MSK PROTOCOL COVER SHEET

A Phase 2 Trial of Durvalumab [MEDI4736](anti-PD-L1 Antibody) with or without Tremelimumab (anti-CTLA-4 antibody) in Patients with Persistent or Recurrent Endometrial Carcinoma and Endometrial Carcinosarcoma

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Table of Contents

Date:

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

Appendix B Durvalumab DOSE Volume CALCULATIONS

Appendix C Tremelimumab DOSE VOLUME CALCULATIONS

Appendix D Biomarkers

1.1 PROTOCOL SUMMARY AND/OR SCHEMA

A Phase 2 Trial of Durvalumab [MEDI4736] (anti-PD-L1 Antibody) with or without Tremelimumab (anti-CTLA-4 antibody) in Patients with Persistent or Recurrent Endometrial Carcinoma and Endometrial Carcinosarcoma.

This is a prospective, randomized, phase 2 study which will assess the efficacy and safety of a single agent versus combination immune checkpoint inhibition for patients with persistent or recurrent endometrial carcinoma or endometrial carcinosarcoma. Eighty women with persistent or recurrent endometrial carcinoma or endometrial carcinosarcoma , who have had at least one prior platinum chemotherapy regimen and have progressed will be eligible for treatment if they have measurable disease and adequate organ function. Approximately 40 patients will be randomized to treatment on one of two arms: Durvalumab alone or Durvalumab in combination with Tremelimumab. Patients with clinically significant autoimmune disease will be excluded. Durvalumab would be administered intravenously (IV) every 4 weeks until unacceptable toxicity or progression of disease (whichever occurs first (and Tremelimumab would be administered intravenously (IV) every 4 weeks for up to 4 cycles or until unacceptable toxicity or progression of disease (whichever occurs first). Treatment cycles will be 28 days.

Primary Endpoints

- Determine the effectiveness of the each arm by measuring Overall Response Rate [ORR = Complete Response (CR) + Partial Response (PR)] by RECIST v 1.1
- Determine Progression Free Survival (PFS) rate in each arm at 24 weeks (+/- 1 week)

Secondary Endpoints.

- Overall response rate in each arm evaluated by Immune-related Response Criteria in Solid Tumors (irRECIST) criteria. irRECIST assessments will only be completed for patients continuing treatment beyond PD.
- Clinical benefit (CR + PR + Stable Disease [SD]) rate in each arm by 24 weeks +/- 7 days Duration of response in each arm
- Determine the rate of immune-related Adverse Events (irAE)
- Determine the rate of serious adverse events (SAE)
- Establish safety of each arm

Date:

Exploratory Endpoints

- Determine the ability of the laboratory parameters to predict clinical benefit:
  - Archival tumor tissue PD-L1 expression IHC
  - Archival tumor tissue immune-related gene expression profiles
  - Archival tumor tissue IHC
  - Peripheral blood immune phenotyping
  - Peripheral blood gene expression profiling
  - Peripheral blood T cell receptor repertoire
  - Peripheral blood serologic responses

Patient Population:

- Sample size: 80 patients; 40 patients in each arm
- Patients with recurrent or persistent endometrial carcinoma or carcinosarcoma, which is refractory to curative therapy or established treatments.
- Patients whose disease has progressed following completion of at least one prior platinum regimen with the following histologic epithelial cell types are eligible:
  - Endometrioid adenocarcinoma
  - Serous adenocarcinoma
  - Undifferentiated carcinoma
  - Mixed epithelial carcinoma
  - Adenocarcinoma not otherwise specified (N.O.S.)
  - Carcinosarcoma
- Adequate organ function and performance status ECOG 0-1
- At least 1 target lesion, which is measurable by RECIST and was not previously irradiated
- Expression of PD-L1 will be assessed from stored tissue samples, but not required for eligibility

Treatment Plan:

Arm 1: Patients will receive intravenous (IV) infusion of durvalumab 1500mg Fixed Dose every 4 weeks until patient develops a loss of clinical benefit or experiences unacceptable toxicities.

Arm 2: Patients will receive durvalumab + tremelimumab combination therapy. Patients will receive 1500 mg Fixed Dose durvalumab via IV infusion q4w for up to 4 cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 cycles, and then continue 1500 mg Fixed Dose durvalumab every 4 weeks until patient develops a loss of clinical benefit or experiences unacceptable toxicities.

Radiologic tumor assessment will be repeated every 8 weeks +/- 7 days for the first 48 weeks and then every 12 weeks +/- 7 days until PD. For patients who remain progression free 2 years post completion of protocol directed treatment, every 6 months +/- 1 month. Treatment will continue until progression, intolerance, withdrawal, study completion, or study

termination. It is estimated that full accrual will be achieved within 24 months; 3 years is estimated between time of opening and time of last treatment.

Patients will be randomized to either:

- Arm 1: durvalumab (anti-PD-L1 Antibody) alone, or
- Arm 2: durvalumab with tremelimumab (anti-CTLA-4 antibody)

Patients will be stratified by histology, and we will limit enrollment of stratum 1 to 10 patients per arm.

- Stratum 1: endometrial carcinosarcoma patients **OR** MSI-high endometrial carcinoma patients
- Stratum 2: other histologies

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Endpoints:

- Determine the effectiveness of the each arm by measuring Overall Response Rate [ORR = Complete Response (CR) + Partial Response (PR)] by RECIST v 1.1
- Determine Progression Free Survival (PFS) rate in each arm at 24 weeks (+/- 1 week)

- **Secondary Endpoints**

  - Overall response rate in each arm evaluated by Immune-related Response Criteria in Solid Tumors (irRECIST) criteria. irRECIST assessments will only be completed for patients continuing treatment beyond PD
  - Clinical benefit (CR + PR + Stable Disease [SD]) rate in each arm by 24 weeks +/- 7 days Duration of response in each arm
  - Determine the rate of immune-related Adverse Events (irAE)
  - Determine the rate of serious adverse events (SAE)
  - Establish safety of each arm

Exploratory Endpoints:

- Determine the ability of the laboratory parameters to predict clinical benefit:
  - Archival tumor tissue PD-L1 expression IHC
  - Archival tumor tissue immune-related gene expression profiles
  - Archival tumor tissue IHC
  - Peripheral blood immune phenotyping
  - Peripheral blood gene expression profiling
  - Peripheral blood T cell receptor repertoire

- Peripheral blood serologic responses

3.0 BACKGROUND AND RATIONALE

Introduction

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

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

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. T cells play a critical role in antitumor immunity and their infiltration and activity have been linked to improved prognosis in a number of cancers (Nakano et al, 2001; Burt et al, 2011). Immune evasion, primarily through suppression of T-cell activity, is now recognized as one of the hallmarks of cancer. Such evasion can occur via a range of mechanisms including production of suppressive cytokines suchas IL-10, secretion of chemokines and growth factors that recruit and sustain suppressive regulatory T cells (Tregs) and inflammatory macrophages, and expression of inhibitory surface molecules such as B7-H1. Tumor types characterized as being responsive to immunotherapy-based approaches include melanoma (Weber et al, 2012), renal cell carcinoma (RCC; McDermott, 2009), bladder cancer (Kresowik, 2009), and malignant mesothelioma (Bograd et al, 2011). Inhibition of CTLA-4 signaling is a validated approach to cancer therapy, as shown by the approval in 2011 of ipilimumab for the treatment of metastatic melanoma based on statistically significant and clinically meaningful improvement in OS (Hodi et al, 2010).

In general, tumor response rates to anti-CTLA-4 therapy are low (~10%). However, in patients who respond, the responses are generally durable, lasting several months even in patients with aggressive tumors such as refractory metastatic melanoma. Because these agents work

through activation of the immune system and not by directly targeting the tumor, responses can occur late and some patients may have perceived progression of their disease in advance of developing disease stabilization or a tumor response. In some cases, early growth of pre-existing lesions or the appearance of new lesions may have been due to immune-cell infiltration into the tumor and not due to proliferation and extension of neoplastic cells, per se (Wolchok et al, 2009). Overall, although the impact on conventionally-defined PFS can be small, durable response or stable disease seen in a proportion of patients can lead to significant prolongation of OS. The melanoma data with ipilimumab clearly demonstrate that a small proportion of patients with an objective response had significant prolongation of OS, supporting the development of this class of agents in other tumors. Although Phase 2 and Phase 3 studies of tremelimumab in metastatic melanoma did not meet the primary endpoints of response rate and OS, respectively, the data suggest activity of tremelimumab in melanoma (Kirkwood et al, 2010; Ribas et al, 2013). In a large Phase 3 randomized study comparing tremelimumab with dacarbazine (DTIC)/temozolomide in patients with advanced melanoma, the reported median OS in the final analysis was 12.58 months for tremelimumab versus 10.71 months for DTIC/temozolomide (HR = 1.1416, p = 0.1272; Ribas et al, 2013).

Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors. Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors. This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-H1 (programmed cell death ligand 1 [PD-L1]).

Immunotherapy with checkpoint inhibition is improving long-term disease control for patients with diverse malignancies (Topalian 2012; Hamid 2013; Wolchok 2013; Powles 2014), including patients with ovarian cancer (OC) (Hodi 2008; Brahmer 2012). The primary mediators of adaptive immune blockade, whose targeting in clinical trials have yielded results, include CTLA-4 (Hodi 2010; Ribas 2013), PD-1 (Topalian 2012; Hamid 2013; Robert 2014), and PD-L1 (Brahmer 2012). Responses in tumors such as melanoma, non-small cell lung cancer, and renal cell cancer have been impressive.

Durvalumab (MEDI4736): anti-PD-L1 Monoclonal Antibody.

The non-clinical and clinical experience is fully described in the current version of the durvalumab Investigator's Brochure (IB Version 9.0).

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

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

Durvalumab has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of the DCO dates (15Apr2015 to 18Sep2015, durvalumab IB version 9.0), a total of 1,910 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 subjects, 1,279 received durvalumab monotherapy, 454 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

As of 09Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (Cmax) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC0-14) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.

