (higher response rates, prolonged progression free survival, longer overall survival and more complete responses) than either agent alone [49]. As expected, the incidence of grade 3 and 4 toxicity was greater in the combination arm. The most common adverse events included diarrhea, fatigue, and pruritis.

Patients with metastatic non-small cell lung cancer (NSCLC) also benefit from checkpoint inhibitors. A phase III trial enrolled patients with treatment resistant NSCLC to standard docetaxel versus the PD-1 inhibitor, nivolumab and demonstrated an improvement in progression free survival on the nivolumab arm [9.3 mo vs 6 mo, ($p<0.001$, HR, 0.59)] [50]. A recently published phase III trial of nivolumab as compared to everolimus for the second-line treatment of renal cell carcinoma demonstrated a greater than 5 month improvement in OS of the checkpoint inhibitor over the mTOR targeting agent, which was the historic standard [51]. Phase III trials of PD-1 inhibitors and PDL-1 inhibitors, in the first-line setting compared to standard platinum-based therapy and in second-line therapy compared to docetaxel, for patients with metastatic NSCLC are ongoing. Other active areas of research include metastatic bladder cancer ([52], NCT02451423), and mismatch repair deficient tumours such as colorectal cancers [53].

1.1.6 Clinical trials of checkpoint inhibitors in recurrent ovarian cancer

Data on 11 heavily pretreated patients with ovarian cancer receiving therapy with ipilimumab [54,55] reported 6 to have clinical benefit - 2 with transient responses, 3 with stable disease of 2 months duration, and one with confirmed RECIST response. Treatment related side effects did include 2 cases of grade 3 inflammatory toxicity manifesting as diarrhea. Grade 1 rash was documented in 7 patients.

A phase II study of anti-PD-1 therapy with Nivolumab in platinum resistant ovarian cancer demonstrated that amongst 10 patients treated at 1 mg/kg, 1 (10%) had a partial response. Ten patients received 3 mg/kg dose, and 2 (25%) had a durable complete response, one with recurrent HGSC and the other with recurrent clear cell carcinoma of the ovary [56]. The patients were heavily pretreated, with a medial of 4 prior therapies. The agent was well tolerated; however, dose independent toxicities such as rash, increased liver enzymes, hypothyroidism, fever, arthralgia, low albumin, and lymphocytopenia were reported.

A phase Ib open expansion study of an anti-PD-L1 agent, avelumab, in recurrent ovarian cancer [57] reported on efficacy data on the first 23 evaluable patients who were followed for at least 2 or more months. Four patients have an unconfirmed partial response (by RECIST 1.1 criteria [58]) as best overall response, and 2 patients had >30% tumour shrinkage after initial progression was reported, one of whom had clear cell carcinoma of the ovary. Reported drug-related treatment-emergent adverse events were reported in 18 patients (78.3%) with 2 (8.7%) experiencing ≥ grade 3 toxicity (increased lipase [n=1] and elevated creatine kinase and autoimmune myositis that led to treatment discontinuation [n=1]). No serious drug-related treatment-emergent adverse events were observed. The most commonly reported drug-related treatment-emergent adverse events (> 10%) were fatigue, nausea, and diarrhea.

Therefore, the PD-1/PD-L1 immune regulators warrant further study in ovarian HGSCs.

1.1.7 Durvalumab

For full details please refer to the current IB.

Durvalumab is an engineered human IgG1κ monoclonal antibody (mAb) with high affinity and selectivity for PD-L1 [59]. Durvalumab is non-immunogenic at the phase III dose of 10mg/kg, hence pharmacokinetics (PK) and pharmacodymics (PD) were not affected. Only 2/196 patients treated at 10mg/kg developed measurable anti-drug antibodies (ADA) [59]. Exposure of the drug was sustained throughout the dosing intervals (>1 yr). The engineering of the durvalumab Fc domain (which is triply mutated) has removed the antibody-dependent cell mediated cytotoxicity (ADCC) activity.

1.1.8 Clinical experience with durvalumab

For full details of the clinical information, please refer to the current IB.

Durvalumab has been given to humans as part of ongoing studies where it is given either as a single drug or in combination with other drugs. As of September 2015, 1,910 subjects have been treated across 30 ongoing durvalumab studies. The majority of the safety data for durvalumab have been pooled from 4 durvalumab monotherapy studies (CD-ON-MEDI4736-1108, D4190C00002, ATLANTIC and D4193C00001 [HAWK])in patients with advanced solid tumours, receiving durvalumab at 10 mg/kg Q2W. 1645 are included in the pooled analysis. [59-64]. Two hundred and fifty-two patients (252) with NSCLC and 62 with squamous cell carcinoma of the head and neck (SCCHN) were treated as part of the phase I expansion cohort study [60,61]. Adverse events (AEs) on this trial (including expansion cohorts) occur at a rate of 30-60%. The vast majorityof AEs are low grade (Grades 1-2) and are easily managed. The most frequently reported (≥10% of subjects) treatment-emergent AEs (all grades) include (in decreasing order of frequency): fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. An newly recognized adverse event is the occurrence of serious hemorrhagic events in pateit

AEs of Grade 3 or higher considered related todurvalumab were reported in 164 patients (10.0%): of these, 144 patients (8.8%) had events of Grade 3, 12 patients (0.7%) had events of Grade 4 and 8 patients (0.5%) had Grade 5 (fatal) events..
Grade 3 events occurring in ≥1% of patients were: anaemia (5.5%); dyspnoea (4.4%); hyponatraemia (4.1%); fatigue (2.9%); gamma-glutamyltransferase (GGT) increased (2.7%); abdominal pain (2.0%); decreased appetite and back pain (1.9% each); pneumonia (1.8%); aspartate aminotransferase (AST) increased and dehydration (1.6% each); hypertension (1.3%); blood alkaline phosphatase (ALP) increased, hypokalaemia, urinary tract infection and vomiting (1.2% each); alanine aminotransferase (ALT) increased and pleural effusion (1.1% each); bilirubin increased, asthenia, nausea and pulmonary embolism (1.0% each). Grade 3 eventsconsidered related to durvalumab occurring in ≥0.5% patients were fatigue (1.2%), GGT increased (0.8%) and AST increased (0.6%).

Treatment-related AEs were reported in 49.8% of cases (820/1645). Grade 3 events occurring in ≥1% of patients were: anaemia (5.5%); dyspnoea (4.4%); hyponatraemia (4.1%); fatigue (2.9%); gamma-glutamyltransferase (GGT) increased (2.7%); abdominal pain (2.0%); decreased appetite and back pain (1.9% each); pneumonia (1.8%); aspartate aminotransferase (AST) increased and dehydration (1.6% each); hypertension (1.3%); blood alkaline phosphatase (ALP) increased, hypokalaemia, urinary tract infection and vomiting (1.2% each); alanine aminotransferase (ALT) increased and pleural effusion (1.1% each); bilirubin increased, asthenia, nausea and pulmonary embolism (1.0% each). Grade 3 events considered related to durvalumab occurring in ≥0.5% patients were fatigue (1.2%), GGT increased (0.8%) and AST increased (0.6%).Grade 4 events considered related to durvalumab occurring in ≥2 patients were GGT increased and pneumonitis (0.1% each). Grade 5 event considered related to durvalumab occurring in ≥2 patients was pneumonitis (0.1%).

Serious bleeding events have been observed in patients receiving durvalumab, with or without tremelimumab across 6 studies of patients with squamous cell carcinoma of the head and neck. Eleven of 238 patients (4.6%) monotherapy with durvalumab and episode of hemorrhage. When disease-related, or other etiologies were accounted for, 4/238 events of bleeding were attributed to durvalumab (1.7%). Durvalumab combined with tremelimumab has also lead to hemorrhages in 14/238 patients (6.9%). Once again, when other etiologies were accounted for, treatment related serious bleeding events were seen in 4/238 cases (2%).

Early reports, from phase I and II trials, demonstrate activity of durvalumab in patients with a variety of malignancy types, including NSCLC, SCCHN, melanoma, and urothelial carcinoma. Responses have included disease stabilization and partial responses, some of which have lasted >43 weeks at last reporting [61]. Thus far, no subjects have experienced a complete treatment response. Data from phase III trials remain to be reported.

1.2 Radiotherapy and Immunogenic Cell Death

A key step in immune system activation is T cell priming through tumour antigen exposure. There is compelling evidence that radiation can induce immunogenic tumour cell death characterized by signals that promote uptake of dying cells by dendritic cells, cross-presentation of the tumour-derived antigens to T cells, and activation of anti-tumour T cells (Reviewed in [65] and [66]). Radiation can also alter the tumour microenvironment and enhance recruitment of anti-tumour T cells [67].

A rare phenomenon called the abscopal (Latin *ab-scopus*, meaning away from) response has been observed clinically where patients receiving local radiotherapy experience anti-tumor responses at a distant untreated site. This phenomenon has been described in a patient with metastatic melanoma demonstrating disease progression while on maintenance ipilimumab. Radiation to a symptomatic pulmonary focus lead to systemic disease response and correlates of immune activation were observed in the blood following the localized radiation treatment. [68]. The proposed mechanism to explain the abscopal effect is that radiation results in both

appropriate changes in the tumour microenvironment and T-cell priming. When inhibition is weak (rarely in natural setting, but now manipulatable by checkpoint regulatory drugs) the delivery of focal radiotherapy may be sufficient to activate local cellular immunity. As the active immune cells enter the circulation, they also excerpt their anti-cancer effect on distant metastatic sites.

Therefore, it may be possible to exploit the immune activating properties of focal radiotherapy and simultaneously overcome the state of immune tolerance, with the goal of enhancing anti-tumour immunity.

1.2.1 Pre-clinical data of radiotherapy and checkpoint regulators

There are no pre-clinical studies of localized radiotherapy delivered with anti-PD-1 or PD-L1 agents. However, studies of focal radiotherapy given with anti-CTLA treatment have been conducted, mainly in models of non-ovarian tumor types. Arguably, a valid model of ovarian cancer does not exit. The widely used mouse ID8 model, which forms peritoneal disease and ascites, is derived from the surface epithelium of the mouse ovary. However, HGSCs of the ovary and peritoneum have their origin in the fallopian tube. In addition, unpublished studies from our team found that p53 is highly expressed in ID8 tumors. This is in contrast to publically available data from the TCGA showing that greater than 10% of all tumors display recurrent mutations in p53 (among many other examples). Thus, the mutational landscape of murine ID8 tumors differs from HGSC, which may have profound consequences on the responses to radiation therapy.

Using a syngeneic murine breast and colon cancer model, it has been demonstrated that local radiotherapy combined with anti-CTLA-4 antibody induces effective systemic anti-tumour responses [69,70]. Likewise, using syngeneic murine models, it has been demonstrated that fractionated treatment (using 8 Gy x 3 fractions) elicited the greatest response of tumour locally and at distant sites as compared to other dose and fractionation schedules and anti-CTLA-4 therapy alone [71]. Our own studies have uncovered similar synergy between radiation and anti-CTLA4 in a prostate tumor mode whereby animals receiving fractionated radiation followed by anti-CTLA4 exhibited significantly better survival than animals receiving anti-CTLA4 alone. Moreover, the timing of anti-CTLA4 relative to radiation treatment was crucial for clinical responses. Animals that received anti-CTLA4 closest to the time of radiation survived longer than animals that received anti-CTLA4 furthest from the time of radiation. As preclinical data is limited, and the optimal strategy for combining focal XRT with immune modulation remains to be defined. There are data to suggest that radiation regimens with minimal tumour cell-kill and tumour growth inhibition may adequately sensitize tumours to rejection by cytotoxic T lymphocytes [72]. The goal is to deliver the radiation such that it will act as an in situ vaccine [73], allowing release of tumor-associated antigens as well as other immunogenic signals (e.g. HMGB1), antigen uptake and cross-priming by antigen presenting cells.

1.2.2 Clinical data of combined focal radiation and checkpoint inhibition

The strategy of adding XRT to checkpoint inhibitors to potentiate immune activation is currently being explored in multiple tumour types. One phase III trial in patients with metastatic castration resistant prostate cancer (mCRPC) [74] randomized participants in a 1:1 ratio to receive a single fraction of bone-directed radiation therapy at 8 Gy followed by ipilimumab at 10 mg/kg (n=399) or placebo (n=400). The HR for OS on the intervention arm changed over time, but was not significant as an assessment of the proportional hazards assumption was shown to be violated. An exploratory, post-hoc analysis did demonstrate an OS benefit of the ipilimumab arm in patients with the best prognostic factors (absence of visceral metastases, absence of anemia, and normal or only mild elevations of alkaline phosphatase). However; it is not possible to assess the contribution of the fraction of irradiation to the outcomes on treatment, as the control arm received placebo treatment, rather than ipilimumab alone. At the present time, there are no other published reports of the combination of focal, immune-sensitizing XRT and a checkpoint regulator, although many trials are ongoing. PD-1 inhibition (e.g. MK3475/pembrolizumab) combined with focal radiation in the setting of metastatic melanoma (NCT02407171, NCT02562625), or in metastatic NSCLC (NCT0244741, NCT02407171) is under active study. Anti-CTLA4 therapy using ipilimumab combined with focal radiotherapy is also being studied with may trials recruiting patients with solid tumours, melanoma, NSCLC (all listed in www.clinicaltrials.gov).