As of 09Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

Tremelimumab: Anti-CTLA-4 Monoclonal antibody

The non-clinical and clinical experience is fully described in the current version of the tremelimumab Investigator's Brochure (IB Version 6.0).

Date:

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

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures. In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. Refer to the tremelimumab IB, Edition 5.0, for more information. Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data (1 November 2015 for monotherapy studies and 15 April 2015 to 12 July 2015 for combination therapy studies), 34 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these, 13 studies have completed and 21 are ongoing. Eight tremelimumab monotherapy studies have been completed and 3 are ongoing. As of the data cutoff date of 1 November 2015, 973 patients received tremelimumab in completed monotherapy studies and the ongoing Study D4881C00024 and 569 patients have been treated in the ongoing blinded Phase IIb monotherapy Study D4880C00003 [DETERMINE]). In the 3rd ongoing monotherapy study (D4884C00001), no patients have been treated as of the data cutoff. In addition, approximately 59 patients have been treated with tremelimumab in monotherapy arms of combination studies. Five studies of tremelimumab in combination with other anticancer agents have been completed and 18 are ongoing. In total, 250 patients with a variety of tumor types have received tremelimumab in combination with other anticancer agents. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 11.0 for guidance on management of tremelimumab-related toxicities. Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22 days. Overall, a low incidence of ADAs (<6%) was observed for treatment with tremelimumab.

Durvalumab in combination with tremelimumab

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

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/PDx, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients

with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

Study D4190C00006: As of 20Feb2015 102 patients have been treated, and durvalumab PK (n = 55) and tremelimumab PK (n = 26) data were available from 10 cohorts (1a, 2a, 3a, 3b, 4, 4a, 5, 5a, 8, and 9) following durvalumab every 4 weeks (Q4W) or Q2W dosing in combination with tremelimumab Q4W regimens. An approximately dose-proportional increase in PK exposure (Cmax and area under the concentration-time curve from 0 to 28 days [AUC0-28]) of both durvalumab and tremelimumab was observed over the dose range of 3 to 15 mg/kg durvalumab Q4W and 1 to 10 mg/kg tremelimumab Q4W. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. It is to be noted that steady state PK parameters are based on limited numbers of subjects. The observed PK exposures of durvalumab and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

As of 20Feb2015, ADA data were available from 60 subjects for durvalumab and 53 subjects for tremelimumab in Study D4190C00006. Four of 60 subjects were ADA positive for anti-durvalumab antibodies post treatment. One of 53 subjects was ADA positive for anti-tremelimumab antibodies post treatment. There was no clear relationship between ADA and the dose of either durvalumab or tremelimumab, and no obvious association between ADA and safety or efficacy.

Durvalumab has also been combined with other anticancer agents, including gefitinib, dabrafenib, and trametinib. To date, no PK interaction has been observed between durvalumab and these agents.

As an antibody that blocks the interaction between PD-L1 and its receptors, durvalumab may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile. Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In addition, durvalumab monotherapy has shown durable responses in NSCLC in Study 1108 (see Section 1.4.1.1).

The rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity. In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma

induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable. Similar results have been

observed in an ongoing study of durvalumab + tremelimumab in NSCLC, with further updated details presented in this clinical study protocol.

Durvalumab + tremelimumab combination therapy dose rationale

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

In order to reduce the dosing frequency of durvalumab to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety, and efficacy profile, cohorts were narrowed to 15 and 20 mg/kg durvalumab q4w. PK simulations from the durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUCss; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w durvalumab. The observed durvalumab PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of durvalumab 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median Cmax at steady state (Cmax,ss) is expected to be higher with 20 mg/kg q4w (approximately 1.5 fold) and median trough concentration at steady state (Ctrough,ss) is expected to be higher with 10 mg/kg q2w (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

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

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of

tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity

when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

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

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

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

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

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

Long term data

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up.

Similar data have been presented for other anti-PD-1/PD-L1 targeting antibodies:

- Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients

(doses 1 and 10 mg/kg) at the time of data analysis. Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis.

- MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported

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

Immune checkpoint Inhibition in endometrial carcinomas

Endometrial carcinomas encompass several different histologies, which include endometrioid, serous, clear cell, and carcinosarcoma. Endometrial cancer is the second leading cause of death from gynecologic cancer with an estimated 8,590 women dying in the United Stated annually (Seigel et al, 2014)). Carboplatin and paclitaxel is the standard first line treatment regimen (Miller et al, 2012) for advanced recurrent or persistent disease, but unfortunately, there are no FDA approved treatments for patients who progress on first line therapy with the exception of Megace as a palliative treatment for advanced endometrial carcinomas. As a result, there is tremendous opportunity for the development of rationally therapeutic agents in the recurrent/persistent endometrial cancer space. Specifically, strategies reversing tumor promoting processes involving the interaction between tumor-infiltrating T-cells and the host microenvironment would be tremendously worthwhile, especially in genetically unstable tumors.

While patients with endometrial cancer have not been included in the initial studies using immune checkpoint inhibitors, there is a high rationale for such studies. Multiple studies have investigated the tumor microenvironment in different subtypes of endometrial cancer. Similarly to other tumor types, tumor-infiltrating CD8 T lymphocytes have been demonstrated to carry positive prognostic implications for patients with endometrial cancer (Kondratiev, 2004), while hypermutated genotypes are associated with increased numbers of tumor-infiltrating lymphocytes and PD-L1 expression (Howitt, 2015), as discussed below.

Early work in endometrial cancer has shown that the majority of tumor infiltrating lymphocytes (TILs) in endometrial carcinomas express the CD8+ suppressor/cytotoxic phenotype, and minor subsets express B-lymphocyte and macrophage markers. The earliest evidence demonstrating that increased numbers of CD8+ T lymphocytes (CTLs) were associated with survival came from immunohistochemical staining CD8(+) T cells in the following four regions: lymphocytes infiltrating the tumor epithelium at the invasive border, within the underlying tumor stroma, within the superficial tumor epithelium, and in the perivascular areas of the myometrium in endometrial carcinoma patients. Results showed that patients with >10 CD8(+) T lymphocytes/high-power field within the tumor epithelium at the invasive border displayed improved overall survival compared with patients with fewer intraepithelial CD8(+) T lymphocytes (87 and 50%, respectively; P = 0.027). Multivariate analysis revealed that stage, vascular invasion, grade, and the number of intraepithelial

CD8(+) T lymphocytes at the invasive border were the only independent predictors of survival (P < 0.0001, P = 0.001, P = 0.011, and P = 0.025, respectively). Granzyme B(+) cytoplasmatic granules were detected in a high proportion of CTLs, confirming their activated cytotoxic phenotype. (Kondratiev, 2004)

Immunohistochemistry on tissue microarrays containing tumor from 368 FIGO stage I-IV endometrial cancer patients revealed that high numbers of intra-tumoral CD8(+) T-lymphocytes, a high CD8(+)/FoxP3(+) ratio and the presence of CD45R0(+) T-lymphocytes were strongly associated with well-known favorable prognostic factors in endometrial cancer. Furthermore, high numbers of CD8(+) T-lymphocytes and a high CD8(+)/FoxP3(+) ratio were associated with a better disease free survival (DFS). In multivariate analysis, high numbers of CD8(+) T-lymphocytes had an independent prognostic impact for overall survival in the entire cohort (HR 0.48, 95% C.I. 0.26-0.89, p=0.019) and in type II endometrial cancer (HR 0.17, 95% C.I. 0.08-0.36, p<0.001). A high CD8(+)/FoxP3(+) ratio was independently associated with improved survival in type I endometrial cancer (HR 0.44, 95% C.I. 0.23-0.84, p=0.013). CD45R0(+) lymphocytes were an independent factor for improved OS (HR 0.42, 95% C.I. 0.19-0.93, p=0.033). (de Jong, 2009)

The Cancer Genome Atlas (TCGA) recently reported on the genomic, transcriptomic, and proteomic analysis of 373 endometrial carcinomas using massively parallel sequencing and array-based technologies, in combination with DNA methylation, reverse-phase protein array, and microsatellite instability analyses.(Kandoth, 2013) Based on the integration of the somatic gene mutations, microsatellite instability, and somatic copy-number alterations results, endometrial carcinomas were categorized into four genomic groups: (1) A group of 'ultramutated' tumors characterized by very high mutation rates, all harboring mutations in the exonuclease domain of the polymerase epsilon (POLE) gene; (2) A 'hypermutated' group of endometrial carcinomas characterized by microsatellite instability due to MLH1 promoter methylation, with high mutation rates and few copy-number alterations; (3) A 'copynumber low' group comprised of most of the microsatellite stable grade 1 and grade 2 endometrioid carcinomas with low mutation rates; and (4) A group of 'copy-number high' tumors with extensive copy number aberrations, low mutation rates, and recurrent TP53 mutations comprised of serous carcinomas and 25% of FIGO (International Federation of Gynecology and Obstetrics) grade 3 endometrioid adenocarcinomas. With regards to clinical outcome, ultramutated endometrial carcinomas with POLE exonuclease domain mutations had a favorable progression free survival as compared with the other three TCGA genomic groups. (Kandoth, 2013) It has been suggested that hypermutated tumors may harbor more tumor specific neoantigens and increased amounts of TILs. Therefore, an assessment of whether POLE and MSI ECs harbor more neoantigens and TILs than the comparatively hypomutated microsatellite-stable (MSS) ECs was performed. Prediction of neoantigen load was performed using sequencing data from the Cancer Genome Atlas data set. Evaluation of tumor-infiltrating lymphocytes (TILs) and PD-1 and PD-L1 expression was performed in 63 patients with EC referred to our institution. The predicted median (range) neoantigen load (predicted neoepitopes per sample) was proportional to the mutational load: highest in ultramutated polymerase e (POLE) tumors (8342 [628-20 440]), less in hypermutated MSI (541 [146-8063]; P < .001), and lowest in microsatellite-stable tumors (70.5 [7-1877]; P < .001). The POLE and MSI ECs exhibited higher numbers of CD3+ (44.5 vs 21.8; P = .001) and CD8+ (32.8 vs 13.5; P < .001) TILs compared with microsatellite-stable tumors.