A proof-of principle study has demonstrated an abscopal effect of radiotherapy when given with granulocyte-macrophage colony-stimulating factor (GM-CSF) [75]. This phase 2 trial gave GM-CSF (an immune adjuvant that can lead to dendritic cell maturation) and focal radiotherapy to patients with stable or progressing metastatic solid malignancies (having at least 3 distinct measurable sites >1 cm in size). Patients were able to continue on their existing chemotherapy or hormonal therapy. Radiotherapy was given to the chosen target lesions in the following way: lesion 1 was treated daily, starting on day 1, for 10 consecutive days and a total dose of 35Gy; lesion 2 was treated in the same way starting on day 22. Daily GM-CSF (125 µg/m2) was given subcutaneously for 14 days, starting one week after each course of radiotherapy. Responses were assessed 7-8 weeks after starting the study, and the primary outcome was the observation of an abscopal response (defined by a decrease of 30% in any measurable non-irradiated lesion). If multiple lesions were measured, the best response was reported. Forty-one patients were enrolled, and 37 were assessable for response. Abscopal responses were described in 26.8% of cases. This included 2 complete responders. Therefore, this area of research has unexplored potential.

1.2.3 Selection of radiotherapy dose, fractionation, and timing of checkpoint inhibition

There are no pre-clinical or clinical data to guide the optimal radiation dose or schedule to be used in conjunction with durvalumab. Pre-clinical data suggest that fractionation may be important, with 8 Gy X 3 over 3 consecutive days being a superior schedule to single fraction of 20 Gy, or 5 fractions of 6 Gy over 5 consecutive days when studied with ipilimumab [71].

Using a syngeneic mouse model system (melanoma, colon and triple negative breast cancer) Dovedi et al. demonstrated that fractionated radiotherapy leads to increased tumour expression of PD-L1, which may attenuate the anti-tumour immune response. The effectiveness of fractionated radiotherapy (using 2 Gy x 5 fractions) was enhanced when it was combined with an anti-PD-L1 mAb, but not when the radiation and anti-PD-L1 therapies were given sequentially [76]. The potential benefits of combining radiation and checkpoint inhibitors early in the treatment course is also demonstrated in a recently reported trial of patients with refractory NSCLC. Ipilumumb (3 mg/kg) was delivered within 24 hrs of the first dose of fractionated radiotherapy (6 Gy in 5 daily fractions). Of 12 evaluable patients, abscopal responses to therapy included 3 patients with CR, 4 with PR, and 5 with SD [77].

Various dosing strategies are being explored in the clinical trial setting. Many are modeled after the mouse model experiments conducted by Dewan et al. [71], with 3-5, 3-10 Gy, daily fractions of focal radiotherapy being delivered immediately before the start of the chosen checkpoint inhibitor (e.g. NCT02407171, NCT 02562625, NCT 02406183, NCT 01689974).

We propose a unique radiation strategy to exploit the potential immune system priming and immunogenic tumour cell death effects of fractionated radiation combined with the checkpoint inhibition of durvalumab. Two distinct and anatomically separate radiation target lesions will be identified. Each target lesion will be treated with a total of 24 Gy at the starting radiation dose, given as 6Gy x 4 fractions. The radiation will be planned such that there will be NO overlap of the 50% isodose between the targets dose between the targets. Durvalumab will be delivered within 24-36 hours of the first radiation fraction and will be delivered intravenously every 28 days.

Delivering fractionated radiation to two separate lesions may increase the likelihood of releasing a broader set of new tumour antigens, assuming the presence of tumour heterogeneity. This novel strategy may also overcome the practical limitations that may arise if the first radiation target decreases in size in response to the radiotherapy. By fractionating the radiation, and limiting the total dose to 24-32 Gy per target lesion, local radiation toxicity will be mitigated and will be within tissue constraints.

1.3 Research Hypothesis

1) We hypothesize anti-PD-L1 therapy and focal radiotherapy can be safely combined in patients with recurrent platinum resistant ovarian/primary peritoneal or fallopian tube cancer.

2) We hypothesize that radiation-induced immunogenic cell death will enhance the antitumor immune responses of an anti-PD-L1 agent in patients with recurrent platinum resistant ovarian/primary peritoneal or fallopian tube cancer.

1.4 Rationale for Conducting This Study

Platinum resistant ovarian/primary peritoneal or fallopian tube HGSCS have a poor prognosis, with most patients succumbing to progressive disease within 12 months. It has been observed

that PD-L1 is highly expressed in ovarian cancers [35,78], thereby suppressing PD-1 positive T-cells. While the presence of TIL in ovarian cancer has been associated with better clinical outcomes, however, is not sufficient to eliminate the disease.

Durvalumab is a human mAb that selectively binds human PD-L1 with high affinity and blocks its interaction with PD-1 and CD80. Normally this interaction leads to T-cell inactivation; therefore, interference with this interaction may activate the T-cell to recognize and eliminate cancer cells, a concept demonstrated *in vitro* and with xenograft models. Focal radiation has the potential to further augment the immune response.

By combining the T-cell activating capacity of durvalumab with the potential immune augmenting properties of focal radiation therapy, a synergistic effect against malignancies may be induced. This effect may spread to areas of disease outside of the radiation field, and this desired response is called the abscopal effect. This trial will determine safety of delivering a single fraction of focal radiotherapy with each of the first 4 doses of durvalumab (q 28 days) in participants with recurrent, platinum resistant ovarian cancer for whom there remain no highly active standard therapies.

1.5 Benefit/Risk and Ethical Assessment

Patients with recurrent ovarian cancer face a poor prognosis. All patients reach the penultimate state of platinum resistance, and subsequently succumb to this disease. The need to find novel, effective therapies is dire. Patients with platinum resistant ovarian cancer are frequently offered participation in clinical trials as standard therapeutic options are minimally effective [4].

Anti-PD-1 and PD-L1 therapy in ovarian cancer has been demonstrated to be safe with the common anti-PD-1/anti-PD-L1 toxicities being reported. However, the single agent activity of these agents in ovarian cancer, as reported so far, is modest. Methods to augment the effectiveness of immune modulation by checkpoint inhibitors are an important area of current research. Radiation, with its ability to affect immunogenic cell death and to affect local tumour immune suppression, may be enhance the effectiveness of checkpoint inhibitors and lead to tumour regression at sites distant to the radiation field: the so called abscopal effect.

While radiation therapy is not routinely used in the management of recurrent ovarian cancer, palliative radiation is often given for the relief of pain or other symptoms (e.g. pelvic bleeding, obstructing pelvic disease etc.).

Pre-clinical models demonstrate that radiotherapy and checkpoint inhibitors (namely CTLA4 blockade) can be safely combined. Several clinical trials of checkpoint inhibitors, mainly anti-CTLA4 but also anti-PD-1 inhibitors, are ongoing in metastatic melanoma, and also in lung cancer and breast cancer. This will be the first such trial in patients with recurrent, platinum resistant ovarian cancer.

2. STUDY OBJECTIVES

This is an open label, phase I study designed to determine the safety and maximum tolerated doses (MTD) of durvalumab and of focal irradiation when combined in the treatment of patients with recurrent, platinum-resistant ovarian cancer.

2.1 Primary Objective

The primary objective of this study will be to assess the safety and tolerability of durvalumab and focal irradiation, as defined by dose-limiting toxicities (DLTs), and define the maximum tolerated dose (MTD) and treatment schedule that can be safely used for future study of this therapeutic strategy.

2.2 Secondary Objectives

The secondary objectives of this study are to evaluate the clinical activity of durvalumab and focal radiotherapy as measured by:

1) Objective Response rate as evaluated by
    a. RECIST (v 1.1) criteria [79]
    b. GCIG CA-125 response criteria [80]
    c. Immune-related response criteria [81]
2) Progression free survival
3) Overall survival

2.3 Exploratory Objectives

Exploratory objectives of this study include:

1) To collect blood and tissue samples for analysis of immune biomarkers
2) To investigate the relationship between the presence or absence and spatial distribution of lymphocyte subsets within the tumor microenvironment and outcomes
3) To explore biomarkers of radiation and durvalumab and efficacy
4) To analyze biomarkers (e.g. immune, tumor) in different cellular compartments (e.g. tumor, immune, serum, blood) which may influence and/or prospectively identify patients likely to respond to treatment

3. STUDY PLAN AND PROCEDURES

3.1 Overall Study Design

This is a phase I, open label, safety and tolerability assessment of the combination of PD-L1 blockade using the mAb, durvalumab, with focal irradiation of two selected cancer lesions in patients with recurrent, platinum-resistant ovarian cancer. The treatment delivery of both focal radiation and durvalumab is described in Table 1.

Eligible participants will have up to 28 days to undergo screening. During the screening period, they will be confirmed to meet all the study related eligibility criteria and to undergo the required baseline testing.

The study will be conducted as a 3+3+3 dose escalation study of durvalumab and focal radiotherapy (Table 2). Patients enrolled in the study will receive durvalumab according to their assigned dose level (see Table 1) by IV infusion q 28 days ±3 days. Radiation will be delivered to both target lesions at the same time at the assigned dose level (see Table 2).

The study will commence on Day -1 following confirmation of registration by Ozmosis Research Inc. Treatment will start with the first of 2 fractions of focal radiation to the selected target lesions on Day -1, and durvalumab will be delivered on Day 1. For the first 2 cycles of durvalumab, focal radiation to the selected target lesions will be delivered 24-36 hours prior to the infusion of durvalumab on Day 1, Day 1 and 28 of Cycles 1 and days 1 of Cycle 2 (i.e. each cycle will be 28 days).

Durvalumab treatment will be continued on a q 28 day schedule as long as well tolerated for a maximum duration of 12 months. Study drug should be discontinued prior to 12 months if there is confirmed PD (unless the investigator considers the patient continues to receive benefit from study drug), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue study drug occur as outlined in section 6.5.

Table 1. Treatment Delivery Overview

Treatment Cycle	1			2				≥ 3*
Day of Treatment	D-1	D1	D28	D1	D14	D15	D28	D1 of a 28 day cycle
Durvalumab all dose levels		X		X				X
Radiation Dose per Target								
24 Gy	6Gy	6 Gy	6 Gy	6 Gy				
32 Gy	8 Gy	8 Gy	8 Gy	8 Gy				

Radiation Targets treated	A and B	A and B	

* maximum treatment duration = 12 months

3.2 Sample Size

The minimum number of patients required to complete this study will be 3. This would occur if the first 3 patients on dose level 1 experienced DLTs. The study would then stop accrual. The maximum number of patients required to complete this study will be 22. This would occur if at each dose level, the cohorts had to be fully expanded (n=9), and 2 patients at each dose level had to be replaced.

3.3 Enrolment Procedures

The study will be conducted at two Canadian centres. Once 3 subjects are enrolled in a cohort, that dose level will be closed to enrolment until safety assessment of all the 3 subjects is performed at the end of cycle 1 (4 weeks). This procedure will be performed for each dose level cohort. Subjects will be assigned durvalumab and radiation fractionation dose levels based on authorization from the Sponsor in collaboration with Ozmosis Research Inc. Higher dose levels will be assigned to subjects following the dose escalation rules described in Section 3.5 below.

3.4 Definition of Dose-Limiting Toxicity (DLT)

Patients who have received at least one radiation fraction AND one dose of durvalumab will be monitored for DLTs. The safety observation period will be 28 days (one cycle length). This time period will allow for assessments of acute DLTs. Once all 3 patients have completed the observation period, the dose level may be escalated. Patients will be followed long term to monitor for emergence of late toxicity (see 3.5.1).

DLTs will be defined with the use of the Common Terminology Criteria for Adverse Events version 4.03 as any of the following as assessed by the investigator:

- any grade ≥3 adverse event suspected to be related to the study agent or to the radiation
    - radiation necrosis or radiation recall reactions at previously irradiated sites
    - if the radiation field includes bowel, then radiation induced bowel perforation
    - any unexpected grade 3 or greater toxicity at the site of irradiation
- any grade ≥2 allergic or autoimmune event that involves vital organ functions
- any other grade 3 allergic or autoimmune events that does not resolve to grade 1 toxicity before the next scheduled dose of antibody.

In rare instances, an event may fall within the definition of a DLT as defined above but the event may be considered not a DLT (ie: not clinically meaningful/significant). If this occurs, a meeting with the principal investigator, the sponsor and the Data and Safety Monitoring Committee (DSMC) will take place to thoroughly review the event and supporting data and the reasons for not considering the event a DLT will be clearly documented with supporting rationale. In addition other events may occur which do not meet the definition of a DLT but are concerning to the investigators and sponsor and may be then considered to be DLTs.

3.5 Dose Escalation Procedures

Subjects will be enrolled in cohorts of 3 each. Dose escalations/de-escalations for subsequent cohorts will be undertaken as per the dose modification tables below following a standard 3+3+3 design to establish the MTD of the combination of durvalumab and focal radiation.

Table 2. Dose modification scheme based on treatment related DLTs

Dose Level	**Durvalumab dose**	**Total Radiation dose given per target lesion (2 lesions per patient)**	**N**
1 (starting dose level)	1500 mg	24 Gy	3+3+3
2	1500 mg	32 Gy	3+3+3

Three subjects will be treated at an initial dose level of 1500 mg of durvalumab q28 days and 24 Gy of radiation (6Gy X 4) to both radiation targets (delivered as per the treatment schedule shown in Table 1). If 0, 1 or 2/3 subjects experience DLTs during cycle one (first 4 weeks of treatment), 3 additional subjects will be enrolled at the same dose level. If at dose level 1, 2/6 experience DLTs, then 3 more subjects will be enrolled in the trial at the starting dose level. If 0 or 1/6, or <3/9 experience a DLT at dose level 1, then dose escalation to dose level 2 will be permitted. Enrolment onto dose level 2 will follow the same rules as described for dose level 1, following a 3+3+3 design to define the MTD. If at any time on dose level 1, ≥3 subjects (3/3, 3/6, or 3/9) experience a DLT the trial will stop accrual and a MTD will not be defined due to excessive treatment toxicity. If at dose level 2, ≥3 subjects (3/3, >3/6, or 3/9) experience a DLT then accrual will stop and dose level 1 will be selected as the MTD. If at dose level 2, ≤ 1/6 or < 3/9 experience DLTs, then dose level 2 will represent the MTD.

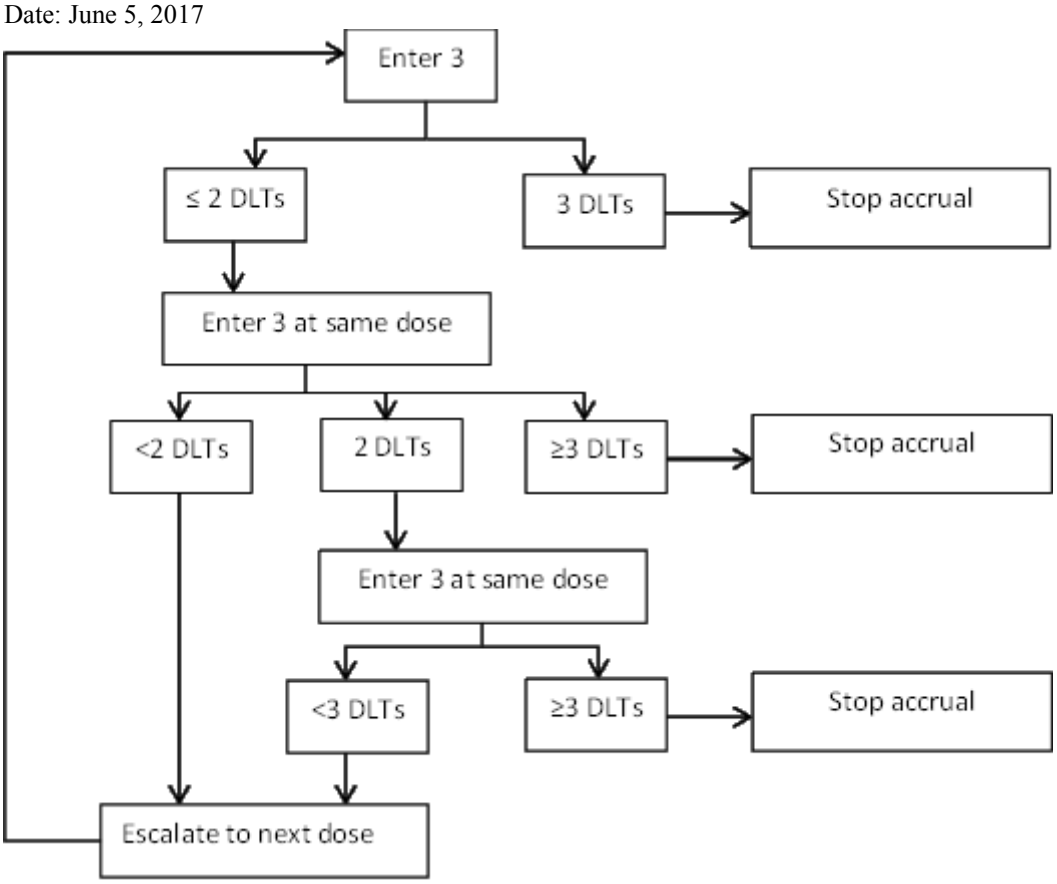

Figure 1. 3+3+3 Dose Escalation Procedures

3.5.1 Assessment of Late Toxicity

Patient follow up will continue until patient death or up to a maximum of 2 years. Assessment for late adverse events will be included in this follow up in order to identify late treatment toxicity (e.g. radiation toxicity such as radiation necrosis, radiation fibrosis, radiation enteritis or colitis, or other toxicities felt to be attributable to the focal radiation treatment, or late durvalumab toxicity such as immunologic events). Patients will be contacted by the research staff every 3 months to assess their status and ask about possible late treatment effects. If needed, patient medical records will be reviewed for evidence of potential late toxicities. Potential toxicities will be reviewed by the study sponsor, Ozmosis, the study Principal Investigator and with the DSMC. If life threatening or severely morbid late toxicities emerge in ≥ 1patient enrolled in the trial, the DSMC will have the capacity to suspend enrolment, and recommend premature closure of the study following discussion with Ozmosis and the study Principal Investigator and the study sponsor.

3.5.2 Safety Cohort Review

At the end cycle 1 of every subject, the following sections of the eCRF and source documentation for laboratory results, must be completed and submitted to Ozmosis Research Inc.:

- Study Drug Administration
- Adverse Events
- Laboratory Results
- Lab normal ranges page, if applicable

Additional information may also be requested by Ozmosis Research Inc. from the study site. It is imperative that the CRF pages listed above are completed as soon as cycle 1 has ended (i.e.: within 24 hours after the end of cycle 1), as the information will be used to assess safety at the opened dose level and to determine the feasibility of proceeding to a new dose level.

An "Accrual on Hold" notice will be sent out to sponsor and sites by Ozmosis Research Inc. once the study has recruited the required number of subjects per cohort. A Safety Cohort Review Meeting will take place between the Principal Investigator, the sponsor, the Data Safety Monitoring Committee (DSMC) and Ozmosis Research to review the patient safety data for each dose level. After a decision is made by the sponsor, in collaboration with Ozmosis Research, based on the data submitted for a cohort regarding whether the study will be re-opened, a cohort will be expanded, or if there will be dose modification/escalation, etc., all applicable parties will be notified by Ozmosis Research. This process for toxicity review and cohort view will continue to be repeated and followed until the MTD is reached.

3.6 Rationale for the Study Design and Doses

Recurrent ovarian cancer is a universally fatal disease. See Background for details on the role of the immune system in ovarian cancer survival, for preliminary data on the results of checkpoint inhibitor trials in recurrent ovarian cancer, and the rationale for combining focal radiation therapy with checkpoint (PD-L1) inhibition.

The 3+3+3 phase 1 design will be used to assess safety and tolerability as defined by DLTs and to identify the MTD of both durvalumab and focal irradiation when given as combination therapy to patients with platinum-resistant ovarian cancer.

3.6.1 Durvalumab

The starting dose of durvalumab chosen for this trial is 1500 mg given intravenously (IV) every 28 day schedule (one cycle of treatment = 28 days). This is a standard fixed dose of durvalumab being studied in future trials of durvalumab, including other trials exploring the combination of durvalumab with focal radiotherapy (e.g.:NCT02639065).

3.6.2 Radiation Fractions

Two radiation targets will be identified per patient. Target selection is described in section 6.2.1. Inverse-planned, CT-simulated IMRT/VMAT will be delivered to both lesions on days -1, 1, and, 28 of Cycle 1 and day 1 of Cycle 2. (see Study Calendar, Section 5). Where possible, radiation should precede administration of durvalumab on days when they are given together.

4. SUBJECT SELECTION CRITERIA

The patient population should be selected without bias.

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

4.1 Inclusion Criteria

For inclusion in the study subjects should fulfill the following criteria:

1. Provision of written informed consent prior to any study specific procedures

2. Female patients aged 19 years and older

3. Platinum-resistant (progression within 6 months of platinum based regimen) or platinum-refractory ovarian/fallopian tube/peritoneal origin.

    - High grade serous, endometrioid, clear cell, mucinous, malignant mixed Mullerian tumor, and low grade serous histotypes are permitted. Non-epithelial tumours will not be permitted.

4. ECOG performance status 0-1.

5. No more than 2 lines of therapy in the platinum-resistant setting.

6. No bowel obstructions within the preceding 6 months.

7. Last radiation therapy treatment ≥3 months prior to enrollment.

8. Expected survival >3 months.

9. All patients much have at least one site of measurable disease as defined by RECIST criteria (v.1.1) [79].

10. All patients must have disease suitable for core biopsy and agree to study related biopsies. Disease suitable for biopsy can serve as radiation targets, but cannot be used for response assessment.

11. All patients must have at least 2 additional sites of disease that serve are suitable radiation targets (see section 6.2.11).

    - Lesions suitable for radiation targeting must meet all of the following criteria:

        - each target must be > 4 cc in volume by standard imaging techniques, such as CT scan, MRI, or radiograph

- for each lesion, partial treatment of a tumour mass is permitted, but the treatment volume cannot be less than the equivalent of a 2cm sphere (4cc) and the two targets cannot be part of the same contiguous mass
- must be outside of previously irradiated fields

12. Adequate organ and marrow function as defined below within 14 days of cycle 1 day 1 and prior to first dose of focal radiotherapy:

- Absolute neutrophil count >1.5 x 10^9/L (1500 per mm^3)
- Platelets >100 x 10^9/L (100,000 per mm^3)
- Haemoglobin ≥9.0 g/dL (5.59 mmol/L)
- Serum creatinine CL >40 mL/min by the Cockcroft-Gault formula [82]or by 24-hour urine collection for determination of creatinine clearance:

Females: Creatinine CL as calculated by Cockcroft-Gault Formula

$$GFR = \frac{1.04 \times (140 - \text{age in years}) \times \text{weight (kg)}}{\text{serum creatinine (micromol/L)}}$$

- Serum bilirubin ≤1.5 x upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinaemia that is predominantly unconjugated in the absence of evidence of haemolysis or hepatic pathology) who will be allowed in consultation with their physician.
- AST and ALT ≤2.5 x ULN.

4.2 Exclusion Criteria

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

1. Subjects who cannot meet all the radiation planning constraints will not be eligible for this trial.

2. Participation in another clinical study with an investigational agent during the last 4 weeks.

3. Concurrent enrolment in another clinical study, the only exception being observational (non-interventional) clinical studies.

4. History of pneumonitis requiring treatment with steroids, or has a history of interstitial lung disease.

5. Patients who have contraindications to receiving radiation therapy, such as: Rheumatoid Arthritis, connective tissue disorders, Lupus, scleroderma, CREST

syndrome, Crohn's syndrome, Ulcerative colitis, or other conditions identified by the Radiation Oncologist as unsuitable for radiation therapy.

6. Current or prior use of immunosupressive medication within 28 days before the first dose of the study drug, with the exception of intra-nasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses, which must not exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

7. Prior exposure to an anti-PD-1 or anti-PD-L1 antibody.(including durvalumab

8. History of acute diverticulitis, intra-abdominal abscess, or GI obstruction.

9. Previous severe hypersensitivity reaction to another monoclonal antibody (mAb).

10. Active autoimmune disease or a documented history of autoimmune disease or syndrome that requires systemic steroids or immunosuppressive agents. Patients with Vitiligo, Grave's disease or psoriasis not requiring systemic treatment (within the past 2 years) or those with resolved childhood asthma/atopy are <u>not</u> excluded.

11. Uncontrolled intercurrent illness including: infection requiring therapy, symptomatic congestive heart failure, uncontrolled hypertension (systolic blood pressure > 150 and diastolic blood pressure >100), unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses.

12. Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from using Fredericia'sCorrection.

13. Positive for Human Immunodeficiency Virus (HIV), Hepatitis B (Hepatitis B Surface Antigen [HBsAg] reactive), or Hepatitis C virus (Hepatitis C Virus Ribonucleic Acid [HCV RNA] (qualitative) is detected).

14. Previous clinical diagnosis of active tuberculosis.

15. Receipt of a live attenuated vaccination within 30 days of study entry or within 30 days or receiving the study drug.

16. History of another malignancy, with the exception of:

    - Malignancy treated with curative intent without evidence of recurrence for ≥ 5 years
    - Adequately treated non –melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease e.g. cervical carcinoma in situ

17. Female patients who are pregnant, breast-feeding or of childbearing potential who are not employing an effective method of birth control (see Table 3).