Date:

PD-1 was overexpressed in TILs (81% vs 28%; P < .001) and peritumoral lymphocytes (90% vs 28%; P < .001) of POLE and MSI tumors. PD-L1 expression was infrequently noted in tumor cells but was common in intraepithelial immune cells and more frequent in POLE and MSI tumors (39% vs 13%; P = .02). (Howitt, 2015)

Taken together, we believe that this data provides abundant rationale to investigate the efficacy of the anti-PD-L1 agent durvalumab with or without the anti-CTLA4 agent tremelimumab in patients with advanced/recurrent endometrial malignancies. At this time, there is tremendous interest in evaluating immune check-point inhibitors in advanced endometrial cancers.

Rationale for combining Durvalumab and Tremelimumab in Endometrial Carcinomas

There is sound rationale for evaluating the combination of durvalumab and tremelimumab for the treatment of advanced endometrial carcinomas. Firstly, the mechanisms of activation of known sites for activity of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity. Secondly, preclinical data in mouse models of transplantable solid tumors, and clinical data emerging from studies in melanoma supports the superior anti-tumor activity of combination therapy over monotherapy, albeit at increased toxicity (Larkin, 2015 #9006). Based upon these observations, combination therapy may generate superior anti-tumor activity, which may translate into higher rates of response in tumors. However, as yet, it is not known whether combination therapy will result in superior activity in comparison to single agent durvalumab in endometrial cancer and whether the combination will be safe in this patient population.

For this study, we hypothesize that durvalumab plus tremelimumab will be well tolerated and will be associated with higher efficacy than the durvalumab alone in patients with advanced endometrial cancer and endometrial carcinosarcoma.

Efficacy Data

Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Data from Study 1108 were presented at the European Society for Medical Oncology 2014 Congress. Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and

neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an RR of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed an RR of 11% and a median OS of 12.6 months in this first line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant. Additionally, a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who had responded or remained stable failed to achieve statistical significance. The primary endpoint of PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

Durvalumab + tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.1.4 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma. Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab in Study

D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

Current experience with single-agent IMT studies suggests that clinical responses may be restricted to a subset of any given patient population and that it might be beneficial to enrich the patient population by selecting patients likely to respond to therapy. To date, no assay has been established or validated, and no single approach has proven accurate, for patient enrichment for IMTs. However, independent data from multiple sources using different assays and scoring methods suggests that PD-L1 expression on tumor cells and/or tumor infiltrating cells may be associated with greater clinical benefit.

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

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

Potential risks

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

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment related AEs were Grade 1 or Grade 2 in severity with ≥ Grade 3 events occurring in 65 subjects (9.4%). Treatment related ≥ Grade 3 events reported in 3 or more subjects (≥ 0.4%) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with

durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

Tremelimumab

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated gastrointestinal (GI) events including enterocolitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; hepatitis including autoimmune hepatitis and increased serum ALT and AST; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratory tract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the data cutoff date of 1 November 2015 (for all studies except D4190C00006 that has a cutoff date of 15Apr2015 and not including 497 patients who have been treated in the

ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events that resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product (IP), and deaths.

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

Study D4190C00006: The safety profile of durvalumab and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjects treated with durvalumab and tremelimumab combination therapy (not including subjects treated with blinded investigational product). As of 15Apr2015, 95 of 102 subjects (93.1%) reported at least 1 AE. All subjects in the tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; subjects in the durvalumab 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest AE rate (77.8%). Treatment-related AEs were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjects being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each), rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related ≥ Grade 3 AEs reported in ≥ 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment-related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase in 2 subjects; myasthenia gravis in 1 subject; and pericardial effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the MEDI4736 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported SAEs, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty-six subjects (35.3%) experienced treatment-related SAEs. Twenty-seven subjects (26.5%) permanently discontinued treatment due to AEs. Treatment-related AEs resulting in discontinuation in ≥ 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3 subjects), and increased AST (2 subjects). Additional safety results from this study are presented in the durvalumab and tremelimumab IBs.

In the literature, using the combination of the same class of drugs (e.g., anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of AEs assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were

noted in 72% of patients, with Grade 3 or 4 events assessed by the Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment-related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment-related in the combination therapy included hepatic events (in 15% of patients), GI events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

Fixed Dosing for durvalumab and tremelimumab

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

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

Similar findings have been reported by others [Ng et al 2006, Wang et al. 2009, Zhang et al, 2012,Narwal et al 2013]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [Zhang et al 2012].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Date:

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

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is an MSKCC investigator-initiated, single-center, randomized, open-label, phase 2 study to evaluate the activity of durvalumab alone (Arm 1) or durvalumab in combination with tremelimumab (Arm 2) in patients with recurrent or persistent endometrial carcinoma or endometrial carcinosarcoma. The safety and tolerability of these agents in this patient population will also be evaluated.

Patients will be randomized to Arm 1: durvalumab alone or Arm 2: durvalumab with tremelimumab. Randomization will be accomplished by the method of random permuted block, and patients will be stratified by histology (stratum 1: endometrial carcinosarcoma patients OR MSI-high endometrial carcinoma patients and stratum 2: other histologies). We will limit enrollment of stratum 1 to 10 patients per arm.

MSI-high patients will be identified based on immunohistochemistry or MSI testing of tumor by department of pathology or via known mutations found in mismatch repair genes via the Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) assay through MSKCC IRB# 12-245.

Each cycle will be 28 days in duration. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination.

Radiologic tumor assessment will be repeated every 8 weeks +/- 7 days for the first 48 weeks and then every 12 weeks +/- 7 days until PD. For patients who remain progression free 2 years post completion of protocol directed treatment, every 6 months +/- 1 month. Safety will be evaluated through the monitoring of all serious and non-serious AEs and irAE's, graded according to the current version of National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v. 4.03).

4.3 Intervention

Eligible patients will undergo screening and baseline procedures per the Study Schedule. Study inclusion and exclusion criteria will be applied per section 6.0. Enrolled patients will receive treatment on one of two treatment arms based on randomization:

Arm 1: Patients will receive intravenous (IV) infusion of durvalumab 1500mg Fixed Dose every 4 weeks until patient develops a loss of clinical benefit or experiences unacceptable toxicities.

Date:

Arm 2: Patients will receive durvalumab + tremelimumab combination therapy. Patients will receive 1500 mg Fixed Dose durvalumab via IV infusion q4w for up to 4 cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 cycles, and then continue 1500 mg Fixed Dose durvalumab every 4 weeks until patient develops a loss of clinical benefit or experiences unacceptable toxicities.

Dosing outside the window should be discussed with the Principal Investigator. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion (±5 minutes). A 1 hour observation period is required after the first infusion of single agent durvalumab and combination durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Treatment will continue until progression, intolerance, withdrawal, study completion, or study termination.

Radiologic tumor assessment will be repeated every 8 weeks +/- 7 days for the first 48 weeks and then every 12 weeks +/- 7 days until PD. For patients who remain progression free 2 years post completion of protocol directed treatment, every 6 months +/- 1 month. Patients who discontinue treatment for reasons other than progression may continue efficacy assessments until progression is demonstrated. Patients who demonstrate radiologic progression by RECIST criteria may be considered for continued therapy (but not primary efficacy analysis) if they are deemed to be clinically benefiting, according to predetermined permitted criteria (section 12.4). Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs and irAEs, graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events (CTC v.4.03).

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

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

5.1 Tremelimumab

Background:

Tremelimumab (formerly CP-675,206) is a human immunoglobulin (Ig)G2 monoclonal antibody (mAb) being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation.

Formulation:

Tremelimumab Drug Product is formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, 0.27 mM disodium edetate dihydrate (EDTA), pH 5.5.

Date:

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution for infusion after dilution. The solution contains 20 mg/mL of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA); it has a pH of 5.5. Tremelimumab must be used within the individually assigned expiry date on the label. The normal fill volume is 20 mL.

Storage:

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab is administered as an IV infusion after dilution in sterile, normal saline for injection. The product should be protected from light when not in use.

Refer to the Tremelimumab investigator brochure for detailed information about this agent.

5.2 Durvalumab (MEDI4736)

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

Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Durvalumab must be used within the individually assigned expiry date on the label.

The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL (500 mg/vial). The solution will be diluted with 0.9% (weight/volume) saline for IV infusion.

Unopened vials of liquid Durvalumab must be stored at 2°C to 8°C (36°F to 46°F). Durvalumab must be used within the individually assigned expiry date on the label.

In use storage and stability

Total in-use storage time from needle puncture of Durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. Durvalumab does not contain preservatives and any unused portion must be discarded.

Study drug preparation

Calculate the dose volume of Durvalumab and number of vials needed for the subject to achieve the accurate dose according to Appendix B.

Preparation of infusion bags

The preparation of infusion bags should be done under aseptic conditions by trained personnel; it should **not** be prepared on the ward.

An additional volume of 0.9% (weight/volume) saline equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab.

The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

Vials should be used for specific subjects and should not be shared between subjects.

Patient weight at baseline should be used for dosing calculations in patients ≤30 kg unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

Dose administration

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein.

Following preparation of Durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2-µm in-line filter. Less than 55 minutes is considered a deviation.

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.

The Durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.

Monitoring of dose administration

Subjects will be monitored during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessments (Section 10.0).

In the event of a Grade ≤ 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50%, or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent

medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade ≥ 3 or higher in severity, study drug will be discontinued.

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

Durvalumab + tremelimumab combination therapy

Patients in the durvalumab + tremelimumab combination therapy group will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w starting on Week 16. Dosing outside the window should be discussed with the Principal Investigator. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion (±5 minutes). A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

Study drug preparation of durvalumab and tremelimumab
Based on average body WT of 75 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

Preparation of durvalumab doses for administration with an IV bag
The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

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

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

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.1 mL of durvalumab (ie, 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Date:

For patients <30kg, Calculate the dose volume of durvalumab and tremelimumab and number of vials needed for the subject to achieve the accurate dose.