18. Any condition that, in the opinion of the investigator, would interfere with evaluation of the study drug or interpretation of patient safety or study.

4.3 Subject Enrollment and Registration

All patients will be screened by one of the principal investigators or sub-investigators prior to entry into this study and before any study-specific procedures are performed. Procedures that are part of standard of care may occur before informed consent is obtained. An explanation of the study and discussion of the expected side effects and full disclosure of the "informed consent" document will take place. Eligible and consented patients will be registered into the study.

At the time of screening, the Principal Investigator, or delegate, will refer the potential participant to a Radiation Oncologist for consultation and review to determine whether all radiation eligibility criteria have been met to initiate treatment planning for focal radiation therapy (see Section 6.2).

Registration will be done through Ozmosis Research Inc. Sites will assign each patient with a patient ID number which should be used on all documentation and correspondence.

Prior to registering a patient, each institution must have submitted all necessary regulatory documentation to Ozmosis Research Inc. Access to the eCRFs will only be granted once this has been received. All sites should call Ozmosis Research Inc. Clinical Trials Manager/Specialist (CTM/CTS) at the number listed on the front page to verify study availability.

No patient can receive protocol treatment until eligibility has been confirmed and the Patient Enrollment Fax has been submitted to Ozmosis Research Inc. All eligibility criteria must be met at the time of enrollment. There will be no exceptions. Any questions should be addressed with Ozmosis Research Inc. prior to enrollment.

The Patient Enrollment Fax must be completed, and signed by the investigator prior to enrollment of each patient. There are 2 sections to the Patient Enrollment Fax:

- SCREENING (top section): This section is completed by the site and should be faxed to Ozmosis at 416-598-4382 at the time of screening.

- ENROLLMENT (middle section): This section is completed by the site at the time of enrollment. The site will fax the signed and completed Patient Enrollment Fax to Ozmosis Research Inc. at 416-598-4382.

- CONFIRMATION OF REGISTRATION (bottom section): Ozmosis Research will assign the dose level and return a Confirmation of Registration to the site. Only after this has been received can the patient receive study drug.

Protocol treatment should begin within 5 working days of patient registration. All eligible patients enrolled into the study will be entered into a patient registration log at Ozmosis Research Inc.

The following information will be required at the time of registration:

- Trial code
- Treatment centre and investigator
- Patient's initials and/or date of birth
- Completed Patient Enrollment Checklist

Note: It is the responsibility of the investigator in charge to satisfy him or herself that the patient is indeed eligible before requesting registration.

5. STUDY CALENDAR

	Screening[1]	Cycle 1							Cycle 2[2]			Cycles 3+[3]			End of Treatment[4]	Follow-up
Day of Treatment	*Within 28 days of C1D1*	*D-2*	*D-1*	*D1*	*D5*	*D15*	*D27*	*D28*	*D1*	*D15*	*D 28*	*D1*	*D9*	*D28*	*±2 days after coming off treatment*	*±7 days window*
Inclusion/ Exclusion	X															
Demographics & Medical history	X															
Confirm diagnosis and disease status	X															
Concurrent medications	X	Continuous assessment														
Vital signs[a]	X			X		X			X	X		X			X	
Medical oncologist physical exam & ECOG[b]	X			X		X			X	X		X			X	
Hematology[c]	X			X		X			X	X		X			X	
Coagulation[d]	X			X		X			X	X		X			X	
Chemistry[e]	X			X		X			X	X		X			X	
Urinalysis[f]	X			X		X			X	X		X			X	
ECG[g]	X														X	
HIV test[h]	X															
Hepatitis B & C test[i]	X															
Serum pregnancy test[j]	X															
Durvalumab infusion[k]				X					X			X				
Radiation oncologist review[l]	X	X					X									X
CT Simulation[m]	X					X										
Focal radiation[n]			X	X				X	X							
Tumor measurement[o]	X										X			X	X	X
CA-125[p]	X										X				X	X
Core needle biopsy[q]	X				X								X			
Peripheral blood for immune markers[r]	X			X		X			X	X			X			X
Adverse event evaluation				Continuous assessment												
Survival status[s]																X

1: Screening: to be performed within 28 days of C1D1 (unless otherwise indicated) and prior to the first dose of focal radiotherapy. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

2: All pre-treatment assessments as described in a, b, c, d, e, and f can be performed within 48 hours of the durvalumab infusion on day 1 and 15 of each cycle.

3: Patients on treatment >12 months and deemed stable by the treating physician will be required to be seen within 48 hours of D1of each cycle.

4: End of Treatment visit: Patients who complete study treatment or are discontinued from the study prematurely will complete the End of Treatment visit ±2 days of coming off treatment.

a: Vitals signs: systolic blood pressure (BP) and diastolic BP, pulse, respiratory rate, body temperature and oxygen saturation. Vitals will be performed within 30 minutes prior to the start of durvalumab infusion and every 30±5 minutes during infusion and observation periods (1 hour for the first infusion and suggested 30 minutes after subsequent infusions provided no clinically significant infusion reactions are observed during or after the first cycle. Refer to section 6.1.6).

b: Physical exam: Complete physical exam including height, weight and ECOG performance status. Height will only be measured at screening.

c: Hematology: hemoglobin, hematocrit, RBC count, platelet count, absolute neutrophil count and differential WBC count

d: Coagulation: prothrombin time, activated partial thromboplastin time (APTT) and international normalised ratio (INR).

e: Chemistry: total protein, albumin, calcium, phosphorous, random plasma glucose, uric acid, creatinine, creatinine clearance, total bilirubin, ALP, sodium, potassium, magnesium, bicarbonate, chloride, AST, ALT and LDH.

f: Urinalysis: specific gravity, pH and excretion of proteins, glucose, ketones and blood in the urine.

g: 12-lead ECG: to be performed at screening and then as clinically indicated.

h: HIV test: to be performed if not done in the last 6 months.

i: Hepatitis B and C test: Hepatitis B (Hepatitis B Surface Antigen [HBsAg] reactive), or Hepatitis C virus (Hepatitis C Virus Ribonucleic Acid [HCV RNA] (qualitative) will be performed if not done in the last 6 months.

j: Serum pregnancy test (βHCG): for subjects of childbearing potential at screening and as clinically indicated.

k: Durvalumab infusion: Patients enrolled in the study will receive durvalumab according to their assigned dose level by iv infusion q28d ±3 days for a maximum of 12 months.

l: Review with Radiation Oncologist can be on day -2 or -1 as long as the review precedes radiation therapy

m: CT simulation will occur approximately within 14 days of day 1 of durvalumab Cycle 1 and Cycle 2..

n: Focal radiation: For the first 2 doses of durvalumab, focal irradiation to the selected target lesions will be initiated 24-36 hours prior to infusion of durvalumab (i.e. on days -1 & 1 of cycle 1 and day 28 of cycle 1 and day 1 of cycle 2) . Where possible, radiation should precede administration of durvalumab on days when they are given together.

o: Tumour measurement: CT/MRI scans of the chest and abdomen will be performed within 28 days of C1D1 and prior to the first dose of focal radiotherapy. Tumour measurement will be repeated every 8 weeks (± 7 days) for the first 12 months after cycle 1 day 1 and every 12 weeks (± 7 days) thereafter until confirmed PD, irrespective of the reason for stopping study drug and/or subsequent therapy.

p: CA-125: at screening and every 8 weeks (± 7 days) for the first 12 months after cycle 1 day 1 and every 12 weeks (± 7 days) thereafter until confirmed PD, irrespective of the reason for stopping study drug and/or subsequent therapy. For the purposes of assessing CA-125 response, there must be a baseline CA-125 drawn within 14 days of starting therapy.

q: Core needle : A core needle biopsy on one of the target tumor lesions that is accessible and can be accomplished within reasonable safety will be performed at baseline (prior to starting focal radiation), cycle 1 day 5 for immune marker analysis.. Cycle 3 day 9 biopsy will be optional.

r: Peripheral blood for immune marker analysis: A 30 mL peripheral blood sample will be obtained at baseline, cycle 1 day 15, cycle 2 day 1 and 15,and cycle 3 day 9.

s: All patients will be followed for late toxicity and survival status in clinic or by phone once every 3 months (± 7 days) for a maximum of 2 years.

6. STUDY TREATMENT

6.1 Durvalumab

6.1.1 Identity of investigational product(s)

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the investigator as a lyophilised powder for reconstitution. The saline solution for the matching placebo will be sourced locally.

Investigational product	Dosage form and strength	Manufacturer
durvalumab	Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration	AstraZeneca

6.1.2 Product preparation of durvalumab

The dose of investigational product for administration must be prepared by the investigator's or site's designated investigational product manager using aseptic technique. Commercially available water for injection and 0.9% (weight/volume) saline will be supplied by each site. Total in-use storage time from reconstitution of durvalumab to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36 to 46°F). If the in-use storage time exceeds these limits, a new dose must be prepared from new vials. durvalumab does not contain preservatives and any unused portion must be discarded.

6.1.3 Reconstitution of investigational product

Durvalumab requires reconstitution prior to use. The reconstitution should be performed with 4.0 mL sterile water for injection for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted durvalumab should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

6.1.4 Preparation of durvalumab doses for administration with an IV bag

Durvalumab 1500 mg will be administered using a 250 mL iv bag containing 0.9% (weight/volume) saline and delivered through an iv administration set with a 0.2-µm in-line filter. Dextrose may also be used as an alternate diluent.

No incompatibilities between durvalumab and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed.

6.1.5 Study drug administration

Following preparation of durvalumab (see Section 6.1.2 – 6.1.4) the entire contents of the iv bag should be administered as an iv infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter. The iv line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the iv bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed. Since the compatibility of durvalumab with other iv medications and solutions, other than normal saline (0.9% [weight/volume] sodium chloride for injection), is not known, the solution should not be infused through an iv line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of study drug administration must be recorded in the source documents.

6.1.6 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 calendar (section 5). Patients will be observed for 1 hour after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, a 30 minute observation period is suggested for subsequent infusions; however this is at the Investigator's discretion.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

6.1.7 Management of toxicity

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

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

2. If the symptoms promptly resolve with supportive care, consideration should be

given to continuing study drug along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted (see below).

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

In addition, there are certain circumstances in which study drug should be permanently discontinued (see Appendix 1).

6.1.8 Missed treatment doses

Following the first infusion of study drug, subsequent administration of study drug can be modified based on toxicities observed as described in Appendix 1. All toxicities will be graded according to CTCAE Version 4.03. Dose reductions are not permitted. Treatment delays > 2 weeks will be permitted only after review and approval by the medical monitor.

If during Cycles 1 or 2 a patient receives focal radiation without receiving the corresponding durvalumab dose for that dose level, there will be no make-up doses of the durvalumab. The patient may continue on therapy as scheduled assuming they remain eligible for treatment.

Dose modifications will not be required for AEs that are clearly not attributed to study drug (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dosing may continue despite concurrent vitiligo of any AE grade.

6.1.9 Immune-related adverse events

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and nivolumab including immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies [43,83]. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate aetiology (eg, infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendix 1.

6.1.10 Durvalumab 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 and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. AESIs for durvalumab include but are not limited to events with a potential inflammatory or

immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

- Infusion-related Reactions
- Diabetes Mellitus type I
- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism, and hypopituitarism)
- Dermatitis including rash and pruritis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Serious bleeding events

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

6.1.10.1 Pneumonitis

Pneumonitis has been reported in association with the use of anti-PD-L1/anti-PD-1 antibodies [41] [42]. It is also seen in 5% to 15% of patients irradiated for breast, lung, and mediastinal tumours. The risk of developing radiation pneumonitis is directly related to the volume of irradiated lung, the amount of radiation given, and the use of concurrent chemotherapy. Additional risk factors include co-morbid lung disease, poor baseline pulmonary function testing, and low performance status.

Symptoms of radiation pneumonitis, include low-grade fever, congestion, dry cough, pleuritic chest pain, and a sensation of chest fullness.

Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Prednisone, in dosages of at least 50 to 60 mg per day for 1 week followed by an extended taper, has been shown to abate symptoms and improve lung function. Bronchodilators and supplemental oxygen may be necessary.

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

6.1.10.2 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy [42]. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

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

6.1.10.3 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies [42]. Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

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

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

6.1.10.4 Gastrointestinal disorders

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

6.1.10.5 Endocrine disorders

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

6.1.10.6 Pancreatic disorders

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

6.1.10.7 Neurotoxicity

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

6.1.10.8 Nephritis

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

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

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

6.1. 10.9 Serious Bleeding Events

Serious bleeding events have been identified across 6 studies that enrolled patients with head and neck squamous cell carcinomas. Durvalumab alone was noted to cause serious bleeding events in 11 or 238 patients (4.6%) but when accounting for bleeding related to disease or alternative etiologist, the incidence of serious hemorrhage is 4/238 (1.7%). Durvalumab used with tremelimumab in 238 patients resulted in 14 cases of serious hemorrhage (6.9%), but the rate was lower (4/238, 2%) when alternative etiologies were accounted for.