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

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

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

Durvalumab hold and infusion times

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

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

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

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

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

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Doses of 75 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from

0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter. Remove 3.8 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8 mL of tremelimumab (ie, 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/mL to 10 mg/mL (IV bag volumes 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

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

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

The IV line will be flushed with a volume of 0.9% (w/v) saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

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

Tremelimumab hold and infusion times

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

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

Monitoring of dose administration

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

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial

rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued.

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

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

1. Subjects must have recurrent or persistent endometrial carcinoma (including: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, dedifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.), mucinous adenocarcinoma, squamous cell carcinoma, and transitional cell carcinoma) or endometrial carcinosarcoma). Histologic documentation of diagnosis of carcinoma is required. MSI-high patients will be identified based on immunohistochemistry or MSI testing of archival tumor specimens by department of pathology or via known mutations found in mismatch repair genes via the Integrated Mutation Profiling of Actionable Cancer Targets (IMPACT) assay through MSKCC IRB# 12-245.

2. All patients must have measurable disease. Measurable disease is defined by RECIST (version 1.1). Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3. Patients must have at least one “target lesion” to be used to assess response on this protocol as defined by RECIST version 1.1 (Section 12.0). Tumors within a previously irradiated field will be designated as “non-target” lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

4. Age ≥ 18 years and life expectancy of ≥ 12 weeks.

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

6. Resolution of (non-laboratory) adverse effects of recent surgery, radiotherapy, or chemotherapy to Grade ≤1 prior to first study treatment (with the exception of alopecia or neuropathy).

7. Patients must have had one prior platinum-based chemotherapeutic regimen for management of endometrial carcinoma or carcinosarcoma. Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or

consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.

8. Patients are allowed to receive, but are not required to receive, three additional cytotoxic regimen for management of recurrent or persistent disease. Hormonal therapies will not count toward the prior regimen limit.

9. Adequate normal organ and marrow function defined by the following laboratory results obtained within 14 days prior to first treatment:

   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (> 1500 per mm^3)
   - Platelet ≥ 100 x 10^9/L (>100,000 per mm^3)
   - Hemoglobin ≥ 9.0 g/dL
   - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). (Unless Gilbert's Syndrome, for which Bilirubin ≤ 3 x institutional upper limit of normal (ULN) , without concurrent clinically significant liver disease)
   - AST (SGOT)/ALT (SGPT) ≤ 3 x institutional upper limit of normal (ULN) unless liver metastases are present, in which case it must be ≤ 5x ULN
   - Serum creatinine ≤ 1.5 x institutional upper limit of normal (ULN)

10. Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: ≥55 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

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

12. Patients must have been enrolled, or agree to consent to the companion genomic profiling study MSKCC IRB# 12-245. Results must be available before starting treatment on protocol.

13. Patients must have signed an approved informed consent and authorization permitting release of personal information.

6.3 Subject Exclusion Criteria

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

2. Participation in another clinical study with receipt of an investigational product during the last 4 weeks.

3. Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab or any anti-CTLA4, including tremelimumab.

4. History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of study drug and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease (eg, cervical cancer in situ)
- Adequately treated stage 1 breast cancer.

5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies) < 21 days prior to the first dose of study drug. Receipt of the last dose of hormonal therapy within < 7 days prior to the first dose of study drug.
6. Any prior radiation therapy must be discontinued at least four weeks prior to registration.
7. At least 4 weeks must have elapsed since the patient underwent any major surgery (e.g., major: laparotomy, laparoscopy) There is no delay in treatment for minor procedures (e.g., central venous access catheter placement).
8. Patients should not be candidates for further surgical resection or definitive tumor-directed XRT based upon prior therapies and/or extent of disease at recurrence.
9. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs)
10. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab or durvalumab and tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Patients who have received acute, low dose, systemic immunosuppressant medications (*e.g.*, dexamethasone for nausea or steroids as CT scan contrast premedication) may be enrolled.
11. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE > Grade 1
12. Active or prior documented autoimmune disease within the past 2 years
NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
13. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
14. History of primary immunodeficiency

Date:

15. History and/or confirmed pneumonitis or interstitial lung disease

16. History of allogeneic organ transplant

17. History of hypersensitivity to durvalumab or any excipient

18. History of hypersensitivity to tremelimumab

19. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent

20. Known history of previous clinical diagnosis of tuberculosis

21. History of leptomeningeal carcinomatosis

22. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab.

23. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results

24. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.

25. Subjects with uncontrolled seizures.

26. Patients who are pregnant or breastfeeding or patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period

27. History of small or large bowel obstruction within 3 months of registration, including subjects with palliative gastric drainage catheters. Subjects with palliative diverting ileostomy or colostomy are allowed if they have been symptom free for more than 3 months.

28. Ongoing bowel perforation or presence of bowel fistula or abscess within 3 months of registration.

29. Subjects with refractory ascites, defined as ascites needing drainage catheter or therapeutic paracentesis more often than every 4 weeks.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator or research team within the Gynecologic Medical Oncology Group at

Memorial Sloan Kettering Cancer Center (MSKCC). Patient recruitment will occur in the Gynecologic Medical Oncology clinics at MSKCC. The investigator will discuss the study with suitable participants, and should the patient consent to proceed with protocol therapy, will enroll their patients in the research study. Approximately 4 patients will accrue onto this study per month. All participants will be women.

8.1 PRETREATMENT EVALUATION

Within 28 days prior to treatment start:

- Written informed consent
- History and Physical examination
- Review of concomitant medications
- Vital signs (blood pressure, heart rate and temperature), weight and height
- ECOG Performance status
- Toxicity assessment
- 12-lead ECG (in triplicate)
- Radiographic tumor measurements (CT C/A/P, MRI)
- Confirm sufficient tissue is available (10-20 PPFE slides or tissue block).

Within 14 days prior to treatment start:

- Complete Blood Count (CBC) with differential and platelets
- Comprehensive profile (BUN, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)
- Thyroid function tests (TSH and fT4)
- Amylase
- Lipase
- Coagulation tests: prothrombin time, APTT and INR (PT/PTT)
- Magnesium
- Uric Acid
- CA125
- Urinalysis
- Pregnancy test (in women of child bearing potential)

ECGs are required during screening and on Cycle 1 Day 1. See section 10.
Vital signs will be evaluated according to the assessment schedules. See section 10.
Situations in which vital signs results should be reported as AEs are described in Section 11.0.

9.1 TREATMENT/INTERVENTION PLAN

All subjects will be randomized to one of two treatment arms in a 1:1 fashion.

Arm 1: Patients will receive intravenous (IV) infusion of durvalumab 1500mg Fixed Dose every 4 weeks until patient develops a loss of clinical benefit or experiences unacceptable toxicities.

Arm 2: Patients will receive durvalumab + tremelimumab combination therapy. Patients will receive 1500 mg Fixed Dose durvalumab via IV infusion q4w for up to 4 cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 cycles, and then continue 1500 mg Fixed Dose durvalumab every 4 weeks until patient develops a loss of clinical benefit or experiences unacceptable toxicities.

Date:

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

1. Patients will receive study treatment until disease progression, intolerable toxicity, elective withdrawal from the study, study completion, or study termination.

2. Radiologic tumor assessment will be repeated every 8 weeks +/- 7 days for the first 48 weeks and then every 12 weeks +/- 7 days until PD. For patients who remain progression free 2 years post completion of protocol directed treatment, every 6 months +/- 1 month.

3. Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs and irAEs, graded according to the current version of the National Cancer Institute Common Terminology Criteria for Adverse Events. Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments (Section 10.0).

4. Pre- and post-treatment blood and serum samples, as well as archival tumor tissue (when available) will be collected for biomarker analysis (as per Appendix E).

5. Assessments for subjects who have completed durvalumab and tremelimumab treatment and achieved disease control, or have discontinued durvalumab or tremelimumab due to toxicity in the absence of progressive disease are provided in Appendix A.

Assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to PD are presented in Appendix A.

Duration of treatment and criteria for retreatment with durvalumab and tremelimumab combination

On both study arms, the patients will continue to receive the study drugs as long as they continue to experience clinical benefit and have no unacceptable toxicities. For patients in the durvalumab + tremelimumab arm, patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab monotherapy portion of the combination regimen, according to RECIST 1.1, may receive re-treatment with another 4 cycles of the combination regimen (only once).

Before restarting their assigned re-treatment, the Investigator should ensure that the patient:

a. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient

b. Still fulfils the eligibility criteria for this study, including re-consenting to restart durvalumab and tremelimumab

Date:

c. Has not have received an intervening systemic anticancer therapy after their assigned treatment discontinuation.

d. Has had a baseline tumor assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial treatment.

During the retreatment period, patients receiving durvalumab + tremelimumab may resume durvalumab dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for 4 cycles each. Patients will then continue with durvalumab monotherapy at 1500 mg q4w, beginning at Week 16, 4 weeks after the last dose of combination regimen therapy.

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient.

Patients who AstraZeneca and/or the Investigator determine may not continue treatment will enter follow-up.

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

10.0 EVALUATION DURING TREATMENT/INTERVENTION

All assessments to be performed pre-infusion unless stated otherwise. A Cycle is 28 Days.