Serious bleeding events much be managed in an emergent fashion, with appropriate medical evaluation, patient stabilization, reversal of underlying coagulopathies and emergent consultation with appropriate medical specialists to offer appropriate interventions to achieve control of bleeding (e.g. surgeons, interventional radiologists, intensive care physicians etc.).

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo

- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

6.1.11 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

The label will include the following information:

- Name of sponsor
- Study drug dosage form, route of administration, and quantity of dosage units
- Storage conditions
- Study code
- Enrolment code
- Directions for use
- The name of the Principal Investigator, where applicable (this may be pre-printed or
- added on the label when the study drug is dispensed)
- The period of use eg, expiry date.
- Product Lot Identifier
- Medication Identity Number
- For clinical study use only.

6.1.12 Storage

All study drugs should be kept in a secure place under appropriate storage conditions and may only be dispensed by a pharmacist or a qualified designee. The investigational product label on the kit specifies the appropriate storage. durvalumab must be stored at 2°C to 8°C.

6.2 Radiation Therapy

6.2.1 Radiation Target Selection

The function of radiotherapy in this study is to cause acute release of tumour antigen; response of the radiation target is not a primary endpoint of this study whereas safety and potential immunogenic tumour response are primary endpoints. With these goals in mind, two radiographically identifiable target lesions will be selected by Radiation Oncologists with expertise in treatment of gynecologic cancers. Target sites in the central nervous system and above the neck will not used. The two targets must not be part of the same contiguous tumour mass. Part or all of each target lesion may be treated but the minimal volume of each target that will be treated will be no smaller than the equivalent of a 2cm sphere (4cc); there is no upper limit on the size of each target as long as OAR constraints are met.

GTV will be defined as tumour visible on diagnostic imaging (CT, MRI or PET-scan).

Two Gross Target Volumes (GTV) will be defined, GTV1 and GTV2. CTV will not be used.

The part of each GTV which will be treated will be defined as GTV(t). The part of GTV1 and GTV2 which will be treated will be designated GTV(t)1 and GTV(t)2, respectively.

Planning Tumour Volume (PTV) margin of 1-5 mm will be added onto GTV (t
) depending on the site of disease. If a GTV(t) is >=5mm within the periphery of the tumor, then PTV margin may not be necessary to avoid geographical miss, in this case, PTV can be GTV(t). A 5mm margin will be generally used. The PTV's associated with GTV1 and GTV2 will be designated PTV1 and PTV2, respectively.

Internal GTV (IGTV) can be defined for mobile lesions per institutional standard.

6.2.2 Immobilization

Immobilization devices will be tumor (GTV(t)) site specific, institutional standard for SABR.

6.2.3 Pre-Treatment Simulation

Simulation will be per institutional standard for SABR and potentially include:

-4DCT for mobile lesions secondary to respiration.

-Planning CT slice thickness <=2.5mm.

-IV contrast or fiducial markers at the discretion of the treating Radiation Oncologist

6.2.4 Relevant Organs at Risk (OAR)

The relevant OAR's will depend on the location of the PTV's. and will be outlined from the planning CT-scan.

As a general rule, OAR's within 5cm of the PTV's should be contoured.

Please refer to Appendix 5 for a list of structures that should be considered for different sites and for OAR constraints.

6.2.5 Treatment Planning/Technique

Each doublet of radiation fractions will be separately planned from 2 separate CT-simulations done in the 2 weeks prior to each doublet of radiation fractions.

Radiotherapy will be inverse planned for IMRT/VMAT treatment per institutional standard for stereotactic body radiotherapy (SBRT).

For BCCA, dose calculation algorithm will be type II only (Eclipse AAA or Acuros) with inhomogeneity corrections on. Dose calculation grid in the treatment planning system (TPS) must be <=2.5.

6.2.6 PTV Prescription Isodose

Each patient will have 2 radiotherapy plans for the first and second doublet of radiotherapy fractions. PTV prescription will be per protocol. OAR constraints for each plan will be half of the 4-fraction OAR listed in Appendix 5 (see column for constraints to be used for each 2 fraction plan).

i. For each target PTV, 95% isodose to cover 95% of the PTV (V95%=95%)

ii. The RECIST defined response target lesion must receive < 25% of prescription dose (Dmax<25% prescription)

iii. PTV hotspot<150%

iv. All OAR's will have a higher planning priority than the PTV's.

-Planning constraints i – iv about must be met in order for patients to be eligible for treatment.

At the starting radiation dose, both PTV1 and PTV2 will receive 6Gy x 4 fractions (given as doublets) 24-36 hours prior to durvalumab (e.g., targets 1 and 2 will receive 6Gy of radiation on days -1 & 1 of Cycle 1, and on day 28 of cycle 1 and day 1 of Cycle 2). Where possible, radiation should precede administration of durvalumab on days when they are given together.

6.2.7 Treatment Verification and Imaging

Pre-treatment cone beam CT-scan (CBCT) prior to each fraction.

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6.2.8 Quality Assurance

GTV, IGTV, PTV and all relevant OAR contours will be reviewed and signed off by a second radiation oncologist prior to treatment.

Dose volume histogram parameters will be evaluated by the planning dosimetrist(s), physicist(s) and radiation oncologist(s).

6.3 Concomitant Medications

6.3.1 Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" in Section 6.3.3 below.

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

Female patient of child-bearing potential

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 3) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of durvalumab. Non-sterilised male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 90 days after receipt of the final dose of durvalumab. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 3).

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

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

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

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

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 3. 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 3 Highly Effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method

6.3.2 Blood donation

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

6.3.3 Prohibited concomitant medications

The following medications are not permitted during the study:

- Any investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (eg, by local surgery or radiotherapy).
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor alpha blockers. Use of immunosuppressive medications for the management of study drug-related AEs in patients with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.
- Live attenuated vaccines within 30 days of dosing. Inactivated viruses such as those in the influenza vaccine are permitted.

Other medication, which is considered necessary for the patient's safety and well-being, may be given at the discretion of the investigator and recorded in the appropriate sections of the eCRF.

6.4 Treatment Compliance

Treatment compliance will be assured by site reconciliation of medication dispensed.

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. The investigator or pharmacy must retain records of all study drugs administered. The study monitor will check these records to confirm the compliance with the protocol administration schedule.

6.4.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The study personnel will account for all study drugs dispensed to and returned from the patient.

Study site personnel will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery and destruction should be signed.

6.5 Premature Withdrawal/Discontinuation Criteria

Patients may withdraw at any time. Patients who discontinue from the study will be encouraged to return for the End of Treatment visit.

At the discretion of the Investigator, the investigator may remove a patient from the study (no more clinic visits except for End of Treatment and follow up if patient did not withdraw from further follow-up) for the following reasons:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
- Adverse Event, that in the opinion of the investigator or the sponsor, contraindicates further dosing
- Severe non-compliance to study protocol that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing study drug might constitute a safety risk
- Initiation of alternative anticancer therapy including another investigational agent

- Confirmed PD and investigator determination that the patient is no longer benefiting from treatment

- Pregnancy or intent to become pregnant.

Disease progression requires confirmation. In the absence of clinically significant deterioration the investigational site is advised to continue the patient on study drug until progression has been confirmed. If progression is not confirmed, then the patient should continue on study drug and on treatment assessments.

6.5.1 Subject replacement rule

Any patient who withdraws from the study within 28 days after cycle 1 day 1 for any reasons other than toxicity will be replaced.

7 STUDY PROCEDURES

7.1 Study Visits

7.1.1 Screening Visit

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Confirm diagnosis and disease status
- Review of prior/concomitant medications
- Vitals signs, weight and height
- Complete physical exam
- ECOG Performance Status
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Clinical laboratory tests for:
    - Hematology (see Table 4)
    - Coagulation
    - Chemistry (see Table 6)
    - Urinalysis
    - HIV
    - Hepatitis B & C
    - Serum pregnancy test (for women of childbearing potential only)
    - Imaging by CT/MRI
    - CA-125

- Core needle biopsy (refer to Section 8.3)
- Peripheral blood for immune markers (refer to Section 8.3)

7.1.2 Treatment Phase

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

7.1.3 End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. Patients who complete study treatment or are discontinued from the study prematurely will complete the End of Treatment visit ± 2 days of coming off treatment.

All patients will be followed for survival status in clinic or by phone once every 3 months (± 7 days) for a maximum of 2 years.

7.2 Description of study procedures

7.2.1 Physical examination, electrocardiogram, and vital signs

Physical examinations will be performed on study days noted in the Study Calendar
A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

An ECG is required during screening and then as clinically indicated during the study.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Study Calendar. Vitals will be performed within 30 minutes prior to the start of durvalumab infusion and every 30±5 minutes during infusion and observation periods (1 hour for the first infusion and suggested 30 minutes after subsequent infusions provided no clinically significant infusion reactions are observed during or after the first cycle. Refer to section 6.1.6)

7.2.2 Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Study Calendar):

- Coagulation parameters:
    - prothrombin time, activated partial thromboplastin time (APTT) and international normalised ratio (INR).
- Pregnancy test (female subjects of childbearing potential only):
    - Serum beta-human chorionic gonadotropin
- Other laboratory tests
    - Hepatitis B Surface Antigen [HBsAg] reactive or Hepatitis C Virus Ribonucleic Acid [HCV RNA] (qualitative)
    - HIV antibody
    - CA-125

Table 4. Hematology Laboratory Tests

Hemoglobin	Absolute neutrophil count
Hematocrit	Differential WBC count
RBC count	
Platelet count	

Table 5. Clinical chemistry Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	
	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin
Chloride	Total protein
Creatinine	Phosphorus
Creatinine clearance	Uric acid

Table 6. Urinalysis Tests

	pH
Blood	Protein
Glucose	Specific gravity
Ketones	

8 MEASUREMENT OF DRUG EFFECT

8.1 Safety Assessment

The adverse effects durvalumab and radiotherapy will be assessed for dose limiting toxicities, AEs, vital signs and by clinically significant changes in the laboratory evaluations and ECGs.

AEs will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.03 for adverse event reporting.

8.2 Efficacy Assessment

8.2.1 RECIST 1.1 Criteria

RECIST 1.1 criteria will be used to assess patient response to treatment by determining ORR and PFS. The RECIST 1.1 guidelines for measurable, non-measurable, target and non-target lesions and the objective tumour response criteria (CR, PR, NED, SD or PD) are presented in Appendix 2.

The methods of assessment of tumour burden used at baseline CT/MRI scans of the chest and abdomen (including liver and adrenal glands) must be used at each subsequent follow-up assessment. Additional anatomy should be imaged based on signs and symptoms of individual patients, including new lesions at follow-up.

Efficacy for all patients will be assessed by objective tumour assessments every 8 weeks for the first 12 months (relative to the date of cycle 1 day 1), then every 12 weeks thereafter until confirmed objective disease progression as defined by RECIST 1.1 (irrespective of the reason for stopping study drug and/or subsequent therapy). If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits.

Patients who achieve and maintain disease control (ie, CR, PR, NED, or SD) through to the end of the 12-month treatment period may restart treatment with study drug upon evidence of PD (according to RECIST 1.1), with or without confirmation, during follow-up. To restart study drug the patient must not have received an intervening systemic anti-cancer

therapy post-study drug discontinuation. Patients who restart study drug must have a baseline tumour assessment within 28 days of restarting study drug, all further scans should occur every 8 weeks (relative to the date of restarting study drug) (maximum of 12 months of further treatment).

For patients who discontinue study drug due to toxicity or a reason other than confirmed PD, objective tumour assessments should be continued every 8 weeks for 12 months (relative to the date of cycle 1 day 1) then every 12 weeks thereafter until confirmed objective disease progression.

Disease progression requires confirmation, the confirmatory scan should occur preferably at the next scheduled visit and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. A biopsy (optional biopsy at suspected progression) may assist with the differentiation of malignant tumour from post-radiation changes and may be of assistance at the investigator sit in confirming the malignant origin of regrowth within the radiation field. However, confirmatory radiological assessments should still be performed at the next schedule visit to confirm radiological progression.

Administration of study drug will continue between the initial assessment of progression and confirmation for progression. For all patients who are treated through progression and patients who achieve disease control and restart study drug upon evidence of PD (according to RECIST 1.1) during follow-up, the investigator should ensure patients do not have any significant, unacceptable or irreversible toxicities that indicate continuing treatment will not further benefit the patient, and that the patient still meets all of the inclusion criteria and none of the exclusion criteria for this study including re-consenting to continue or restart treatment. Patients with rapid tumour progression or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumour compression, spinal cord compression) will not be eligible to continue to receive study drug.

Progression, would be considered confirmed if the following RECIST 1.1 criteria are met:

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

  The assessment of progression of ≥20% increase in the sum diameters of target lesions compared with the nadir is at the first progression time point relative to the nadir (the smallest sum of diameters and this may be at baseline or subsequent follow-up visit). The confirmed scan confirms the persistence of the ≥20% increase relative to the nadir
- and/or significant progression (worsening) of non-target lesions or new lesions at the confirmatory PD time-point compared with the first time point where progression of non-target lesions or new lesions identified
- and/or additional new unequivocal lesions at the confirmatory PD time-point compared with the first time point new lesions identified.

In the absence of clinically significant deterioration the investigator should continue the patient on study drug until progression is confirmed.

If progression is not confirmed, then the patient should continue study drug and on treatment assessments.

If a patient discontinues study drug (and/or receives a subsequent cancer therapy) prior to progression then the patient should still continue to be followed until confirmed objective disease progression.

Categorizationz of objective tumour response assessment will be based on the RECIST 1.1 criteria of response: CR, PR, SD and PD. Patients with no evidence of disease at follow-up in the absence of new lesions will be assigned a response of NED. Target lesion progression will be calculated in comparison to when the tumour burden was at a minimum (ie, smallest sum of diameters previously recorded on study). In the absence of progression, tumour response (CR, PR) and SD will be calculated in comparison to the baseline tumour measurements obtained before starting study drug.

If the investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion or the appearance of a new lesion, it is advisable to continue study drug until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

To achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status.

Following confirmed progression, patients should continue to be followed up for survival every 3 months as outlined in the study calendar. An exception is patients with confirmed PD that continue to receive study drug at the discretion of the investigator (following consultation with the sponsor); these patients can receive study drug for a maximum of 12 months and will have scans every 8 weeks until study drug is stopped.

Study drug should be discontinued if there is confirmed progression of disease (PD) following a previous response (PR or CR) to study drug.

8.2.2 Gynecological Cancer Intergroup (GCIG) Guidelines for Response Using CA125

To be evaluable for response by CA125 requires two pretreatment samples at least twice the upper limit of normal and at least two additional samples after the start of treatment. A response to CA125 has occurred if after two elevated levels before therapy there is at least a 50% decrease that it is confirmed by a fourth sample [80]. The four samples must satisfy the following criteria:

1. The two pretreatment samples must both be at least twice the upper limit of normal and at least 1 day but not more than 3 months apart.
2. At least one of the two pretreatment samples should be within 2 weeks of starting treatment.
3. The third sample must be ≤ 50% of the second sample.
4. The confirmatory fourth sample must be ≥ 21 days after sample 3.

Patients are not evaluable by CA 125 if they have received mouse antibodies or if there has been medical or surgical interference with their peritoneum or pleura during the previous 28 days. Patients who have a fall of CA 125 to within the reference range but whose initial CA 125 was less than twice the upper limit of the reference range have not had a CA 125 response and cannot therefore be classified as a CA 125 complete responder.

CA125 response is defined as a 50% reduction in level from a pre-treatment sample. The response must be confirmed and maintained for at least 28 days. The date when CA125 level is first reduced is the date of the CA125 response. Appendix 4 summarized how CA125 response is incorporated into response assessment when measurable disease is also present.

8.2.3 Immune-related Response Criteria (irRC)

The assessment of the effect of cytotoxic agents has utilized the Response Evaluation Criteria in Solid Tumours (RECIST) and the World Health Organization (WHO); however, responses to immunotherapeutic agents may occur after disease progression as defined by assessment methods used for cytotoxic agents. A novel method of assessment has been specifically adapted for immunotherapeutic agents.

The immune-related response criteria (irRC) is intended to address the response patterns observed with immunotherapeutic agents [81]. The irRC is outlined further in Appendix 4. Response to therapy will be reported by irRC in addition to RECIST 1.1 criteria.

8.3 Exploratory Samples

All patients must be available and agree to have a core biopsy performed at pretreatment and on Cycle 1 day 5, on one of the target tumor lesions that is accessible and can be accomplished within reasonable safety. The lesion chosen for biopsy can also be chosen as a radiation target. A Cycle 3 day 9 biopsy is optional. Core biopsies will be processed for immune marker analysis.

A pre-treatment blood sample (100 mL = 10 heparin (green) + 1 SST (tiger) + 1 PST (green tiger)) will be obtained during the screening period. Subsequent post-treatment blood samples will be collected as follows: Day 5 (50 mL), Day 15 (30 mL), Cycle 2 Day 1 (30 mL), Cycle 2 Day 15 (50 mL), Cycle 3 Day 9 (50 mL) and follow-up at the end of the study (50 mL). All 50 mL collections will be done as: 5 heparin (green) + 1 SST (tiger) + 1 PST (green tiger).

Primary preference will be a biopsy from a radiation target lesion and secondary preference to another non-targeted metastatic lesion including ascites.

Ascites collection will be performed whenever possible.

Blood specimens will be processed into serum, plasma and peripheral blood mononuclear cells (PBMCs) and cryopreserved in vapour nitrogen until analysis. Whenever possible, tumor-infiltrating lymphocytes (TILs) or tumor-associated lymphocytes (TALs) will be harvested and expanded by standard protocols and cryopreserved for further assessment of tumor-reactive T cells.

Exploratory objectives	**Outcome measures**
1. To collect blood and tissue samples for analysis of immune biomarkers	Biomarker analysis to assess exploratory markers include but are not limited to: immune cell gene expression profiles in the peripheral blood and tumor, frequency of lymphocyte subsets as defined by cell surface markers, presence of functional markers of immune activity, tumor associated antibodies
2. To investigate the relationship between the presence or absence and spatial distribution of lymphocyte subsets within the tumor microenvironment and outcomes	Tumor and tumor associated expression of immune checkpoints and their spatial distribution within the tumor microenvironment relative to OS, PFS, ORR
3. To explore biomarkers of radiation and durvalumab and efficacy	Biomarkers in the serum and tumor before and after treatment will be assessed and correlated with response to treatment and/or tumor progression
4. To analyze biomarkers (e.g. immune, tumor) in different cellular compartments (e.g. tumor, immune, serum, blood) which may influence and/or prospectively identify patients likely to respond to treatment	Correlate expression of biomarkers with response to treatment and/or progression

For items 1-4 above, the following analysis will be performed on the respective tissues/blood specimens:

> Profiling of PBMCs: This will include standard flow cytometric analysis of lymphocyte subsets. We will use panel established by the Human Immunology Consortium Project (as well as additional in-house markers) to enumerate the frequency of lymphocytes before and at various time points post-treatment. In particular, we will assess for the frequency of PD-1 positive cells. We will also perform T cell receptor beta sequencing (TCR-seq) on tumor-reactive CD8+ and

CD4+ T cells. In some cases, we will conduct tetramer analysis to common ovarian cancer testis antigens (e.g. NY-ESO-1).

Serum: We will measure serum markers for immunogenic cell death following radiation. This will be assessed by a standard commercial ELISA kit. An assessment of new reactive antibodies before and after treatment will also be conducted against tumor cell lysates.

Plasma: Using protocols established, we will assess for circulating tumor DNA and RNA (whenever feasible based on quality of material) to identify mutations that are present in both the primary and secondary tumor. These tumor specific mutations will be tracked over the duration of the treatment to ascertain the frequency of mutation specific T cells in the periphery and TIL.

Tumor: We will assess the presence or absence of different lymphocyte subsets and their geographic localization within the tumor by multi-parametric immunostaining (up to 5 markers per section). This analysis will include expression of PD-L1 and PD-1. A complete RNA profile will be measured NanoString nCounter Pan Cancer Immune Profiling Panel which will include additional markers.

All of the studies above will be correlated with response to therapy to identify signatures of response.

9 SAFETY AND REPORTING REQUIREMENTS

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

A DSMC will be formed to review the all DLTs and SAEs and oversee the conduct of the trial. The Principal Investigator and 2 independent clinicians will constitute the DSMC. Each should have experience in clinical trials, specifically phase I trials. At least one member will have experience with immunotherapy and at least one member will have experience with radiation therapy.

9.1 Definition of Adverse Events

An **AE** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product during the course of a study and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Disease signs, symptoms, and/or laboratory abnormalities already existing prior to the use of the product are not considered AEs after administration of the study product unless they

reoccur after the subject has recovered from the pre-existing condition or they represent an exacerbation in intensity or frequency.

A laboratory test abnormality considered clinically relevant (e.g. causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations) or judged relevant by the Investigator should be reported as an adverse event.

9.2 Adverse Event Documentation

Adverse events will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE). This study will utilize the CTCAE Version 4.03 for adverse event reporting.

All AEs must be recorded on case report forms (CRFs). Documentation must be supported by an entry in the subject's file. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product as judged by the Investigator, action taken and outcome.

9.3 Definitions of Serious Adverse Event

A serious adverse event is an AE occurring at any dose 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/incapacity or substantial disruption of the ability to conduct normal life functions

Is a congenital abnormality or birth defect

Is an important medical event that may not be immediately life threatening or result in death or hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (example: intensive treatment in an emergency room or at home for bronchospasm, convulsions that do not result in hospitalization). Medical and scientific judgment should be exercised in deciding whether some events should be considered as serious because their quick reporting to the sponsor may be of interest for the overall conduct of the study.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission results in a hospital stay of less than 12 hours; or

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study or for prophylactic insertion of a gastric feeding tube); or

- The admission is not associated with an adverse event (eg, social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition.

Any death (regardless of cause except if death is due to PD) that occurs from the time of administration of the first dose of study therapy until 90 days after the final administration of the study drug, and any death occurring after this time that is judged at least possibly related to prior treatment with the study drug, will be promptly reported. Death due to PD does not need to be reported as a SAE.

Progressive disease will not be reportable as an SAE in this study. Progression of the underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer and this PD must be documented clearly in the patient's source documents. Clinical symptoms of progression may be reported as an adverse event if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study. If there is any uncertainty of an adverse event being due only to the study disease, it should be reported as an AE or SAE.

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

9.4 Reporting of Serious Adverse Events

All SAEs defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all serious adverse events must be reported by using the SAE form and must be submitted to Ozmosis Research Inc.

Serious Adverse Event Reporting Instructions

All serious adverse events must be reported as follows:

Within 24 hours: Report initial information (on trial specific SAE report form) by fax to:

Ozmosis Research Inc.
Phone: 416-673-6522
Fax: 416-598-4382

The initial information should always contain:

- Name of Reporter/Investigator,
- Subject Identification,
- Adverse Event Term,
- Study Drug Dose and Start/Stop Dates

On the next working day: Fax completed trial-specific Serious Adverse Event form

9.5 Reporting of Adverse Events of Special Interest

The following AESIs will be subject to the same reporting procedures as described in Section 8.4:

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

9.6 Procedure for Expedited Reporting

9.6.1 Responsibility for Reporting Serious Adverse Events to Health Canada

Ozmosis Research Inc. will provide expedited reports of SAEs to Health Canada according to applicable guidelines and regulations (including the 7-day notification for death and life-threatening events), i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment cannot be ruled out).

9.6.2 Responsibility for Reporting Serious Adverse Events to Drug AstraZeneca

Ozmosis Research Inc. will be responsible for submitting SAE (Initial and/or Follow-up reports) and AESIs to Astra Zeneca using the Ozmosis SAE form. The SAE form must be faxed to 1-800-267-5743 at the latest by 15 days after the investigator is made aware of the SAE. The foregoing is applicable to all SAEs, irrespective of causality.

9.6.3 Reporting Serious Adverse Events to Local Research Ethics Boards

Ozmosis Research Inc. will notify all Investigators of all Serious Adverse Events that are reportable to regulatory authorities in Canada from this trial or from other clinical trials involving durvalumab as reported to AstraZeneca. This includes all serious events that are unexpected and related to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Investigator Site File. Documentation that serious adverse events (SAEs) have been reported to REBs must be kept on file at Ozmosis Research Inc.

Documentation can be any of the following:

- letter from the REB acknowledging receipt
- stamp from the REB, signed and dated by REB chair, acknowledging receipt
- letter demonstrating the SAE was sent to the board

All expedited serious adverse events occurring within a centre should also be reported to local REBs.

9.6.4 Overdose

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

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to Ozmosis Research, who will in turn notify the sponsor and AstraZeneca (using the designated mailbox AEMailboxClinicalTrialTCS@astrazeneca.com) . If the overdose results in an AE, the AE must also be recorded as an AE (see Section 8.2). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 8.4). There is currently no specific treatment in the event of an overdose of durvalumab. The investigator will use clinical judgment to treat any overdose.

9.6.5 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 6.1.9.3) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to Ozmosis Research who will in turn notify the sponsor and AstraZeneca (using the designated mailbox AEMailboxClinicalTrialTCS@astrazeneca.com), unless a

definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

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

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

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

9.6.6 Pregnancy and 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 Ozmosis Research within **24 hours** of when he or she becomes aware of it. Ozmosis will in turn notify the sponsor and AstraZeneca (using the designated mailbox AEMailboxClinicalTrialTCS@astrazeneca.com).

9.6.7 Pregnancy and Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study

team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

9.7 Follow Up of Adverse and Serious Adverse Events

For the SAEs that have been deemed by the investigator as unrelated to protocol treatment, the SAE reporting period begins after patient signs informed consent and ends 90 days after discontinuation of the study drug. For the SAEs that have been deemed by the investigator as at least possibly related to protocol treatment, the SAE must be reported even if this occurs 30 days after discontinuation of the study drug.