Treatment Arm 1: Durvalumab

Parameter	Screening		Cycle 1			Cycles 2-4		Cycles 5 onward		End of Treatment	Follow-up
Day	Within 28 days before[a]	Within 14 days before	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15		90 days post-dose
Consent	x										
Medical History	x		x		x	x	x	x	x	x	x
Concomitant Medications	x		x		x	x	x	x	x	x	x
Request Archival tumor tissue	x										
Physical Examination	x		x		x	x	x	x	x	x	x
ECOG	x		x			x		x		x	x
Weight	x		x			x		x		x	x
Vital Signs (BP, HR, and temperature) height [e]	x		x		x	x	x	x	x	x	x
Adverse Event Assessment	x		x		x	x	x	x	x	x	x
CBC		x	x			x		x			x
Comprehensive Profile		x	x		x	x	x	x	x		x

Date:

Parameter	Screening		Cycle 1			Cycles 2-4		Cycles 5 onward		End of Treatment	Follow-up
Day	Within 28 days before[a]	Within 14 days before	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15		90 days post-dose
TSH		X	X			X		X			X
Free T4[f]		X	X			X		X			X
PT/PTT		X	As clinicallyindicated								
Magnesium		X									
Amylase		X	X			X		X			X
Lipase		X	X			X		X			X
Uric Acid		X	X			X		X			X
CA-125		X				X		X		X	
Hepatitis B surface antigen	X										
Hepatitis B Core Ab (total)	X										
Hepatitis C antibody	X										
HIV antibody[g]	X										
Urinalysis		X				X		X			
Pregnancy Test[d]		X	As clinicallyindicated								
Research bloods[b]			Days 1,8,29, and 57								
12- Lead ECG (in triplicate)[c]	X		X	As clinicallyindicated							
Durvalumab			X			X		X			
Radiographic disease assessment[h]	X		Every 8 weeks +/- 7 days x 48 weeks, then every 12 weeks +/- 7 days (For patients who remain progression free 2 years post completion of protocol directed treatment, every 6 months +/- 1 month.)							X	

Treatment Arm 2: Durvalumab and Tremelimumab

Parameter	Screening		Cycle 1			Cycles 2-4		Cycles 5 onward		End of Treatment	Follow-up
Day	Within 28 days [a]	Within 14 days	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15		90 days post-dose
Consent	X										
Medical History	X		X		X	X	X	X	X	X	X
Concomitant Medications	X		X		X	X	X	X	X	X	X
Request Archival tumor tissue	X										
Physical Examination	X		X		X	X	X	X	X	X	X
ECOG	X		X			X		X		X	X
Weight	X		X			X		X		X	X

Date:

Parameter	Screening		Cycle 1			Cycles 2-4		Cycles 5 onward		End of Treatment	Follow-up
Day	Within 28 days [a]	Within 14 days	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1	Day 15		90 days post-dose
Vital Signs (BP, HR, and temperature) height [e]	x		x		x	x	x	x	x	x	x
Adverse Event Assessment	x		x		x	x	x	x	x	x	x
CBC		x	x			x		x			x
Comprehensive Profile		x	x		x	x	x	x	x		x
TSH		x	x			x		x			x
Free T4 [f]		x	x			x		x			x
PT/PTT [j]		x	As clinicallyindicated								
Magnesium		x									
Amylase		x	x			x		x			x
Lipase		x	x			x		x			x
Uric Acid		x	x			x		x			x
CA-125		x				x		x		x	
Hepatitis B surface antigen	x										
Hepatitis B Core Ab (total)	x										
Hepatitis C antibody	x										
HIV antibody [g]	x										
Urinalysis		x				x		x			
Pregnancy Test [d]		x	As clinicallyindicated								
Research bloods [b]			Days 1,8,29, and 57								
12- Lead ECG (in triplicate) [c]	x		x	As clinicallyindicated							
Durvalumab			x			x		x			
Tremelimumab			x			x					
Radiographic disease assessment[h]	x		Every 8 weeks +/- 7 days x 48 weeks, then every 12 weeks +/- 7 days (For patients who remain progression free 2 years post completion of protocol directed treatment, every 6 months +/- 1 month.)							x	

NOTE: 3 day window for all parameter's (except for ECG [see c] and Radiographic disease assessment [+/- 7days])

[a] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Cycle 1 Day 1. Results for cbc and liver enzymes (AST/ALT) must be available and reviewed before commencing an infusion.

[b] Research bloods will consist of 6 CPT tubes and will be drawn at 4 time points:

- Day 1 (Cycle 1, Day 1)
- Day 8 (Cycle 1, Day 8)
- Day 29 (Cycle 2, Day 1) – may be drawn up to 3 days prior to day 29

Date:

- Day 57 (Cycle 3, Day 1) – may be drawn up to 3 days prior to day 57

[c] ECGs will be obtained in triplicate (with 2-5 minute lag time between each). All 12-lead ECGs should be recorded while the subject is in the supine position. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. On Cycle 1, Day 1: ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion.

[d] Pre-menopausal female subjects of childbearing potential only

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

- At the beginning of the infusion (at -30 to 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- For the first infusion only, in the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes)
- If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).
  If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

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

[g] If already done at MSK prior to study entry, does not need to be repeated.

[h] irRECIST assessments will only be completed for patients continuing treatment beyond PD.

Post-treatment follow up.

All patients will need a study completion/early termination visit 28 +/- 3 days after they receive the last infusion of the study treatment. If the 28 day follow up visit coincides with the progression of disease (POD) visit, then assessments for both visits can be combined. The patients will continue to be followed for toxicity for 90 days after the last infusion of the drug.

11.1 TOXICITIES/SIDE EFFECTS

The dose delay and reduction instructions provided in this section are intended to serve as guidelines to allow ongoing treatment for patients experiencing clinical benefit without signs or symptoms of progression while ensuring patient safety. Patients may temporarily suspend dosing of study drug for up to 14 days if they experience toxicity that is considered related to study drug and requires that a dose be held. Patients who miss ≥ 28 consecutive days of scheduled study treatment because of drug-related AEs will be discontinued from the study. Exceptions may be made after discussion with and approval by the Principal Investigator.

Patients may suspend dosing of study drug for radiation therapy or surgery that is considered by the treating physicians to be of clinical benefit for the patient. After completion of the intervention, patients may restart the study drug as long as all criteria for dosing are met and there is no evidence of disease progression (unless approved by PI and sponsor as noted previously).

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab or tremelimumab along with appropriate continuing supportive care.
- In addition, there are certain circumstances in which durvalumab or tremelimumab should be permanently discontinued.

Following the first dose of durvalumab or tremelimumab, subsequent administration of durvalumab or tremelimumab can be modified based on toxicities observed (see Table 4). Dose reductions are not permitted

Based on the mechanism of action of durvalumab or tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, pancreatitis and nephritis . Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, pancreatitis and nephritis 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 Tables 5 and 6.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 11.4.3. All toxicities will be graded according to NCI CTCAE v4.03.

For patients who are being treated with both durvaluab and tremelimumab, both agents will be held/discontinued in the event of a toxicity as described in Tables 4-6.

TABLE 4:

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Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumabor Tremelimumab Monotherapy) 28 October 2021 Version

Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03 (unless indicated otherwise). In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune0mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **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 asymptomatic amylase or lipase levels of > 2.0xULN, 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.

Date:

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. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed 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. – Consider Pulmonary and Infectious Disease Consults.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity 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 (<10mg prednisone or equivalent).	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, Consider Pulmonary and Infectious Disease Consults. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started

Date:

			– If still no improvement within 2 to 3 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as tumor necrosis factor (TNF) inhibitors (eg, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with Clinical Study Lead.
	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 consults; consider discussing with Clinical Study Lead, as needed. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg IV, maybe repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	General Guidance	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Permanently discontinue study drug for any grade of intestinal perforation – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections),

			including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – 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 and other supportive care measures. – If symptoms persist consider checking lactoferrin; if positive treat as Grade 2 below. If negative and no infection, continue Grade 1 management
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: symptomatic; medical intervention indicated*) *"medical intervention" is not invasive	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10mg prednisone, or equivalent).	**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 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, gastrointestinal (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 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – If perforation is suspected, consult a surgeon experienced in abdominal

			surgery immediately without any delay. – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indicated, peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated) *This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective	**Grade 3** – For patients treatet with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone per day, or equivalent). – For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study investigator, in discussion with AstraZeneca Clinical Study Lead. – <u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy</u>, Permanently discontinue study drug for 1) Grade 3 diarrhea colitis or 2) Any grade large intestine perforation in any patient treated with immune checkpoint inhibitor (ICI).	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 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 2 days continue steroids and promptly add further immunosuppressant agents (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.

Date:

		Grade 4 – Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Elevations in AST, ALT or TB as Described Below**	General Guidance	**For Any Grade:** – Patients should be thoroughly evaluate to rule out alternative etiology (e.g, viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – For hepatitis B + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg). – For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb) +: Evaluate for both HBV and HCV as above. –
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevatedat baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation.**	–
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline	Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0xULN. • If toxicity worsens, then treat as described for	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved.

Date:

Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated>ULN at baseline	elevation in the row below. If toxicity improves to AST or ALT ≤5.0xULN, resume study drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximabshould NOT be used.**
Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated>ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN and after completion of steroid taper (<10mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (e.g., mycophenolate mofetil 0.5 – 1g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with study Clinical Lead if mycophenolate is not available. **Infliximabshould NOT be used.**
Isolated AST or ALT >20×ULN,	Permanently discontinue study drug/study regimen.	**Same as above**

Date:

	whether normal or elevatedat baseline		**(except recommendobtaining liver biopsy early)**
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – 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). – Consider using steroids 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	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent).	**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 beyond 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, consider additional workup. – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – 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 an immunosuppressive in consultation with a nephrologist.
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Patients should be thoroughly evaluated to rule out alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). – Hold study drug if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or other severe cutaneous adverse reaction (SCAR) is suspected – Permanently discontinue study drugs if SJS, TEN or SCAR is confirmed
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent).	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy. – 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 Clinical Study Lead, as needed, 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 week or recurs.
	Grade 3 or 4	**For Grade 3:**	**For Grade 3 or 4:**

Date:

		Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10mg prednisone or equivalent). **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (eg, hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	General Guidance	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1:** – Monitor patient with appropriate endocrine function tests.

Date:

			– For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2, 3, or 4	For Grade 2 endocrinopathy other than hypothyroidism and type 1 diabetes mellitus (T1DM), consider holding study drug/study regimen dose until patient is clinically stable. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper (<10mg prednisone or equivalent). Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Neurotoxicity (to include but not be limited to non-infectious meningitis, non-infectious 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).

Date:

			– Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurology consult as appropriate. – For transverse myelitis, permanently discontinue for any grade.
	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. Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days.	**For Grade 2:** – Consider discuss with the Clinical Study Lead. – 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 2 to 3 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 or other immunosuppressive depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with Clinical Study Lead. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG or other immunosuppressive depending on the specific imAE).
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 neurology consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Consider discussing with the Clinical Study Lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
	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:** – Consult a neurologist. – Consider discussing with the Clinical Study Lead, as needed. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – 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

Date:

			important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). *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 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider discussing with the Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and obtain neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.

Date:

			○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ○ Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Amylase/Lipase increased	**Any Grade**	General Guidance	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression, viral infection, concomitant medications, substance abuse). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g, abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modification	
	Grade 2, 3, or 4	In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade**	General Guidance	– Consider gastroenterology referral

Date:

	Grade 2, 3, or 4	**For Grade 2 or 3** Hold study drug/study regimen dose until resolution to Grade ≤1. If toxicity improves to Grade <1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen	– Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent – IV hydration
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis	– The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 2, 3, or 4	**If Grade 2-4** Permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Promptly start IVmethylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to

Date:

			complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen) – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximablabel for general guidance before using infliximab. Infliximabis contraindicated for patients who have heart failure.**
Myositis/Polimyositis	**Any Grade**	General Guidance	For Any Grade – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be newonset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the Clinical Study Lead. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory workup as indicated, including a number of

			possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
	Grade 1	No dose modification	– Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the Clinical Study Lead.
	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.	– Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IVmethylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
	Grade 3, or 4	**For Grade 3:**	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult

Date:

		Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consider discussing with the Clinical Study Lead as needed. – Promptly start IVmethylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximablabel for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.

Other-Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications	Monitor as clinically indicated
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. • Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade ≤1 upon treatment with systemic steroids and following full taper.	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines (e.g., NCCN, ESMO)
Grade 3	Hold study drug/study regimen	

Date:

Grade 4	Permanently discontinue study drug/study regimen	

Table 5	**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 , appropriate clinical practice guidelines, and society guidelines.

Date:

Table 6	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.

Abbreviations: AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

NOTE: Patients should have ANC >= 1, hemoglobin >= 9 and platelet count >= 100 on cycle 1, day 1 (See section 6.1, Subject Inclusion Criteria). Patients should have ANC >= 1 and platelet >= 75 on Day 1 of subsequent cycles (Cycle 2 Day 1 and onward) for retreatment.

Restrictions during the study and Concomitant treatment(s)

Restrictions during the study

Contraception

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

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 7) from the time of screening and

Date:

must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab regimen therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period. Male partners of a female subject must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

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 (defined 12 months with no menses without an alternative medical cause).

Highly effective methods of contraception are described in Table 7. A highly effective method of contraception is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. 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 7 Highly Effective[a] Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system(eg, Mirena®)[b]	• 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] Highly effective (i.e. failure rate of <1% per year)

[b] This is also considered a hormonal method

Permitted concomitant medications

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

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

Date:

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

Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than the protocol specified therapies

2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment, other than the protocol specified therapies. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy)

3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).

4. Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Date:

Table 8. Prohibited and Rescue Medications

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

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

Blood donation

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

Date:

11.3 General

It is expected that patients with nausea, emesis, diarrhea, or constipation will receive appropriate medical management without dose modification. However, patients with persistent (≥ 24 hours) Grade ≥3 toxicity in spite of optimal medical management require reduction of one dose level and delay in subsequent therapy for a maximum of 2 weeks until recovered to Grade 1.

Other non-hematologic toxicities with an impact on organ function of Grade ≥2 require delay in subsequent therapy for a maximum of 28 days until recovered to Grade 1, or pre-therapy baseline.

Hematopoietic Growth Factors and Blood Products

Erythropoietin, darbepoetin alfa, romiplostim and/or hematopoietic colony-stimulating factors for treatment of cytopenias should be administered according to institutional guidelines. Transfusion thresholds for blood product support will be in accordance with institutional guidelines.

11.4 Assessment of Safety

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

Safety Parameters

11.4.1 Definition of adverse events

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

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

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

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new

sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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

11.4.2 Definition of Serious Adverse Events (SAE's)

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

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

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

11.4.3 Durvalumab + Tremelimumab Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring 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 and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination regimen therapy. An immune-related adverse

event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with durvalumab and tremelimumab include:

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

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

Pneumonitis

AEs of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Table 4.

Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time. For all infusion reactions, SAEs should be reported to AstraZeneca Patient safety as described in Section 17.2.

Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions

against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in Table 4.

Hepatic function abnormalities (hepatotoxicity)

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

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving tremelimumab are provided in Table 4.

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 Table 4.

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 Table 4.

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 Table 4.

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 Table 4.

11.4.6 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.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Antitumor Effect

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) (Eisenhauer, 2009)]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment on study.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease reevaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease reevaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each

identified and reported lesion at baseline and during followup. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

CA125: CA125 alone cannot be used to assess response. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

12.4 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 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 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 includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of CA125 level above the normal limits.

Date:

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
**** .

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

*

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Date:

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* '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 so to assign this category when no lesions can be measured is not advised		

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from start of treatment to time of recurrence, progression, or death, whichever occurs first.

Survival

Survival is defined as the duration of time from start of treatment to time of death or the date of last contact whichever occurs first.

Permitted Deviations from RECIST

The study's efficacy objectives will be evaluated according to the standard, unmodified RECIST v1.1 criteria described in section 12.3, and that, within the context of this protocol, the only purpose of the modifications to the criteria is to allow certain patients to continue the study treatment despite meeting RECIST criteria for progression of disease.

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

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

Date:

As long as they are receiving treatment on protocol, patients will be permitted to continue study treatment after RECIST v 1.1 criteria for POD are met if they meet all of the following criteria:

- Absence of symptoms and signs indicating unequivocal progression of disease
- No decline in ECOG performance status
- Absence of tumor growth at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Patients for whom approved therapies exist must provide verbal consent to acknowledge deferring these treatment options in favor of continuing study treatment at the time of initial apparent progression

Patients with radiographic disease progression at the at subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above and have evidence of clinical benefit.

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

The primary reason for study treatment discontinuation should be documented on the eCRF.

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

irRECIST

Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. are presented below. irRECIST assessments will only be completed for patients continuing treatment beyond PD.

I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1.

II Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

A key difference in irRECIST is that the appearance new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured

tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

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

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

C. Follow-up for New Non-Measurable Lesions

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

III <u>Overall Assessments for irRECIST</u>

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

Overall Assessments by irRECIST	
Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with **<u>no target lesions at baseline</u>**, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation

Date:

	• irRECIST can be used in the **adjuvant setting**, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response. • Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.
Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. . • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening
Other	**irNE:** used in exceptional cases where insufficient data exist. **irND:** in adjuvant setting when no disease is detected **irNN:**, no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

12.5 Biomarker Assessment

The study will include analyses of archival tumor tissue and peripheral blood to define the biomarkers that could predict/correlate with response. Research bloods will be collected pre-treatment at 4 pre-specified time points: Day 1, Day 8, Day 29, Day 57, with a window of -3 Days for each draw. 6 CPT tubes will be collected at each time point.

12.5.1 Tissue PD-L1 expression **(MedImmune)**

The levels of PD-L1 expression in tumor cells and tumor-infiltrating immune cells will be assessed using SP263 antibody on archival tissue

12.5.2 Tissue gene expression profiling and IHC **(MSKCC, Zamarin, Wolchok lab)**

By using Nanostring nCounter PanCancer Immune Profiling Panel, and immunofluorescence microscopy, archival tumor tissue will be assessed for tumor infiltration with various immune cell subsets, including CD8 cells, CD4+ effector cells (FoxP3-), CD4+ regulatory T cells (FoxP3+), and myeloid cells (CD68+). Tumors will also be assessed for the expression of the known activating co-stimulatory receptors such as 4-1BB (CD137), OX40, GITR, CD40, and ICOS, as well as known immune inhibitory components such as PD-L1, indoleamine dioxygenase (IDO), B7-H3, B7-H4, LAG3, TIM-3, PD-1, CTLA-4, VISTA, and BTLA. The expression of each gene will be treated as a continuous variable. For exploratory biomarker analyses, patients will be dichotomized on the basis of the primary efficacy endpoint.

12.5.3 PBMC immunophenotyping **(MSKCC: IMF)**

By using multi-parameter flow cytometry, we will explore whether peripheral blood biomarkers could serve as early predictors of clinical benefit and provide targets for further combinations, with a particular focus on targetable markers of T cell activation (ICOS, CD137, OX40, GITR), and inhibition (LAG3, TIM3, PD-1, BTLA, VISTA), as well as percentages of peripheral inhibitory immune subsets such as MDSCs and Tregs.

Date:

12.5.4 PBMC gene expression analyses **(MSKCC, Zamarin, Wolchok lab)**
RNA extracted from PBMCs collected at baseline and on-treatment will be analyzed on the Nanostring platform using Nanostring nCounter PanCancer Immune Profiling Panel, to define gene signatures associated with clinical benefit.

12.5.5 PBMC T cell receptor (TCR) repertoire analyses **(MSKCC: IMF, Zamarin, Wolchok lab)**
Maintenance and expansion of particular T cell receptor (TCR) clones in the peripheral blood may be associated with clinical response. PBMC¹s collected during the study will be banked for potential future TCR repertoire analyses. DNA isolated from PBMC¹s will be send for deep sequencing of TCR CDR regions at Adaptive Biotechnologies to determine whether maintenance or emergence of particular oligoclonal populations of T cells in the periphery is predictive of clinical benefit.