SAEs that occur prior to dosing will not be reported in an expedited fashion to any health authority, and will be summarized and described in the clinical study report. The investigator shall provide follow-up information as and when available in a new follow-up SAE form. All SAEs must be followed until resolved, become chronic, or stable unless the subject is lost to follow up. Resolution status of such an event should be documented on the eCRF.

The eCRF should capture all AEs occurring from the first dose of focal radiation until 30 days after discontinuation of the study drug. In addition, any known untoward event of any severity that occurs subsequent to the AE reporting period that the Investigator assesses as at least possibly related to the study therapy (i.e., the relationship cannot be ruled out) should also be reported as an AE.

9.8 Relationship

For all AEs, relationship to study drug will be reported on the appropriate AE eCRF page. The PI must judge whether the study drug caused or contributed to the AE in which case it is considered to be an ADR, and report it as either:

Related (definitely, probably or possibly): there is a reasonable possibility that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for the determination of relatedness:

- There is a plausible time sequence between onset of the AE and study drug administration;
- There is a plausible biological mechanism through which study drug may have caused or contributed to the AE;

Not related: It is highly unlikely or impossible that the study drug caused or contributed to the AE; this conclusion may be supported by the following observations, though these are not required for a determination of not related:

- another cause of the AE is evident and most plausible;
- the temporal sequence is inconsistent between the onset of the AE and study drug administration; a causal relationship is considered biologically implausible;

10 ETHICAL AND REGULATORY REQUIREMENTS

10.1 Informed Consent

Subject / Legally acceptable representative (LAR) (as applicable) consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements prior to any study-specific screening procedures. It will be the responsibility of the local participating investigator to obtain the necessary clearance, and to indicate in writing to Ozmosis Research Inc. that such clearance has been obtained, before the trial can commence at that centre. Sample English consent forms for the trial will be provided. A copy of the initial full board REB approval and approved consent form must be sent to Ozmosis Research Inc. The subject/LAR must sign consent prior to registration.

10.2 Ethics Board Approval

Each participating centre will have on file with Ozmosis Research Inc., a list indicating the composition of its REB consistent with Canadian (applicable) regulatory guidelines. This list will be updated as appropriate.

For Canadian sites, a Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation may be included in the signed local ethics approval document. This documentation must be received by Ozmosis Research Inc. before the centre can be locally activated.

Initial approval: All study sites are required to obtain full board local ethics approval of the protocol and consent form by the appropriate REB prior to commencement of the clinical trial at each site.

Continuing approval: Annual (or as required by the REB) re-approval may be required for as long as subjects are being followed on protocol. It will be investigator's responsibility to apply for and obtain the re-approval.

Amendment: All protocol amendments will be confirmed in writing and submitted, as appropriate, for review by the REB and health authorities. Amendments will be reviewed and approved by applicable regulatory authorities prior to central implementation of the amendment, and by REBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects or when the change(s) involves only logistical or administrative aspects of the trial.

REB Refusals: If an REB refuses to approve this protocol (or an amendment/revision to this protocol), Ozmosis Research Inc. must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to Health Canada.

Serious Adverse Events, Safety Updates and Investigator Brochure Updates: During the course of the study serious adverse events, safety updates or investigator brochure updates

may be sent to you for reporting to your REB. If/when this occurs, documentation of REB submission of this information must be forwarded to Ozmosis Research Inc.

11 EVALUATION AND CALCULATION OF VARIABLES

The primary objective of this trial is to assess the safety and tolerability of durvalumab combined with focal radiotherapy, and hence determine the MTD of this combination. Safety endpoints will include DLTs, AEs, SAEs and deaths.

Secondary endpoints will include clinical measures of treatment outcome: ORR (as measured by RECIST v 1.1, GCIG CA125 response, and immune related response criteria), PFS and OS.

11.1 Calculation or derivation of safety variable(s)

11.1.1 Exposure to investigational product

The total time on study treatment, as well as total exposure to study treatment and amount delivered relative to intended amount will be summarized for the radiation and the durvalumab components.

11.1.2 Adverse events, laboratory changes, vital signs

Safety profiles will be assessed in terms of AEs and laboratory data, vital signs, and ECG data that will be collected for all patients. Treatment-emergent AEs are defined as any AE which initiates on or after the first day of study drug up through 30 days after study drug discontinuation.

11.1.3 Other significant adverse events (OAE)

The DSMC and Ozmosis Inc. will routinely review the list of AEs that were not reported as SAEs or as AEs leading to discontinuation of treatment. Based on judgment, AEs of particular clinical importance may, after consultation with the DSMC, be considered an other adverse event (OAE) and reported as such in the study report. A similar review of laboratory, ECG and vital sign data will be performed for identification of OAEs. Examples of these are marked haematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2 Calculation or derivation of efficacy variable(s)

ORR will be determined using the evaluable patient population. ORR is defined by the percentage of patients who have at least one assessment demonstrating CR or PR prior to evidence of disease progression. The best overall response designation (per RECIST V 1.1) recorded between the date of the start of trial therapy (day -1, the first day of radiation

therapy) and the date of objectively documented disease progression, or study cessation, whichever occurs first. Each patient will be assigned a RECIST response of CR, PR, SD, or PD depending on the status of their disease compared to baseline and previous assessments. The ORR will be the proportion of patients achieving CR or PR as the best response to therapy. Radiation target lesions will not be suitable for assessing RECIST response, and will not be eligible to be used as baseline target lesions for RECIST based assessment of response. GCIC CA125 response will be determined and Immune-Mediated RECIST response criteria will also be reported.

PFS, for the evaluable study population, will be determined from the start of trial treatment (day -1, as the first day of radiation therapy) to the date of RECIST 1.1 defined progression or death (by any cause in the absence of progression). Those who are alive without disease progression follow up will be censored at the date of the last disease assessment without progression. DoR, for the evaluable study population, will be calculated, using the time from documented disease response to disease progression, and will be reported for the entire study population. OS will be calculated from the date of the start of trial therapy (day -1, as the first day of radiation therapy) to the date of death from any cause. Patients lost to follow up, or who do not have documentation of death at the time of the final analysis will be censored at the date of last assessment.

12 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1 Description of analysis sets

12.1.1 Evaluable for Adverse Events

For the primary objectives of this study (i.e. safety and MTD), the evaluable population will consist of patients who completed Cycle 1 of planned therapy, unless a DLT was encountered. Patients who did not complete Cycle 1 and did not experience a DLT will be replaced.

All patients registered to the study who receive at least one dose of durvalumab will be assessed of safety and toxicity, but may not necessarily be included in the evaluable population for the primary endpoints (see definition above). For example, if a patient received one dose of durvalumab, and then declined further treatment, or had rapid disease progression, then they would be assessed for treatment toxicity at the time of the end treatment visit. If DLTs were not encountered the patient would be replaced in the study. Subjects who receive radiation without receiving durvalumab will not be included in the safety analysis. Such patients will receive no more than 8Gy to a single disease target. At this radiation dose level, toxicity is not expected from radiation alone.

12.1.2 Evaluable for Response

The efficacy analysis set will include all evaluable patients registered to the study. The evaluable population will consist of patients completing planned Cycle 1 of therapy, unless a DLT was encountered. Patients who did not complete Cycle 1 and came off treatment due to disease progression will not be included in the efficacy analysis.

12.2 Methods of statistical analyses

All safety analyses will be performed on the safety population. The incidence of events that are new or worsening from the time of the first dose of treatment with durvalumab will be summarized by dose level, organ system, severity and relationship to the study treatment and reported by CTCAE grade. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by primary system/organ and type of adverse event. The analysis of secondary endpoints will be descriptive. Time-to-event endpoints (i.e., PFS, OS) will be summarized for the aggregated sample

The final analysis for the primary objectives will occur after the last patient to enroll in the study has completed Cycle 1 of therapy. The final analysis for secondary endpoints will occur when data are mature or within 6 months of study completion.The study size will be determined by dose escalation following a 3+3+3 design. The minimum number of participants in the trial will be 3. This would occur if the first 3 patients enrolled in dose level 1 experienced DLTs. The study would then stop accrual. The maximum possible study size would be 22. This would occur if at each dose level, the cohorts had to be fully expanded (n=9) and 2 patients at each dose level had to be replaced.

13 DOCUMENTATION, RECORD ACCESS AND MAINTENANCE OF STUDY RECORDS

13.1 Documentation of Subject's Participation

A statement acknowledging the participation of a subject in this clinical trial must be documented in the subject's medical records along with the signed ICF.

13.2 Regulatory Requirements

The following documents are required:

For participating Canadian centres:

- All Investigators must complete and sign the Health Canada Qualified Investigator Undertaking form. The completed forms must be returned to the Ozmosis Research Inc. prior to any drug shipment.
- All applicable regulatory documents as listed in the Protocol Activation Checklist provided by Ozmosis Research Inc. to the sites.
- Ozmosis Research Inc. will submit via fax to Health Canada a completed Health Canada Clinical Trial Site Information Form after local activation of each participating Canadian centre.

13.3 Subject Confidentiality and Access to Source Data/Documents

Any research information obtained about the subject in this study will be kept confidential. A subject will not be identified by name, only by his/her study number. The subject's name or any identifying information will not appear in any reports published as a result of this study.

However, information obtained from individual subject's participation in the study may be disclosed with his/her consent to the health care providers for the purpose of obtaining appropriate medical care. The subject's medical records/charts, tests will be made available to Ozmosis Research Inc., BCCA, its potential eventual partners, the Canadian HPFB/TPD, the REB and any other regulatory authorities. This is for the purpose of verifying information obtained for this study. Confidentiality will be maintained throughout the study within the limits of the law.

A subject's name will not be given to anyone except the researchers conducting the study, who have pledged an oath of confidentiality. All identifying information will be kept behind locked doors, under the supervision of the study Principal Investigator and will not be transferred outside of the hospital.

A subject may take away his/her permission to collect, use and share information about him/her at any time. If this situation occurs, the subject will not be able to remain in the study. No new information that identifies the subject will be gathered after that date. However, the information about the subject that has already been gathered and transferred may still be used

and given to others as described above in order to preserve the scientific integrity and quality of the study.

13.4 Confidentiality of the Study

Data generated as a result of this study are to be available for inspection on request by local health authority auditors, the Sponsor's Study Monitors and other personnel (as appropriate) and by the IRB/EC. The Investigator shall permit sponsor, authorized agents of the sponsor, CRO and regulatory agency employees to enter and inspect any site where the drug or records pertaining to the drug are held, and to inspect all source documents. The protocol and other study documents contain confidential information and should not be shared or distributed without the prior written permission of sponsor.

13.5 Registration of Clinical Trial

Prior to the first subject being registered/enrolled into this study, the Sponsor will be responsible for ensuring that the clinical trial is registered appropriately to remain eligible for publication in any major peer-reviewed journal, adhering to the guidelines put forth by the International Committee of Medical Journal Editors (ICMJE).

13.6 Data Reporting and Data Management

The data will be collected on electronic CRFs during this study. All data for this trial will be analyzed using the Medidata Rave database. Data management will be conducted by Ozmosis Research Inc.

13.7 Case Report Forms

Electronic CRFs will be used for this study. This also applies to records for those patients who fail to complete the study. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to document the outcome clearly.

The completed eCRF should be reviewed, signed, and dated by the Investigator in a timely fashion.

Please see the study-specific eCRF completion guidelines which have been provided to your site by Ozmosis Research Inc. The timelines and details for submission of eCRFs are included in these guidelines.

13.8 Maintenance of Study Records

To enable evaluations and/or audits from Regulatory Authorities, Ozmosis Research Inc. or the Sponsor, the Investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of

treatment disposition. The Investigator should retain these records for 25 years after study close-out as required by Canadian regulations or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, then the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to the Sponsor. The investigator must obtain the Sponsor's written permission before disposing of any records.

14 QUALITY ASSURANCE AND QUALITY CONTROL

As per the Guidelines of Good Clinical Practice (CPMP/ICH/135/95), the sponsor will be responsible for implementing and maintaining quality assurance and quality control systems.
On Site Monitoring / Auditing

Ozmosis Research Inc. will organize on-site monitoring of this study to be conducted twice a year at each site depending on accrual.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Products and Food Branch Inspectorate. Other audits may be conducted by the study sponsor, Ozmosis Research Inc., and/or the company supplying the drug for the study.

15 ADMINISTRATIVE PROCEDURES

15.1 Amendments to the Protocol

Modifications of the signed protocol are only possible by approved protocol amendments authorized by the Sponsor. All protocol amendments will be approved by the REB prior to implementation. The Investigator must not implement any deviation from, or change to the protocol, except where it is necessary to eliminate an immediate hazard to trial subject or when the change(s) involves only logistical or administrative aspects of the trial.

15.2 Protocol Deviations and Violations

All violations or deviations are to be reported to the site's REB (as per REB guidelines). All REB correspondence is to be forwarded to Ozmosis Research. The site must notify Ozmosis Research and/or sponsor immediately of any protocol violations.

15.3 Premature Discontinuation of the Study

The Sponsor reserves the right to discontinue the trial for any reason but intends only to exercise this right for valid scientific or administrative reasons. After such a decision, the Investigators must contact all participating patients immediately after notification. Standard therapy and follow-up for subjects will be assured and, where required by the applicable regulatory requirement(s), the relevant regulatory authority(ies) will be informed.

The REB will be informed promptly and provided with a detailed written explanation for the termination or suspension.

As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

16 LEGAL ASPECTS

16.1 Publication Policies and Disclosure of Data

For publications, the first author will be the Principal Investigator of the study. Additional authors will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the Principal Investigator.

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18 LIST OF APPENDICIES

Appendix 1 Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions

Appendix 2 RECIST 1.1 Guidelines

Appendix 3 GCIC Response Criteria

Appendix 4 Immune-Related Response Criteria

Appendix 5 Radiation Treatment Planning Constraints

APPENDIX 1: DOSING MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE- MEDIATED, INFUSION RELATED, AND NON IMMUNE-MEDIATED REACTION

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) 19 August 2016 Version

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

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	**Any Grade**	General Guidance	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider pulmonary and infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			(refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain pulmonary and infectious disease consult. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Enterocolitis	**Any Grade**	General Guidance	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc.

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × ULN)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		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 (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × 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,

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines].

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Consult endocrinologist. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than	**For Grade 2 (including those with**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		hypothyroidism, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**symptomatic endocrinopathy):** – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Initiate hormone replacement as needed for management. – Evaluate endocrine function, and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.	**For Grade 3 or 4:** – Consult endocrinologist. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** − Discuss with the study physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** − Discuss with the study physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present,

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Discuss with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* 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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

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

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

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

Infusion-related Reactions

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

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

Non-immune-mediated Reactions

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

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

In addition to the dose modifications shown in Appendix 1, it is recommended the management guidelines for irAEs are followed.

Management of immune-related adverse events

1. Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, infections, etc)

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

3. Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events

4. Systemic corticosteroids (eg, prednisone or intravenous equivalent) should be considered for persistent low-grade or severe (Grade ≥3) events

5. If symptoms recur or worsen during corticosteroid tapering, increase the corticosteroid dose until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate

6. More potent immunosuppressives – TNF antagonist class (eg, infliximab) or mycophenolate, etc) should be considered for events not responding to systemic steroids after discussion with study physician

7. Discontinuation of study drug is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumour response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc.)

APPENDIX 2: RECIST 1.1 GUIDELINES

Response Criteria

Evaluation of target lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Special notes on the assessment of target lesions

• **Lymph nodes** identified as target lesions should always have the actual short axis measurement recorded even if the nodes regress to below 10 mm on study. When lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met since a normal lymph node is defined as having a short axis of <10 mm.

• **Target lesions that become 'too small to measure'.** While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small. However, sometimes lesions or lymph nodes become so faint on a CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', in which case a default value of 5 mm should be assigned.

• **Lesions that split or coalesce on treatment.** When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR-Non-PD/ Stable Disease (SD)	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. **When patient has measurable disease**. To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. **When patient has only non-measurable disease.** There is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified, a useful test that can be applied is to consider if the increase in overall disease burden based on change in nonmeasurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large' or an increase in lymphangitic disease from localized to widespread.

New Lesions

The appearance of new malignant lesions denotes disease progression:

- The finding of a new lesion should be unequivocal (i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, especially when the patient's baseline lesions show partial or complete response).
- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

- A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and disease progression.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until the end of treatment taking into account any requirement for confirmation.

Evaluation of Best Overall Response – Patient with Target (+/- non-target) disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR-Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD/or not all evaluated	No	PR
SD	Non-PD/or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of Best Overall Response – Patient with Non-Target Disease

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR-Non-PD	No	Non-CR/Non-PD[1]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

[1] Non-CR / non-PD is preferred over 'Stable Disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials. To assign this category when no lesions can be measured is not advised.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response.

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point.

If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would most likely happen in the case of PD.

Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

However, in all other circumstances, (i.e., in randomized phase II or III trials or studies where stable disease or progression are the primary endpoints), confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

- The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

APPENDIX 3: GCIC RESPONSE CRITERIA

Definition of Response

A CA 125 response is defined as at least a 50% reduction in CA 125 levels from a pretreatment sample. The response must be confirmed and maintained for at least 28 days. Patients can be evaluated according to CA 125 only if they have a pretreatment sample that is at least twice the upper limit of the reference range and within 2 weeks before starting the treatment.

Evaluation of best overall response in patients with measurable disease and who are also evaluable by CA 125

Target Lesion*	**Non-targetNontarget†**	**New Lesion**	**CA-125**	**Overall Best Response**
CR	CR	No	Normal	CR
CR	Non-CR Non-PD	No	Not PD	PR
CR	CR	No	PR but not normal	PR
CR	NE	No	PR	PR
PR	Non-PD or NAE	No	Not PD	PR
NAE	Non-PD	No	PR	PR
PD or New > 28 days from CA 125 PR‡			PR	PR
SD§	Non-PD	No	PR	PR
SD§	Non-PD	No	Not PR or SD	SD
PD or New < 28 days from CA 125 PR‡			PR	PD
PD	Any	Yes or No	Any	PD
NE	PD	Yes or No	Any	PD
NE	Any	Yes	Any	PD
NE	Any	Yes or No	PD	PD

*Target lesions include up to 5 measurable lesions (2 per organ) as defined by RECIST 1.1.

†Nontarget lesions include ascites and peritoneal thickening which are not measurable according to RECIST 1.1.
‡Patients who have a CA 125 response that occurs more than 28 days from PD according to RECIST 1.1 are considered a PR, according to best response, but PD if the RECIST 1.1 PD is within 28 days of CA 125 response.
§ The protocol should specify the minimum time interval between 2 measurements for classification as stable disease.
NE, Not evaluated; NAE, not all evaluated.

APPENDIX 4: IMMUNE-RELATED RESPONSE CRITERIA

Antitumor response based on total measurable tumor burden:

For the irRC, only index and measurable new lesions are taken into account (in contrast to conventional WHO criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden).

At the baseline tumour assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated.

At each subsequent tumour assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 X 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total time-point tumour burden:

$$\text{Tumor Burden} = SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$$

Time-point response assessment using irRC:

Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening).

Overall response using the irRC:

The overall response according to the irRCis derived from time-point response assessments (based on tumor burden) as follows:

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented

• irPR, decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment at least 4 wk after first documentation

• irSD, not meeting criteria for irCR or irPR, in absence of irPD

• irPD, increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) confirmation by a repeat, consecutive assessment no less than 4 wk from the date first documented

APPENDIX 5: RADIATION TREATMENT PLANNING CONTRAINTS

Organ at Risk (OAR)	Dose Constraint for 4 Fractions	Dose Constraints for each 2 fraction plan
Spinal Cord PRV **(PRV=2mm on cord)** **(Canal for lung)** **(Cord for spine)**	Dmax ≤ 26Gy [1] V20.8Gy < 0.35cc [1] V13.6Gy < 1.2cc [1]	Dmax ≤ 13Gy [1] V10.4Gy < 0.35cc [1] V6.8Gy < 1.2cc [1]
Brainstem	Dmax<28Gy [*2] V21 Gy < 0.5cc [*2]	Dmax<14Gy [*2] V11.5 Gy < 0.5cc [*2]
Cauda equina	Dmax < 29 Gy [*2] V27 Gy < 5 cc [*2]	Dmax < 14.5 Gy [*2] V13.5 Gy < 5 cc [*2]
Sacral plexus	Dmax <29 Gy [*3] V 27Gy < 5 cc [*3]	Dmax <14.5 Gy [*3] V 13.5Gy < 5 cc [*3]
PBT and PT PRV (prox. Bronchial tree & prox. Trachea)	Dmax < 34.8 Gy [1] V15.6 Gy < 4cc [1]	Dmax < 17.4 Gy [1] V7.8 Gy < 4cc [1]
Bronchus - smaller airways	V38.7Gy < 0.1cc [4]	V19.3Gy < 0.1cc [4]
Lungs-GTV **(Lungs-GTV-PT-PBT)**	1500cc < 11.6Gy [1] 1000cc <12.4Gy [1] V20 Gy < 6%[6](10% [1,5]) Mean < 6Gy [5]	1500cc < 5.8Gy [1] 1000cc <6.2Gy [1] V10 Gy < 6%[6](10% [1,5]) Mean < 3Gy [5]
Contralateral lung	Mean < 3.6	Mean < 1.8 Gy [7]

	Gy [7]	
Chest wall / Ribs:	Dmax < 40Gy [1] V32Gy < 1cc [1] V30 Gy < 30cc [8]	Dmax < 20Gy [1] V16Gy < 1cc [1] V15 Gy < 30cc [8]
Brachial Plexus	Dmax < 23Gy[9] (27.2Gy[1]) V23.6 Gy < 3cc 1	Dmax < 11.5Gy[9] (13.6Gy[1]) V11.8 Gy < 3cc 1
Heart / Pericardium	Dmax < 34 Gy [1] V28 Gy < 15cc [1]	Dmax < 17 Gy [1] V14 Gy < 15cc [1]
Great Vessels	Dmax < 49 Gy [1] V43 Gy < 10cc [1]	Dmax < 24.5 Gy [1] V21.5 Gy < 10cc [1]
Skin	Dmax < 36 Gy [1] V33.2 Gy < 10cc [1]	Dmax < 18 Gy [1] V16.6 Gy < 10cc [1]
Esophagus	Dmax < 30 Gy [1] V18.8 Gy < 5cc [1]	Dmax <15 Gy [1] V9.4 Gy < 5cc [1]
Stomach	Dmax < 27.2 [1] V17.6 Gy < 10cc [1]	Dmax < 13.6 [1] V8.8 Gy < 10cc [1]
Duodenum	Dmax < 29 Gy [*3] V 17Gy < 5cc [*3] V 12 Gy < 10cc [*2]	Dmax < 14.5 Gy [*3] V 8.5Gy < 5cc [*3] V 6 Gy < 10cc [*2]
Jejunum/ileum	Dmax < 32 Gy [*3] V18Gy < 5 cc [*3]	Dmax < 16 Gy [*3] V9Gy < 5 cc [*3]
Small Bowel	Dmax $\leq$ 28 Gy [*10]	Dmax $\leq$ 14 Gy [*10]

	V28 Gy ≤ 1cc V19 Gy ≤ 3cc V13 Gy ≤ 1cc	V14 Gy ≤ 1cc V9.5 Gy ≤ 3cc V6.5 Gy ≤ 1cc
Large Bowel	Dmax ≤ 32 Gy [*10] V28 Gy ≤ 3cc V22.5 Gy ≤ 1cc	Dmax ≤ 16 Gy [*10] V14 Gy ≤ 3cc V11.2 Gy ≤ 1cc
Colon	Dmax < 34 Gy [*3] V23 Gy < 20 cc [*3]	Dmax < 17 Gy [*3] V11.5 Gy < 20 cc [*3]
Rectum	Dmax < 34 Gy [*3] V23 Gy < 20 cc [*3]	Dmax < 17 Gy [*3] V22.5 Gy < 20 cc [*3]
Kidneys (R&L)	200 cc < 16.5 Gy [*10]	200 cc < 8.2 Gy [*10]
Renal Hilum / Vascular Trunk	V21 Gy < 55% [*3]	V10.5 Gy < 55% [*3]
Renal Cortex (R & L)	200cc<16.2Gy [*3]	200cc<8.12Gy [*3]
Liver	700 cc < 19 Gy [*3]	700 cc < 9.5 Gy [*3]
Bladder Wall	Dmax < 34 Gy [*3] V 17 Gy < 15cc [*3]	Dmax < 17 Gy [*3] V 8.5 Gy < 15cc [*3]
Femoral Heads	V27 Gy < 10 cc [*3]	V13.5 Gy < 10 cc [*3]

PRV = Planning organ-at-risk volume
GTV = Gross tumour volume

[1] RTOG 0915, http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915

[2] Benedict SH et al., AAPM TG101, Med.Phys 37(9), 2010 (NB: max pt = 0.035cc)

[3] Timmerman RD., Seminars in Radiation Oncology 18:215-222, 2008

[4] Karlsson K et al., IJROBP, 87(3): 590-595, 2013

[5] Baker R, IJROBP, 85(1):190-195, 2013

[6] Matsuo Yet al., IJROBP, 83(4): e545-549, 2012.

[7] Bongers EM et al., Radiother Onc, 109: 95-99, 2013 (VU EMC TO 2013)

[8] Dunlap NE et al., IJROBP 76(3): 796-801, 2010

[9] Forquer JA et al., Radiother Onc, 93:408-413, 2009

[10] SABR-COMET Trial, Palma et al, v.1.8, Nov 2013 (NB:max pt = 0.035cc)

* EQD2 calculation (a/b=3Gy, except spinal cord a/b = 2Gy)