12.5.6 Plasma assays
Plasma collected with PBMCs will be stored for additional analyses. Current PBMC-based assays are cumbersome and suffer from variability due to differences in PBMC collection. Plasma-based analyses will include analyses of circulating tumor DNA and RNA, multiplex cytokine ELISAs, and serologic assays for antibodies to specific tumor-associated antigens.

12.5.7 Future research
Leftover blood and tissue samples from the study will in addition be stored for future research using the assays currently in development, including new single-cell based technologies. The future research will continue to be directed towards evaluation of potential novel biomarkers of response/resistance to durvalumab and durvalumab/tremelimumab combination.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Patients may withdraw from the study at any time. Any patient who withdraws will be encouraged to return to the study center for a treatment completion visit. Patients who discontinue early should return within 30 days following the final dose of study treatment. The primary reason for discontinuation must be recorded in the medical record.

Permanent discontinuation of treatment with Durvalumab and Tremelimumab

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

- Disease progression, per investigator assessment
- Intolerable toxicity of study drugs
- Withdrawal of consent or lost to follow-up
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Pregnancy or intent to become pregnant
- Grade ≥ 3 infusion reaction

Date:

- Initiation of alternative anticancer therapy including another investigational agent

Other reasons for patient discontinuation may include, but are not limited to, the following:

- Change in patient eligibility
- Non-compliance
- Patient decision
- If treatment is delayed for more than 28 consecutive days
- Withdrawal of consent
- If consent is withdrawn, the subject will not receive any further investigational product or further study observation.
- The investigator has the right to discontinue a patient from the study for any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study; for reasons of noncompliance (e.g., missed doses, visits); or if the investigator determines it is in the best interest of the patient.

14.0 BIOSTATISTICS

This Phase 2 study aims to assess the activity of Durvalumab alone and in combination with Tremelimumab in patients with recurrent or persistent endometrial carcinomas or endometrial carcinosarcomas. Patients will be randomized to Arm 1: Durvalumab (anti-PD-L1 Antibody) alone or Arm 2: Durvalumab with Tremelimumab (anti-CTLA-4 antibody). This is a randomized study however it is not powered to show superiority of one arm versus another.

In this study, all analyses will be performed by treatment arm.
To date, there are no published studies of immune checkpoint inhibitors in this patient population.

Extrapolating from prior monotherapy studies of immune checkpoint inhibitors in ovarian cancer have yielded overall response rates in the range of 10-15%, and may serve as a basis for historical comparison of the doublet tested here.

Study	N	ORR (CR+PR)	DCR (ORR+SD)	Prior Therapy
Nivolumab (anti-PD-1) 1 mg/kg q 2 weeks (cohort 1) 3 mg/kg q 2 weeks (cohort 2)	 10 10	15% (3/20): 10% (1 PR) 20% (2 CR)	 50% (5 SD +1 PR) 40% (2 SD +2 CR)	≥ 2 priors Platinum Resistant
Avelumab (anti-PD-L1) Phase Ib expansion cohort 10 mg/kg q 2 weeks	 75	 10.7% (8 PR)	 55% (33 SD +8 PR)	med 4 priors(1-11) Platinum Resistant
Pembrolizumab (anti-PD-1) Phase Ib expansion cohort 10 mg/kg q 2 weeks	 26	 11.5% (1 CR, 2 PR)	 35% (9 SD+1CR+2 PR)	>80% $\geq$ 4 priors PD-L1+ (IHC)

ORR (defined as CR+PR) will be the primary endpoint. A 10% ORR will be considered low and 25% or higher will be considered promising for further studies. Forty patients provide 90% power and Type I error of 10% using a Simon two stage minimax design. There will be an interim analysis after evaluable 27 patients and if 3 or more responders (CR+PR) are observed out of evaluable 27 patients then the study will continue to the second stage. At the end of the study we require 7 or more responders out of 40 patients to declare this study positive and the arm worthy for further investigation.

Unacceptable response rate: 0.1

Date:

Desirable response rate: 0.25
Error rates: Type I = 0.1 ; Type II = 0.1

# responses required in Stage I	# patients accrued at stage I	# responses required in Stage 2	Total sample size
>=3	27	>=7	40

If the test for ORR is significant, then the PFS rate at 24 weeks (+/- 1 week) will also be tested against the historical control estimate. For PFS rate at 24 weeks (+/- 1 week), we consider a 15% rate as low, and a rate of 35% or higher as indicative of promising activity. This stems from Gynecologic Oncology Group studies of the same patient population we are evaluating in this study which have deemed PFS at 6 months of 15% or less as indicative of lack of activity and PFS at 6 months of 35% or more as indicative of having activity.
This test of PFS rate will be performed only if the ORR analysis is significant, and thus PFS assessment is supplementary to ORR assessment. At the end of the study, if 10 or more out of 40 patients are considered progression free at 24 weeks (+/- 1 week), then that arm will be considered worthy of further study. This study will have 94% power and 7% Type I error to show activity in terms of 6 months PFS rate. The overall Type I error of the study is bounded by the 10% error rate of the first hypothesis of ORR. The hierarchy in the two hypotheses for ORR and PFS ensures the overall error rate to be smaller than 10% (Bretz 2009)

If both arms have >=7 responders the winning arm is the one with higher ORR and if both arms have exactly 7 responders the winning arm will be decided based on the review of all efficacy data (ORR and PFS) and the total safety profile (number and type of grade 3 AE) of each arm.
A treatment arm will be considered promising if the ORR decision rule is met, but the 6 month PFS decision rule is not met. After first stage accrual is complete, we will halt the study for 16 weeks after last patient has been accrued to first stage in order to assess the decision rules to move to stage 2. Based on historical accrual rates in similar populations, we anticipate successful enrollment of 4 patients per month yielding a total accrual time of 20 months. Accrual will continue until 40 patients on each arm(evaluable patients are defined in section 12.1), unless the interim analysis after 27 patients does not support continuation.

Definitions of Statistics to be Reported

- Clinical Benefit Rate (CBR)), defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) by 24 weeks from the start of treatment will be reported and the 90% confidence interval will be estimated using exact binomial proportions. This will be done following RECIST criteria.
- Progression free survival (PFS), defined as the duration of time from start of treatment to time of recurrence, progression, or death due to any cause, whichever occurs first. Patients will be censored at last follow up date. The Kaplan Meier estimate of median PFS will be reported as well as the PFS rate at 24 weeks(+/- 1 week).
- Duration of response (DOR), defined as the time from which measurement criteria are met for CR or PR (whichever status is recorded first using RECIST) until the first date of documented

disease progression, will be estimated using the Kaplan Meier method. Patients without documented progression will be censored at last follow up.

- The rate of response using immune response criteria (refer to irRECIST description in section 12.3, which defines responders and non responders) and the 90% confidence interval will be estimated using exact binomial proportions.
- Adverse events by the current version of Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03) will be tabulated in order to assess the safety profile and tolerability therapy in treated patients.

Safety Analysis

The frequency and severity of observed adverse effects will be evaluated.
The rates of irAE, SAE, therapy completion rate, and protocol completion will also be reported.

Safety will be measured by the frequency of grade 3 or 4 treatment-related clinically significant toxicities (NCI Common Terminology Criteria for Adverse Events version 3.0), aside from Grade 3 or 4 hematologic or laboratory abnormalities, unless they are deemed unexpected or clinically significant.

Frequencies of toxicities will be tabulated. The grade 3 or 4 treatment-related non-hematologic/non-laboratory toxicity will be estimated at the end of the trial along with the 95% confidence interval. With 40 patients per arm, these rates can be estimated within ±16%.

Methods of Efficacy Analysis

Efficacy Variables

The intent of this protocol is to assess checkpoint inhibitors for activity in patients with carcinomas advanced, recurrent endometrial carcinomas and carcinosarcomas.

The principal parameters employed to evaluate the efficacy of the two arms are:

- The rate of ORR and duration of overall objective response (ORR = CR + PR).
- Progression-free survival rate at 24 weeks for all patients evaluable for this endpoint.
- Clinical Benefit Rate (CBR) will be defined as ORR + Stable Disease (SD) rate by 24 weeks.

Patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease reevaluated will be considered evaluable for response and PFS. The primary efficacy analysis will include only patients who are evaluable for response. Patients without post baseline assessment of response will be included in a sensitivity analysis as non responders for ORR, and events for PFS. A 90% confidence interval for PFS will also be provided.

All patients will be followed up for a minimum of 6 months. We do not expect any patient to have a follow up of less than 6 months. If a patient meets all the criteria for being evaluable but has not been followed for 6 months and has not progressed, this patient will be censored at the time of last follow up. This patient will be included in the analysis. For the determination of the decision rule for PFS (ie >=10 patients event free), this patient will be considered a failure.

Date:

For safety, all patients who received at least one cycle of therapy will be included.

As per the standard of reference set by the Gynecologic Oncology Group for recurrent endometrial cancers, if a new agent has a true response rate of 10% or less, it would be considered of little clinical significance. Conversely, if the true response rate is at least 25%, further investigation is clearly indicated. These are the reference ORR numbers used to assess novel agents in the GOG-129 and 229 queue, through which nearly 20 treatments have been evaluated. As a means of comparison, and to further justify this ORR goal, the clinical data for several relevant cytotoxic and biologic agents are tabulated here.

Rx	ORR (%) [PR + CR]	PFS at 24 weeks (%)	# of Patients (n)	Reference
Etoposide	0	8.0	25	Rose et al, Gynecol Oncol 1996
Paclitaxel	25	20.8	48	Ball et al, Gynecol Oncol, 1996
Doxorubicin	9.3	23.3	43	Thigpen et al, Cancer Treat Rep. 1979,
Ixabepilone	12	20.4	49	Dizon et al, JCO, 2009
Bevacizumab	17	41.5	53	Aghajanian et al, JCO, 2011

Given the inherent difficulty in detecting meaningful overall survival (OS) data in patients who will likely frequently receive multiple, and divergent downstream agents after end of study, including possible enrollment in additional clinical trials, PFS at 24 weeks (6 months) is considered an appropriate endpoint for meaningful clinical efficacy. (Sill 2008) This approach has been adopted for recurrent and advanced endometrial cancer.

Exploratory objectives: For exploratory biomarker analyses, patients will be dichotomized on the basis of clinical benefit (CBR) rate (CR+PR+SD) as the outcome measure. Exploratory endpoints will be analyzed by treatment arm. All biomarkers without known cutoffs will be treated as continuous variables For tissue based biomarkers, CBR will be correlated to the level of tissue expression of PD-L1 (binary: positive vs negative), or specific genes/gene signatures identified from transcriptional profiling. Non parametric 2 sample tests will be used to assess differences in the distribution of markers between the 2 groups (responders vs non responders). Archival tumor tissue IHC will be assessed only at baseline while other markers will be assessed at baseline and during treatment and their change from baseline will be analyzed. For markers such as number of infiltrating CD8+ cells and change in ICOS level expression on lymphocytes from baseline levels, we do not have established cutoffs, thus we will examine them as continuous variables. In these biomarkers we will look at changes from baseline to treatment (focused on early changes or changes within 8-12 weeks), and we explore these changes graphically in order to assess potential relationships between responders and non responders.

Date:

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria.Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

Patients will be randomized to Arm 1: Durvalumab (anti-PD-L1 Antibody) alone or Arm 2: Durvalumab with Tremelimumab (anti-CTLA-4 antibody). Randomization will be accomplished by the method of random permuted block, and patients will be stratified by histology(stratum 1: endometrial carcinosarcoma patients or MSI-high endometrial carcinoma patients and stratum 2 :other histologies). We will limit enrollment of stratum 1 to 10 patients per arm.

15.2 Randomization

16.1 DATA MANAGEMENT ISSUES

A research study assistant (RSA) will be assigned to study. The responsibilities of the RSA include project compliance, data collection, extraction and data entry, data reporting, coordination of the activities of the protocol study team and, and of the flow of regulatory paperwork.

The data collected for the study will be entered into a secure database (MediData RAVE). All routine blood test results required per the protocol will be captured in MediData RAVE in addition to baseline medical conditions and disease information, response assessments, off-study documentation, and toxicity grade and attribution. Source documentation will be available to support the computerized patient record.

MSKCC will hold the IND and will be responsible for all safety monitoring. All SAEs will be reported to the MSKCC IRB. The safety of the study will be monitored by the MSKCC Data and Safety Monitoring Committee.

Weekly registration reports will be generated by the RSA and reviewed by the PI to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies.

Accrual rates and extent and accuracy of evaluations and follow up will be monitored periodically throughout the study. Recurrent lapses in data collection, deviations or violations will be discussed with the study team and a corrective plan will be generated. Accrual goals

and factors impacting accrual goals will be discussed at the weekly New Patient/Protocol meetings.

If accrual proceeds more quickly than anticipated, it may be slowed or staggered at the discretion of the Principal Investigator, to account for safety concerns or data management resources.

16.2 Quality Assurance

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

The data and safety monitoring plan at Memorial Sloan Kettering Cancer Center was approved by the National Cancer Institute in September 2001. The plan addressed the new policies set forth by the NCI and the document entitled "Policy of the National Cancer Institute for data and safety monitoring of clinical trials" which can be found at http://grants.nih.gov/grants/guide/noticefiles/not98-084.html. The DSM plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC data and safety monitoring plan can be found on the MSKCC Internet at

http://inside2/clinresearch/Documents/MSKCC Data and Safety Monitoring Plans.pdf. There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. Memorial Sloan Kettering Cancer Center has set up three distinct monitoring processes for our clinical trials program. There are two sub-committees that have the responsibility of data and safety monitoring. These are joint sub-committees with dual-reporting responsibilities. The Data and Safety Monitoring Committee (DSMC) is the sub-committee responsible for monitoring all Phase 1, 2, 1/2, pilot and non-phase clinical trials. The Data and Safety Monitoring Board (DSMB) is the sub-committee responsible for monitoring Phase 3 randomized clinical trials. The Therapeutic Response Review Committee (TRRC) is the sub-committee of Research Council responsible for the independent therapeutic response review for participants in IRB/PB approved clinical trials where therapeutic efficacy is a stated primary objective, typically phase 2 and 3 trials. Formal monitoring of such studies is designed to ensure that the interests of the participants are being scrutinized on a regular basis, and that the trial is progressing in a satisfactory manner.

The DSMC convenes once per quarter and monitors the risk participants are exposed to, the progress of the study, the adequacy of the data storage and whether sufficient data are being entered into the MediData RAVE. The DSMC monitors phase 1, 2, 1/2, pilot and non-phase trials that are not being monitored by an industrial sponsor, and which meet the NCI definition of a Clinical Trial. This trial will qualify for monitoring by the DSMC.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required, and the monitoring procedures will be established at the time of protocol activation. A detailed description of the data to be

collected, process of data collection (i.e., data manager and/or data management office), database that will be utilized for data collection and storage (e.g., MediData RAVE, user-supported software), reporting requirements of the data to the institution (IRB), the sponsor and/or governing agency.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

17.1 PROTECTION OF HUMAN SUBJECTS

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment,

they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 90-days after the participant's last investigational treatment or intervention. Any events that occur after the 90-day period and that are at least possibly related to protocol treatment must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred The adverse event
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form.
- If the SAE is an Unanticipated Problem

For IND/IDE protocols:
If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

Ethical conduct of the study

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

17.3.1 Recording of adverse events and serious adverse events

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

Date:

The following variables will be collected for each AE:

- AE (verbatim)
- The date (and time when clinically relevant) when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab (yes or no)
- Investigator causality rating against tremelimumab (yes or no)
- Action taken with regard to durvalumab
- Action taken with regard to tremelimumab
- Outcome

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

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

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

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

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

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

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

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

Date:

17.2.1.2 Follow-up of unresolved adverse events

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

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

17.2.1.3 Post study events

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

17.2.1.4 Reporting of serious adverse events

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

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

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

Date:

- A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:
- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
    - The trial name/title and AstraZeneca ISS reference number (ESR-15-10965)

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

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com. If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

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

17.2.1.5 Other events requiring reporting

Overdose

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

Any overdose of a study subject with durvalumab + tremelimumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 11.4 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 11.4). 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 11.4). There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

The investigator will use clinical judgment to treat any overdose.

Hepatic function abnormality

Hepatic function abnormality (as defined in Section 11.4) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 11.4 for contact

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

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

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

Pregnancy

Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

Pregnancy in a subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune

Patient Safety or designee using the designated Safety e-mailbox (see Section 17.2.1.4 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. The pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to AstraZeneca/MedImmune Patient Safety.

Date:

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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Date:

Date:

20.0 APPENDICES

APPENDIX A:

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

Evaluation	Time Since Last Dose of Durvalumab							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Physical examination	X							
Vital signs (temperature, blood pressure, pulse)	X							
Weight	X							
Urine hCG or serum βhCG	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated →							
<<World Health Organisation>> <<ECOG>> performance status	X	X	X		X (and month 9)			X
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					X
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and T4)[a]	X							
Pharmacokinetic assessment, if applicable			X					
Immunogenicity assessment (ADA sampling [including ADA neutralising antibodies] to identify ADA responses in subject circulation), if applicable			X		X			
sPD-L1 concentration (to assess target engagement), if applicable			X					
Circulating soluble factors (to assess cytokines, chemokines, growth factors and antibodies against tumor and self antigens in circulation), if applicable	X							

Date:

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

Evaluation	Time Since Last Dose of Durvalumab							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
miRNA/mRNA (to examine immune cell gene expression profiles in circulation), if applicable	X							
PBMCs, if applicable	X							
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 12 weeks relative to the date of **first infusion** thereafter until PD. For subjects who **discontinue Durvalumab due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the relative to the date of **first infusion** as follows: every 8 weeks for the first 48 weeks, then every 12 weeks until PD. For patients who remain progression free 2 years post completion of protocol directed treatment, every 6 months +/- 1 month. Upon PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional).							

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

Date:

Appendix B. Durvalumab DOSE VOLUME CALCULATIONS

For durvalumab fixed dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000 / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

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

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

Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

Dose (mL) = 1.5 g ×1000 / 50 (mg/mL) = 30.0 mL

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

Number of vials = 30.0 (mL) / 10.0 (mL/vial) = 3 vials

Appendix C. Tremelimumab DOSE VOLUME CALCULATIONS

For tremelimumab fixed dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

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

where 20 mg/mL is tremelimumab nominal concentration

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

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

Date:

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

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

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

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

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

APPENDIX D Biomarkers

Archival tissue will be obtained for analysis of primary tumor. 10-20 unstained PPFE slides will be sought from each patient: Half will go to the sponsor, and the remaining ones will remain at MSK. A patient will be required to have a minimum of 10 unstained PPFE slides to be eligible. No biopsy will be performed for procurement of tissue for purposes of meeting eligibility.

- AZ/MEDI will perform assays of PD-L1 expression.
- MSKCC/Zamarin will perform assays for Immunologic markers.

Research bloods will be collected on Day 1, Day 8, Day 29, and Day 57 with a window of -3 Days for each draw. 6 CPT tubes will be collected at each time point (all 6 tubes will remain at MSK).

Research Blood Sample Collection Instructions: 6 CPT tubes will be collected on Day 1, Day 8, Day 29, and Day 57.

1. Invert all tubes several times immediately after collection to ensure mixing with anticoagulant (or clotting activators for serum collection tubes). For serum tubes, allow blood in tube to clot for 30 min at room temperature in a vertical position in a tube rack.
2. Include patient initials, MRN, date, and time of collection on adhesive stickers **attached** to each tube.
3. Fill in date and time of collection in requisition form.
4. Place all collected tubes in a biohazard ziplock bag at room temperature.
5. Send all specimens via Stat Messengers to Immune Monitoring Core located at the MSKCC Zuckerman Research Center (417 E. 68th St, New York, NY), **Room 1513**. Place into blood bin on benchtop.
6. Notify IMF staff of sample delivery

Date: