

**Version Date: May 12, 2017**

**DF/HCC Protocol #: 16-549**

**TITLE:** A Phase 2 Study of Durvalumab in Combination with Tremelimumab in Malignant Pleural Mesothelioma

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**NCI-Supplied Agents:** None

**Other Agents:** Durvalumab (MEDI4736) – AstraZeneca, Tremelimumab (CP-675,206) - AstraZeneca

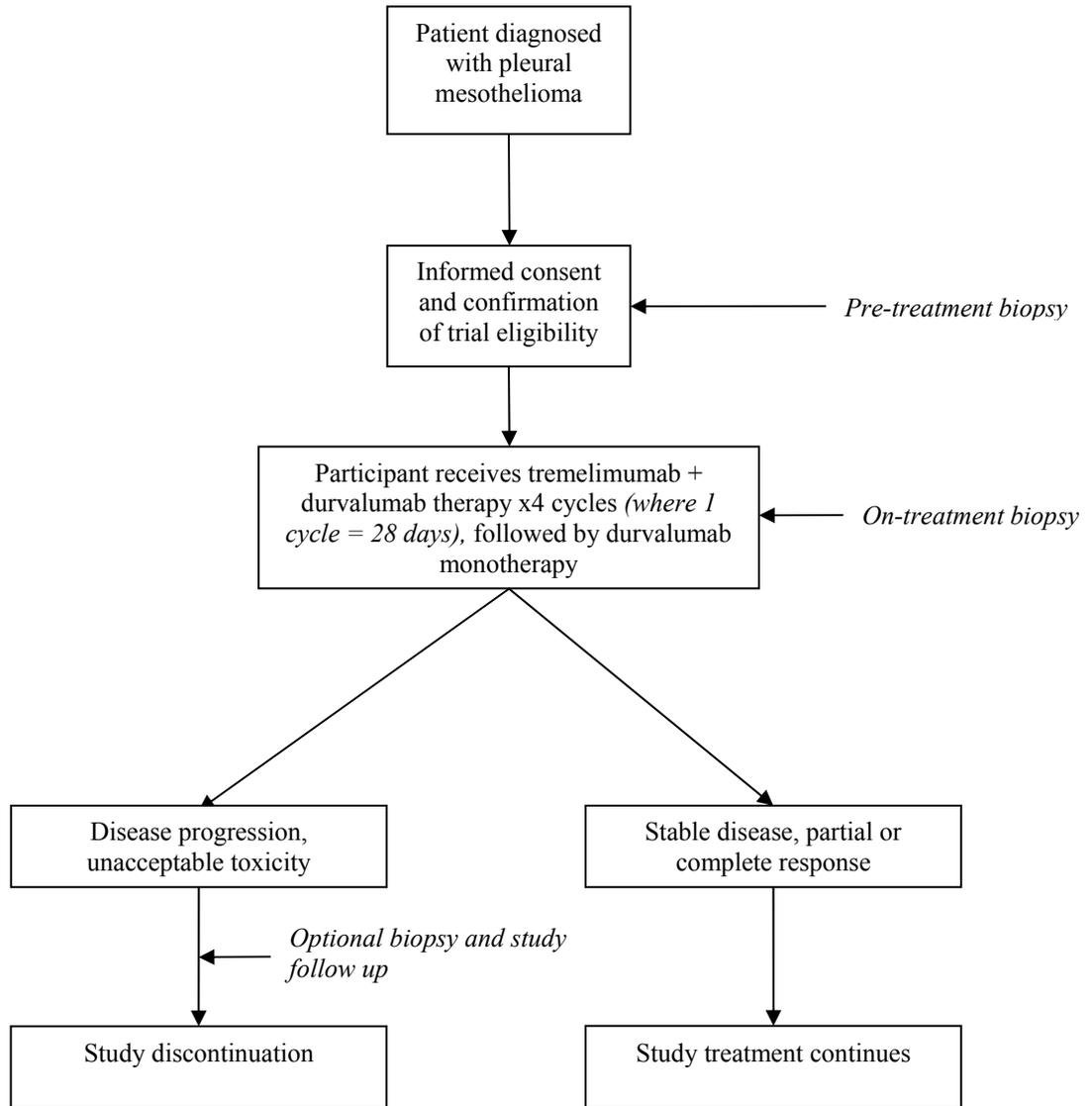
**IND #:** 132044

**IND Sponsor:** Investigator-Initiated Study, Mark Awad MD, PhD

**Protocol Type / Version # / Version Date:** Revised, Version 3, May 12, 2017



**SCHEMA**



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## **1. OBJECTIVES**

The objective of this phase 2 study is to determine the antitumor activity of the CTLA-4 inhibitor tremelimumab in combination with the PD-L1 inhibitor durvalumab (MEDI4736) in malignant pleural mesothelioma. Immunologic and genomic biomarkers of response will also be evaluated through correlative studies incorporated throughout this trial.

### **1.1 Study Design**

This is an open-label, single-arm, phase 2 study of tremelimumab plus durvalumab in patients with previously-treated unresectable malignant pleural mesothelioma.

### **1.2 Primary Objective**

- Examine the overall response rate (ORR) utilizing modified RECIST criteria for mesothelioma

### **1.3 Secondary Objectives**

- Determine the progression free survival (PFS) rate, defined as the time from registration to disease progression or death due to any cause. Participants alive without disease progression will be censored at date of last disease evaluation.
- Determine the overall survival (OS) rate, defined as the time from registration to death due to any cause (or censored at date last known alive).
- Determine the duration of response (DoR), defined as the time from documentation of tumor response to disease progression (or censored at the date of last disease evaluation).
- Evaluate the safety and tolerability of tremelimumab in combination with durvalumab.

### **1.4 Exploratory Objectives**

- Investigate the immunologic determinants of primary response and resistance to tremelimumab in combination with durvalumab in malignant pleural mesothelioma
- Investigate the immunologic mechanisms of acquired resistance to tremelimumab in combination with durvalumab
- Investigate genomic correlates of response to tremelimumab in combination with durvalumab

## **2. BACKGROUND**

### **2.1 Study Disease**

Malignant mesothelioma is an insidious cancer with a very poor prognosis. There are about 3300 new cases of mesothelioma diagnosed in the United States each year, and 80% of these cases are pleural in origin. Mesothelioma results in significant morbidity and mortality typically through local invasion, and patients often experience progressive chest pain, shortness of breath, fatigue,

and hypoxemia related to encasement of the lungs and accumulation of pleural fluid. Extension into other thoracic structures can cause a number of disabling symptoms including dysphagia, spinal cord and brachial plexus injury, superior vena cava syndrome, and cardiac dysfunction.

For patients with unresectable pleural mesothelioma, cisplatin-pemetrexed is the only FDA-approved treatment regimen based on a 2003 randomized phase III first-line trial comparing this combination with cisplatin monotherapy.<sup>1</sup> In this study, chemotherapy-naïve patients who received cisplatin and pemetrexed had a significantly longer median survival time (12.1 vs. 9.3 months) and higher response rates (41.3% vs. 16.7%) compared to those receiving cisplatin alone. There are no effective second-line treatment options for patients with mesothelioma. There was a 16% response to weekly vinorelbine in a single-arm phase II trial of 63 patients with relapsed mesothelioma.<sup>2</sup> A retrospective study of 66 mesothelioma patients treated with second- or third-line vinorelbine or gemcitabine found the response rate to be only 2%.<sup>3</sup>

Immune checkpoint blockade as monotherapy was recently evaluated in a randomized, double-blind, placebo-controlled study of tremelimumab in patients with unresectable pleural or peritoneal mesothelioma (Study D4880C0003, NCT01843374) and unfortunately was found not to extend overall survival. However, in the Keynote-028 phase Ib trial of patients with advanced solid tumors, among 25 PD-L1 positive mesothelioma patients treated with pembrolizumab, a partial response was seen in 7 patients and stable disease was seen in 12 patients<sup>4</sup>. In support of this finding is a growing body of evidence that a substantial number of malignant mesotheliomas express the immune checkpoint marker PD-L1. In one recent study of 106 mesothelioma cases, PD-L1 was detected in 40% of patients by immunohistochemistry (IHC). Furthermore, nearly all samples with sarcomatoid histology expressed PD-L1. Compared to PD-L1-negative specimens, expression of PD-L1 was associated with a significant decrease in median overall survival (5 months vs. 14.5 months).<sup>5</sup>

Recent pre-clinical work has suggested that targeting both PD-L1 and CTLA-4 may have additive or synergistic effects<sup>6</sup>. Based on these results, we hypothesize that PD-L1 inhibition with durvalumab and CTLA-4 inhibition with tremelimumab will result in high response rates in previously-treated patients with malignant pleural mesothelioma.

## **2.2 Durvalumab**

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. 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. 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<sup>7</sup>. 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<sup>8-10</sup>.

### 2.2.1 Summary of Durvalumab Pre-Clinical Studies

Engagement of PD-1 on T cells inhibits activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T-cell function<sup>11-16</sup>.

Durvalumab has shown the following activity as an anti-PD-L1 molecule:

- Durvalumab binds to PD-L1 and blocks its interaction with PD-1 and CD80
- Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation *in vitro*
- Durvalumab inhibits tumor growth in a xenograft model via a T-cell dependent mechanism
- A surrogate anti-mouse PD-L1 antibody resulted in improved survival in a syngeneic tumor model as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy
- In the same study, anti-mouse PD-L1 antibody-treated mice were completely tumor free 3 months after tumor implantation and demonstrated long-term immunity during rechallenge
- In a subsequent study in the same syngeneic model, the combination of an anti-mouse PD-L1 antibody and anti-CTLA-4 antibody resulted in complete tumor regression in all mice treated

The cynomolgus monkey is considered to be the only relevant nonclinical species for evaluation of local and systemic toxicities of durvalumab. In addition, *in vivo* in cynomolgus monkeys, durvalumab suppresses soluble PD-L1 (sPD-L1) in serum and fully occupies membrane PD-L1 on various leukocyte subsets at doses equal to or more than 0.1 mg/kg (lowest dose tested) with a dose-related duration of suppression and occupancy.

In general, there were no durvalumab-related adverse effects in toxicity studies conducted in cynomolgus monkeys with durvalumab considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) pharmacokinetic (PK)/pharmacodynamic and dose range-finding study (4 doses over 5 weeks), and a GLP 4-week repeat-dose toxicity study were consistent with anti-drug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamic, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction based on the presence of ADAs within days of the first dose, acuteness and timing (after repeated dosing) of the death, clinical signs consistent with an anaphylactic reaction, lack of remarkable effects on other study parameters, and lack of histopathologic findings consistent with any other cause of death. In addition, the spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was consistent with ADA-associated immune complex deposition. Similar effects have been observed by MedImmune in cynomolgus monkeys administered other unrelated human MAbs. With durvalumab, ADA immune-complexes were identified in the affected animal in a subsequent

investigative immunohistochemistry study. Given that immunogenicity of human MAbs in nonclinical species is not generally predictive of responses in humans, the ADA-associated morbidity and mortality were not taken into consideration for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab in these studies. Finally, interim audited data from the dosing phase of the pivotal 3-month, repeat-dose GLP toxicity study in cynomolgus monkeys, showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies.

## 2.2.2 Durvalumab Clinical Studies

Durvalumab has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. As of the data cut-off 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.

### 2.2.2.1 Durvalumab Pharmacokinetics

As of 09 Feb 2015, pharmacokinetic (PK) data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 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 ( $C_{max}$ ) 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 ( $AUC_{0-14}$ ) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at  $\geq 3$  mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated clearance at doses  $< 3$  mg/kg and approaches linearity at doses  $\geq 3$  mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab  $\geq 3$  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  $\geq 40$   $\mu\text{g/mL}$  throughout the dosing interval.

As of 09 Feb 2015, 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.

### 2.2.2.2 Durvalumab Adverse Events

A total of 736 subjects with advanced solid tumors have been treated in Study CD-ON-

MEDI4736-1108. Of these subjects, 694 have received durvalumab at 10 mg/kg Q2W, either in the dose-escalation or dose-expansion phase of the study. The 10 mg/kg Q2W cohort represents combined data from subjects treated with this dosing regimen in either the dose-escalation or dose-expansion phase. The 10 mg/kg Q2W cohort comprises subjects with NSCLC (n = 252), SCCHN (n = 62), gastroesophageal cancer (n = 51), HCC (n = 40), pancreatic adenocarcinoma (n = 31), TNBC (n = 28), bladder cancer (n = 28), uveal melanoma (n = 24), and advanced cutaneous melanoma (n = 23). Subjects in the 10 mg/kg Q2W dose cohort were exposed to a median of 6 doses of durvalumab, ranging from 1 to 27 doses. Exposure was generally consistent across the tumor types, with the exception of advanced cutaneous melanoma having a higher median exposure of 13 doses, and gastroesophageal cancer, TNBC, and bladder cancer having lower median exposures of ~3 doses.

In addition, safety data are presented for 42 subjects in the following dose-escalation cohorts: 4 subjects in each of the 0.1 and 0.3 mg/kg Q2W cohorts, 3 subjects in each of the 1 and 3 mg/kg Q2W cohorts, 2 subjects in the 10 mg/kg Q3W cohort, 7 subjects in the 15 mg/kg Q3W cohort, and 19 subjects in the 20 mg/kg Q4W cohort.

Of the 694 subjects treated with 10 mg/kg Q2W, 668 subjects (96.3%) had at least 1 adverse event (AE) (regardless of causality). AEs (all grades) reported in decreasing order of frequency in  $\geq 10\%$  of subjects were fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Across the tumor types, the overall incidence of AEs was generally similar; however, differences were noted by system organ class and preferred term (PT).

Grade 3 or higher AEs were reported in 379 subjects (54.6%) and were manageable by general treatment guidelines. Events occurring in  $> 2\%$  of subjects were dyspnea (7.2%), hyponatremia (4.6%), NSCLC (4.5%), anemia (4.2%), increased GGT (3.9%), fatigue (3.3%), increased AST (3.2%), sepsis (2.7%), pneumonia (2.6%), abdominal pain (2.4%), back pain (2.3%), and malignant lung neoplasm (2.2%).

A total of 378 subjects (54.5%) reported AEs that were considered by the investigator to be related to investigational product. Treatment-related AEs (all grades) reported in  $> 2\%$  of subjects were fatigue (17.7%); nausea (8.6%); diarrhea (7.3%); decreased appetite (6.8%); pruritus (6.3%); rash (6.1%); vomiting (5.0%); hypothyroidism (4.8%); arthralgia (4.0%); increased AST (3.9%); increased ALT, myalgia (3.6% each); dyspnea (3.3%); pyrexia (2.7%); increased GGT, cough (2.4% each); anemia, hyperthyroidism (2.3% each); and asthenia (2.2%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with  $\geq$  Grade 3 events occurring in 65 subjects (9.4%). Treatment-related  $\geq$  Grade 3 events reported in 3 or more subjects ( $\geq 0.4\%$ ) were fatigue (12 subjects, 1.7%); increased AST (7 subjects, 1.0%); increased GGT (6 subjects, 0.9%); increased ALT (5 subjects, 0.7%); and colitis, vomiting, decreased appetite, hyponatremia (3 subjects, 0.4% each). Six subjects (3 NSCLC, 2 HCC, and 1 SCCHN) had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject (NSCLC) had a treatment-related Grade 5 event (pneumonia).

AEs (regardless of causality) reported for  $\geq 2$  subjects in any of the other Q2W dose escalation

cohorts were as follows: pyrexia (3/4 subjects in the 0.3 mg/kg cohort); diarrhea (2/4 subjects in each of the 0.1 and 0.3 mg/kg cohorts); fatigue and arthralgia (2/4 subjects each in the 0.3 mg/kg cohort); rash (2/4 subjects in the 0.3 mg/kg cohort and 2/3 subjects in the 1 mg/kg cohort); and nausea and dizziness (2/3 subjects each in the 1 mg/kg cohort). AEs reported for  $\geq 2$  subjects in the Q3W cohorts (all occurring at 15 mg/kg) were cough (4/7 subjects); nausea, fatigue, pyrexia, dyspnea (3/7 subjects each); and abdominal pain, vomiting, asthenia, musculoskeletal pain, dizziness, and rhinorrhea (2/7 subjects each). In the 20 mg/kg Q4W cohort, AEs reported for  $\geq 2$  subjects were fatigue, decreased appetite (3/19 subjects each); sepsis, back pain, hypoesthesia, and cough (2/19 subjects each). No  $\geq$  Grade 3 events were reported for more than 1 subject in any of these dose-escalation cohorts. Grade 3 events considered by the investigator to be related to durvalumab were fatigue and peripheral motor neuropathy in 1 subject each in the 15 mg/kg Q3W cohort, and increased GGT in 1 subject in the 20 mg/kg Q4W cohort. No treatment-related Grade 4 or 5 AEs, and no DLTs have been reported.

### 2.2.2.3 Durvalumab Serious Adverse Events

A total of 718 serious adverse events (SAEs) (regardless of causality) have been reported in 345 of 694 subjects (49.7%) treated with 10 mg/kg durvalumab Q2W. SAEs reported for 10 or more subjects were dyspnea, NSCLC, pneumonia, pyrexia, sepsis, malignant lung neoplasm, abdominal pain, pleural effusion, general physical health deterioration, pancreatic carcinoma, vomiting, and dehydration. The overall rates for SAEs were generally comparable across the tumor types, except for a much higher rate (80.6%) in the pancreatic cancer cohort and a lower rate (30.4%) in the advanced cutaneous melanoma cohort. The higher frequency of SAEs in the pancreatic cancer cohort could be explained, in part, by the high rate of disease progressions (PT of pancreatic carcinoma; 32.3%) reported in these subjects. Of note, disease progressions were reported as SAEs in this study.

Twenty-five subjects (3.6%) had SAEs considered by the investigator to be related to durvalumab. Treatment-related SAEs that occurred in 2 or more subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were Grade 3 or higher in severity and recovered with or without sequelae. One subject died due to a treatment-related SAE (pneumonia). Prior to the fatal event of pneumonia, the subject experienced treatment-related SAEs of pneumonitis (Grade 4) and pneumonia (Grade 3).

In addition, SAEs were reported for 5 subjects (35.7%) in the other Q2W dose-escalation cohorts, 3 subjects (42.9%) in the 15 mg/kg Q3W cohort, and 7 subjects (36.8%) in the 20 mg/kg Q4W cohort. SAEs (PTs) reported for  $> 1$  subject were abdominal pain, sepsis, and NSCLC (2 subjects each). The majority of the SAEs were  $\geq$  Grade 3 in severity, and none of the events were considered by the investigator to be related to durvalumab.

### 2.2.2.4 Efficacy

Partial efficacy data are available for Study CD-ON-MEDI4736-1108. Tumor assessments were based on RECIST v1.1.

A total of 456 of 694 subjects with advanced solid tumors treated with durvalumab 10 mg/kg

Q2W were evaluable for response (defined as having  $\geq 24$  weeks follow-up, measurable disease at baseline, and  $\geq 1$  follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the overall response rate (ORR), based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma to 20% in bladder cancer, and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in TNBC to 39.1% in advanced cutaneous melanoma. PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest ( $> 10\%$ ) for bladder cancer, advanced cutaneous melanoma, HCC (33.3% each), NSCLC (26.7%), and SCCHN (18.2%). Moreover, in the PD-L1-positive subset, DCR-24w was highest ( $> 10\%$ ) in advanced cutaneous melanoma (66.7%), NSCLC (36.0%), HCC and bladder cancer (33.3% each), and SCCHN (18.2%).

### 2.2.3 Durvalumab Marketing Experience

Durvalumab has not been approved for marketing purposes anywhere in the world.

## 2.3 Tremelimumab

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

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production *in vitro* in whole blood or peripheral blood mononuclear cell (PBMC) cultures<sup>17</sup>. 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. Tremelimumab as monotherapy was recently evaluated in a randomized, double-blind, placebo-controlled study of patients with unresectable pleural or peritoneal mesothelioma (Study D4880C0003, NCT01843374) and unfortunately was found not to extend overall survival. However, when used in combination with durvalumab, it may lead to increased activation of the human immune system and increase anti-tumor activity in patients with mesothelioma.

### 2.3.1 Summary of Tremelimumab Pre-Clinical Studies

Tremelimumab selectively binds to human CTLA-4 and blocks binding of CD80 and CD86 and has been shown to enhance human T-cell cytokine release in response to stimulation. Both *in vitro* and *in vivo* preclinical data suggest that a range of anti-CTLA-4 MAb exposures have the potential to be efficacious, the lower end of the potentially efficacious range being a plasma concentration of approximately 10  $\mu\text{g/mL}$  and the target plasma concentration being 30  $\mu\text{g/mL}$ . The toxicology program conducted for tremelimumab consisted of *in vivo* general toxicology

studies in cynomolgus monkeys for up to 6-months duration, an embryo-fetal development study in monkeys, tissue cross-reactivity studies in both monkey and human tissues, and blood compatibility studies.

Overall, tremelimumab non-clinical toxicities were consistent with inhibition of CTLA-4 and with clinical safety findings, and indicated that chronic clinical use of tremelimumab may lead to adverse effects on the gastrointestinal tract, skin, lymphoid organs, thyroid tissues, and hematological systems. Dose-limiting toxicities identified in chronic toxicity studies in monkeys included skin rash and gastrointestinal effects. Most toxicities were reversible or showed a trend toward reversibility.

An embryo-fetal development study was conducted in pregnant cynomolgus monkeys during the period of organogenesis. Tremelimumab administered intravenously (IV) once weekly from Day 20 to Day 50 of gestation at doses of 0, 5, 15, or 30 mg/kg did not elicit maternal toxicity, developmental toxicity, or teratogenicity.

### 2.3.2 Tremelimumab Clinical Studies

An extensive program of 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 cut-off dates of 1 November 2015 (for all monotherapy studies) or 15 April 2015 to 12 July 2015 (for combination therapy studies), 34 sponsored clinical studies have been conducted as part of the tremelimumab development program. Of these, 13 studies have been completed and 21 are ongoing. As of 1 November 2015, 973 patients have received tremelimumab monotherapy in completed monotherapy trials, and 569 patients have been treated in the ongoing blinded phase IIb monotherapy study D4880C0003. A third ongoing monotherapy trial (D4884C00001) has yet to enroll. Additionally, 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 in these studies.

#### 2.3.2.1 Tremelimumab Pharmacokinetics

Population PK analysis of tremelimumab was performed on combined data from Phase I, Phase II, and Phase III studies (N=654) in patients with metastatic melanoma using nonlinear mixed-effects modeling in NONMEM software. A 2-compartment population PK model adequately described the plasma concentrations of tremelimumab following various dosing regimens.

The population estimate for clearance (CL) and central volume of distribution (V1) was 0.26 L/day and 3.97 L, respectively. The inter-individual variability in CL and V1 was modest (31.8% and 20.4%, respectively). Clearance was faster in males, patients with higher values of creatinine clearance and endogenous Ig, and patients with relatively poor baseline prognostic factors.

Central volume of distribution was higher in males and patients with higher body weight. No dose adjustment was needed based on the magnitude of the change in CL (< 30%)<sup>18</sup>. Preliminary population PK of tremelimumab was performed using data from two second-line, single-arm investigator-initiated Phase II studies (NCT01649024/NCT01655888) in patients with malignant mesothelioma. A total of 40 patients provided evaluable PK data following 15 mg/kg Q90D (NCT01649024) or 10 mg/kg Q4W for 6 months followed by 10 mg/kg Q12W (NCT01655888) dosing regimens.

Tremelimumab PK exposure in mesothelioma patients was similar to previous melanoma studies following 15 mg/kg Q90D. Following the 15 mg/kg Q90D, PK exposure was below the target trough level of approximately 30 µg/mL for about half of the dosing interval with almost all patients below the LLOQ at the end of the 90-day dosing interval. Following more frequent dosing of 10 mg/kg Q4W, PK exposure was increased and maintained at or above the target level in the majority of patients over the entire dosing interval. Tremelimumab PK was best described using a 2-compartment linear model with first order elimination. Following IV dosing, the typical CL and V<sub>1</sub> were 0.2 L/day and 3.5 L, respectively. The between-patient variability for CL and V<sub>1</sub> were 22% and 7%, respectively. The estimated typical PK parameters were similar to other mAbs without target mediated elimination. The baseline body weight and Eastern Cooperative Oncology Group (ECOG) performance status were identified as significant covariates for CL, whereas only baseline body weight was significant covariate for volume of distribution.

Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22.1 days. Overall, a low incidence of ADAs (<6%) was observed for treatment with tremelimumab.

#### 2.3.2.2 Absorption, Distribution, Metabolism, and Elimination of Tremelimumab

Tremelimumab is administered by IV infusion. The absorption of tremelimumab upon extravascular administration has not been investigated.

The mean V<sub>SS</sub> for tremelimumab is 81.2 mL/kg, which is typical of mAbs with limited distribution. No studies of human tissue distribution of tremelimumab have been conducted.

The mean CL for tremelimumab is 0.132 mL/hour/kg. Similar to other mAbs without target mediated drug disposition, tremelimumab is likely to be cleared from circulation by endothelial cell uptake and proteolysis. Since mAbs are not primarily cleared via hepatic/renal pathways, no impact of renal/hepatic functions is expected on tremelimumab elimination. No studies have been conducted in patients with renal/hepatic impairment.

#### 2.3.2.3 Tremelimumab Adverse Events

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. 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%) treated with tremelimumab monotherapy experienced at least 1 AE. Based on integrated data from the

completed and rollover tremelimumab monotherapy studies (N=973), AEs (all grades, regardless of severity) reported in >10% of patients were: diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.9%), pruritus (27.4%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.3%).

Adverse events were considered to be treatment related in 770 of the 973 patients (79.1%). Treatment-related AEs were reported at similar rates in the 10 and 15 mg/kg groups (81.8% and 80.0%, respectively), and were mostly Grade 1 or 2 in severity ( $\geq$ Grade 3 treatment-related AEs reported in 26.1% of patients). The most frequent treatment-related AEs (in >5% of patients) were diarrhea (41.2%), rash (27.2%), pruritus (25.2%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite (11.3%), headache (7.2%), pyrexia (7%), abdominal pain (6.7%), and colitis (5.5%).

Integrated data from completed studies of tremelimumab in combination with other agents (N=116) showed that AEs reported in >15% of patients (all grades, regardless of causality) included: diarrhea (54.3%), nausea (40.5%), fatigue (38.8%), rash (35.3%), pruritus and decreased appetite (30.2% each), vomiting (27.6%), pyrexia (26.7%), influenza-like illness (20.7%), arthralgia (19.8%), constipation (19%), thrombocytopenia and injection site reaction (18.1% each), and increased AST (15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations.

#### 2.3.2.4 Tremelimumab Serious Adverse Events

As of the data cutoff date of 1 November 2015, 355 patients (36.5%) had a total of 859 SAEs. The highest incidence of SAEs occurred in the 10 mg/kg group (42.9%), followed by the 15 mg/kg (36%) and All Doses <10 mg/kg (30.3%) groups. Serious adverse events experienced by >1% of patients were diarrhea, colitis, vomiting, disease progression, dehydration, pyrexia, nausea, abdominal pain, dyspnea, pneumonia, and confusional state. The majority of these events were  $\geq$  Grade 3 in severity and reported at a higher rate in the 15 mg/kg group.

A total of 451 SAEs in 197 patients (20.2%) were assessed as related to investigational product by the investigator. Treatment-related SAEs were reported in more patients in the 10 mg/kg group compared with the 15 mg/kg group (29.9% vs. 20%, respectively), and were  $\geq$  Grade 3 in severity in the majority of patients (84.8%). The most frequent treatment-related SAEs (occurring in >1% of patients) were: diarrhea (9.2%), colitis (3.6%), vomiting (2.3%), and nausea and dehydration (1.8% each).

#### 2.3.2.5 Tremelimumab Efficacy

Across the clinical development program for tremelimumab, a pattern of efficacy has emerged that is similar to that of the related anti-CTLA-4 antibody, ipilimumab. The efficacy of tremelimumab appears to be consistent across tumor types. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in patients who respond, the responses are generally durable, lasting several months even in those with aggressive tumors such as refractory metastatic melanoma. Moreover, a survival benefit was reported even in

patients without radiographic regression in tumor burden. In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg Q90D to patients with refractory melanoma, a response rate of 7% and median OS of 10 months in the second line setting (as compared to approximately 6 months with BSC reported from a retrospective analysis<sup>19</sup>) was observed<sup>20</sup>. In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg Q90D) versus chemotherapy (DTIC or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed a response rate of 11% and median OS of 12.58 months in this first-line setting (as compared to 10.71 months with standard chemotherapy)<sup>21</sup>. Additionally, in a Phase II maintenance study in NSCLC, PFS at 3 months was 22.7% in the tremelimumab arm compared with 11.9% in the BSC arm (Study A3671015).

### 2.3.3 Tremelimumab Marketing Experience

There is no marketing experience for tremelimumab.

## 2.4 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<sup>22</sup>; therefore, AstraZeneca is also investigating the use of durvalumab and tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/pharmacodynamics (PD), and preliminary anti-tumor activity of durvalumab and 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.

### 2.4.1 Durvalumab and Tremelimumab Pharmacokinetics

As of 20 Feb 2015, durvalumab PK (n = 55) and tremelimumab PK (n = 26) data were available from 10 cohorts of study D4190C00006 (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 ( $C_{max}$  and area under the concentration-time curve from 0 to 28 days [ $AUC_{0-28}$ ]) 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 20 Feb 2015, 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.

#### 2.4.2 Durvalumab and Tremelimumab Safety

A total of 102 subjects with advanced NSCLC have been treated with durvalumab and tremelimumab across 10 dose cohorts in Study D4190C00006. Across all dose cohorts, 95 of 102 subjects (93.1%) reported at least 1 AE (regardless of causality). AEs (all grades) reported in >10% subjects in decreasing order of frequency were diarrhea, fatigue, nausea, dyspnea, pruritus, rash, increased amylase, decreased appetite, pyrexia, increased ALT, cough, colitis, and increased lipase. 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 (14 of 18 subjects, 77.8%).

Thirty-one of 102 subjects (30.4%) experienced AEs that were Grade 1 or 2 in severity. These events were manageable by general treatment guidelines. Grade 3 or higher AEs were reported in 64 of 102 subjects (62.7%). These events occurring in > 5% of subjects were colitis (8.8%), diarrhea (8.8%), and increased lipase (5.9%). In addition,  $\geq$  Grade 3 events that were uncoded as of the data cut-off date were verbatim terms (VTs) of gastrohepatic mass resection, elective diagnostic surgical excision of cerebral lesion, and chest pain (all Grade 3 and not related to study treatment); disease progression in 3 subjects (Grade 5 and not related to study treatment); and Grade 5 neuromuscular disorder occurring 42 days after the last dose of durvalumab and considered related to study treatment.

Treatment-related AEs were reported in 74 of 102 subjects (73%). Of these subjects, 12 had Grade 1, 21 had Grade 2, 35 had Grade 3, 4 had Grade 4, and 2 had Grade 5 events as maximum severity. The treatment-related Grade 5 events were polymyositis and an uncoded event of neuromuscular disorder (VT). Treatment-related Grade 3 or higher events that occurred in 2 or more subjects were colitis (9 subjects); diarrhea (8 subjects); increased lipase (6 subjects); increased AST, and pneumonitis (4 subjects each); increased ALT and increased GGT (3 subjects each); and increased amylase, anemia, and increased blood alkaline phosphatase (2 subjects each). Safety data from the durvalumab 15 and 20 mg/kg Q4W cohorts demonstrated a numerical increase in the frequency of treatment-related AEs and AEs leading to discontinuation of investigational product with increasing doses (> 1 mg/kg) of tremelimumab.

Grade 1 or 2 AEs have been managed clinically without requiring dose modifications or delays. Treatment-related Grade 3 AEs have been manageable and reversible with standard toxicity management guidelines including steroids with the exception of 1 subject who experienced Grade 4 myasthenia gravis and polymyositis (with fatal outcome). This event was reported as an SAE (death).

Two subjects in the durvalumab 20 mg/kg plus tremelimumab 3 mg/kg Q4W cohort experienced DLTs. One subject had Grade 3 increased AST on Day 29 of Cycle 1; a second subject had Grade 3 increased amylase and Grade 4 increased lipase on Day 9 of Cycle 1.

A total of 56 subjects (54.9%) reported at least 1 SAE. Most commonly reported preferred terms (> 5%) were colitis (9.8%) and diarrhea (7.8%). SAEs that were not coded at the time of data cut-off were VTs of gastrohepatic mass resection, elective diagnostic surgical excision of cerebral lesion, neuromuscular disorder, progression of disease, progression of malignant neoplasm, and chest pain. The majority of subjects with SAEs (94.6%) had events of Grade 3 or higher severity. Thirty-six (35.3%) subjects experienced SAEs that were considered related to investigational products. Twenty-six subjects (25.5%) discontinued treatment due to SAEs of colitis (7 subjects); pneumonitis (5 subjects each); diarrhea (3 subjects); increased AST and dyspnea (2 subjects each); and pancreatitis, sepsis, increased ALT, arthralgia, malignant neoplasm progression, lung disorder, and NSCLC (1 subject each).

### 2.4.3 Durvalumab and Tremelimumab Efficacy

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.

## 2.5 Rationale

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<sup>23,24</sup>. Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In a study of an anti-PD-L1 therapy in patients with advanced unresectable mesothelioma, an ORR of 14.3% was observed among PD-L1 positive subjects and an 8% ORR was observed among PD-L1 negative subjects<sup>25</sup>. In addition, durvalumab monotherapy has shown durable responses in NSCLC in Phase 1 study, CD-ON-MEDI4736-1108.

The mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity<sup>22</sup>. 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<sup>26</sup>. Similar results have been observed in an ongoing study of durvalumab and tremelimumab in NSCLC<sup>27</sup>.

### 2.5.1 Durvalumab and Tremelimumab Combination Therapy Dose Rationale

A population PK model was developed for durvalumab using monotherapy data from the Phase 1 study, CD-ON-MEDI4736-1108 (N = 292; doses of 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of  $\leq 0.5$ ). The impact of body weight-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 weight of ~75 kg). A total of 1000 subjects were simulated using body weight distribution of 40 to 120 kg. Simulation results demonstrate that body weight-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 of 0.01 to 15 mg/kg Q4W or every 90 days; metastatic melanoma). The population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of  $\leq 0.5$ ). The weight-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body weight of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1,000 subjects with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body weight-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with a fixed dosing regimen.

Similar findings have been reported by others<sup>28-31</sup>. Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies<sup>29</sup>. 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 PK/pharmacodynamics parameters<sup>30</sup>.

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab is equivalent to 10 mg/kg Q2W, 1500 mg Q4W durvalumab is equivalent to 20 mg/kg Q4W, and 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

### 2.5.2 Rationale for 4 Cycles of Combination Therapy Followed by Durvalumab Monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up<sup>32</sup>.

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<sup>33-35</sup>. 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<sup>36</sup>.

MPDL3280A (anti-PD-L1) was evaluated in a phase I study in which patients were dosed for a finite time period. Responses were maintained beyond treatment discontinuation<sup>37</sup>. The same has been reported for combination therapy using nivolumab with ipilimumab<sup>26</sup>.

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

## **2.6 Correlative Studies Background**

Use of combination immune therapies in patients with mesothelioma presents a variety of confounding variables that could contribute to success or failure of the therapy. Correlative studies are designed to both enable better understanding of the possible reasons that durvalumab in combination with tremelimumab may prove to be effective or ineffective in individual patients, and to enable the development of more effective targeting strategies in the future.

### **2.6.1 Collection of Tumor Tissue**

In order to explore the determinants of response and resistance to combination durvalumab and tremelimumab therapy, archival tumor tissue will be collected at baseline from all patients enrolling to the trial. In addition, mandatory pre- and on-treatment fresh tumor biopsies will be obtained whenever clinically feasible from all patients enrolled. An optional final biopsy will be offered to all patients at the time of disease progression. The genetic and immune characteristics identified in the tumor tissue will be correlated to clinical outcome.

Analysis of tumor tissue samples taken at distinct points enables addressing of key questions including: (1) the genomic lesions and immune cell presence at baseline in samples studied and their potential impact upon response, (2) the identification of immediate gene pathways or immune expression programs activated by tumors following durvalumab and tremelimumab combination therapy, and (3) mechanisms of acquired resistance to therapy.

The first correlative question relates to the genetic and immune diversity of the patients enrolled in this study. It is the anticipation that most patients on this study will have had their tumor genomically characterized by either the OncoPanel test at DFCI/BWH (a custom hybrid capture panel which via next-generation sequencing [NGS] will identify mutations and copy-number alterations in cancer associated genes) or via another CLIA-certified method at the time of enrollment. These approaches have enabled comprehensive cataloguing of the mutations in multiple cancer types, thus greatly enhancing our understanding of the genetics and

biology of various malignancies<sup>38</sup>. The archival tissue collected will be analyzed retrospectively by immunohistochemistry (IHC) to examine expression of immune markers such as PD-L1 and CD3. The pre-treatment tumor biopsy will undergo immune profiling by flow cytometry at the immuno-oncology laboratory at the Belfer Center for Applied Cancer Science. The pre-treatment samples will be examined for immune cell subsets (including granulocytes, monocytes, neutrophils, lymphocytes, dendritic cells, and NK cells) as well as immune marker expression on those cells (e.g. PD-L1, PD-1, TIM-3, LAG-3, etc). Additional studies will include RNA analysis to explore gene expression changes and pathway adaptation on-treatment compared to pre-treatment. Advances in high-throughput genomic technologies have enabled an unprecedented understanding of the molecular basis of human cancers<sup>39</sup>. Techniques such as RNA sequencing and Nanostring have enabled highly quantitative assessment of the transcriptome of each tumor sample, thus permitting full analysis of the expression levels of various expressed transcripts.

Another key rationale for performance of biopsies in patients after initiating drug therapy is to address mechanisms of resistance to the combination therapy. The emergence of resistance to therapy is a profound problem in oncology. Such resistance can follow not only acquisition of secondary mutations but also from the ability of cancer cells to activate immediate compensatory mechanisms<sup>39</sup>. Identification of these compensatory reactions is a necessary step in order to design subsequent rational therapies that may lead to even more durable and long-lasting clinical benefit. As such, RNA sequencing will be repeated in the on-treatment biopsies. The expression of immune markers including PD-L1 is a dynamic process, as expression can be induced by activated tumor antigen-specific T cells and levels can also be influenced by prior treatment (including use of non-immune therapies such as tyrosine kinase inhibitors). Evaluation of immune markers at a single time point may not reflect an evolving immune response or predict response to PD-L1/PD-1 pathway blockades<sup>40,41</sup>. To account for these concerns, on-treatment biopsies will undergo repeat immune profiling to search for any changes in the tumor immune microenvironment from pre-treatment.

Optional biopsies obtained at the time of disease progression will be used to characterize the change in the tumor at the time of resistance. Such changes could stem from the acquisition of novel genomic alterations, from activation of compensatory signaling pathways, or the production of anti-inflammatory and immunosuppressive mediators. Biopsies obtained at progression will be submitted for NGS as well as immune profiling to again analyze for tumor immune cell subsets and immune marker expression by immunohistochemistry (IHC) staining. The information collected from these biopsies will be vital to understanding the methods of resistance to the combination therapy and planning subsequent treatment strategies in this population.

### 2.6.2 Non-Invasive Immunoprofiling

Peripheral blood mononuclear cells (PBMCs) will be collected from whole blood to assess immune cell populations and cytokines. Surface staining with a panel of antibodies and intracytoplasmatic cytokine staining followed by flow cytometry will be performed on the samples. Different T cell populations, their activation status, and the production of different cytokines as well as other immune cell populations including myeloid-derived suppressor cells (MDSCs) will be characterized. MDSCs are a heterogeneous group of immature cells which are

greatly expanded in experimental models of cancer. Studies in humans have reported increased frequencies as well as immune-suppressive properties in some of the myeloid-derived subsets of MDSCs present in the peripheral blood of patients with various forms of cancer, including mesothelioma<sup>42,43</sup>. To further explore the relationship of immune cell populations and their potential correlation to clinical outcomes, peripheral blood levels will be serially collected from patients enrolled to the trial.

### 3. PARTICIPANT SELECTION

#### 3.1 Eligibility Criteria

Baseline evaluations are to be conducted within two weeks prior to start of protocol therapy, with the exception of the informed consent and baseline imaging which must be done  $\leq 4$  weeks prior to the start of therapy.

- 3.1.1 Written informed consent obtained prior to any study-specific procedures not considered part of routine medical care.
- 3.1.2 Histologically or cytologically confirmed unresectable or medically inoperable malignant pleural mesothelioma.
- 3.1.3 Disease progression after treatment with at least one line of chemotherapy that included a platinum agent in combination with pemetrexed.
- 3.1.4 Participants must have measurable disease in at least one dimension of at least 10 mm in diameter or thickness, according to modified RECIST for pleural malignant mesothelioma.<sup>44</sup> Bone metastases are not considered measurable. Prior radiation to the only site of measurable disease will make the participant ineligible unless the lesion has been demonstrated to grow after completion of radiation therapy.
- 3.1.5 Participants must be willing and able to undergo a biopsy at the start of this study and an on-treatment biopsy if safe and feasible.
- 3.1.6 Participants must be  $\geq 28$  days from any major surgery.
- 3.1.7 ECOG performance status of 0 or 1. See **APPENDIX A**.
- 3.1.8 Participants must have normal organ and marrow function as defined below:
  - Absolute neutrophil count  $\geq 1.5$  K/uL
  - Platelets  $\geq 100$  K/uL
  - Hemoglobin  $\geq 9$  g/dL (with or without transfusion support)
  - Total bilirubin  $\leq 1.5 \times$  institutional upper limit of normal (ULN)
  - AST(SGOT)/ALT(SGPT)  $\leq 3 \times$  institutional ULN, unless liver metastases are present and then  $\leq 5 \times$  institutional ULN is acceptable

- Serum creatinine  $\leq 1.5 \times$  institutional ULN
- OR**
- Serum creatinine clearance  $>40$  mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance (see APPENDIX B Cockcroft-Gault equation for CREATININE CLEARANCE).

3.1.9 Age  $\geq 18$  years.

3.1.10 Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must agree to use at least one highly effective method of contraception (see **Table 2**) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of investigational product. Male partners of a female subject must also agree to use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as  $\geq 12$  months with no menses without an alternative medical cause).

3.1.11 Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 180 days after the last dose of investigational product. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period. Female partners of a male subject must use a highly effective method of contraception throughout this period. Highly effective methods of contraception are described in **Table 2**.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.1.13 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.

## 3.2 Exclusion Criteria

3.2.1 Previous treatment with a CTLA-4, PD-1, or PD-L1 inhibitor, including prior treatment with either durvalumab or tremelimumab.

- 3.2.2 Known central nervous system metastasis. Patients with known brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease may be enrolled if they have been treated, are no longer taking corticosteroids, and have been stable on imaging for at least 3 weeks.
- 3.2.3 Subjects currently receiving systemic corticosteroids above 10 mg daily of prednisone or equivalent for more than 14 days; subjects receiving other systemic immunosuppressive drugs greater than 10 mg prednisone or equivalent for more than 14 days. Exceptions include: inhaled, intranasal, ophthalmic, and topical corticosteroids, local corticosteroid injections (e.g., intra-articular injections), and subjects requiring corticosteroid pre-medication for hypersensitivity reactions (e.g. CT scan premedication).
- 3.2.4 Subjects with medical conditions that require the chronic use of systemic corticosteroids. Exceptions include: inhaled, intranasal, ophthalmic, and topical corticosteroids, local corticosteroid injections (e.g., intra-articular injections), and subjects requiring corticosteroid pre-medication for hypersensitivity reactions (e.g. CT scan premedication).
- 3.2.5 Active or prior documented autoimmune disease within the past 2 years, including but not limited to systemic lupus erythematosus, sarcoidosis syndrome, or Wegener's granulomatosis. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment within the past 2 years are not excluded.
- 3.2.6 Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis), or any other chronic, serious GI condition associated with diarrhea. NOTE: Subjects with known diverticulosis are permitted to enroll.
- 3.2.7 History of interstitial lung disease or pneumonitis that has required steroid administration.
- 3.2.8 History of primary immunodeficiency.
- 3.2.9 History of allogeneic organ transplant.
- 3.2.10 History of hypersensitivity to tremelimumab, durvalumab, or any excipient.
- 3.2.11 Known history of active tuberculosis.
- 3.2.12 Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab.

- 3.2.13 Participants with a history of a second primary malignancy. Exceptions include: patients with a history of malignancies that were treated curatively and have not recurred within 5 years prior to study entry; resected basal and squamous cell carcinomas of the skin, and completely resected carcinoma *in situ* of any type.
- 3.2.14 Participants who have had chemotherapy, biologic therapy, or investigational therapy within 21 days (including bevizumab) or radiotherapy within 7 days prior to entering the study or those who have not recovered to CTCAE  $\leq$  grade 1 or baseline from adverse events due to agents administered.
- 3.2.15 Any history of a prior  $\geq$  grade 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent.
- 3.2.16 Participants who are receiving any other investigational agents.
- 3.2.17 Uncontrolled intercurrent illness including, but not limited to:
- Ongoing or active infection
  - Gastritis
  - Symptomatic congestive heart failure
  - Severe hypertension (defined as BP  $\geq$  160/100 during the screening period despite optimal medical management)
  - Unstable angina pectoris
  - Cardiac arrhythmia
  - Active bleeding diatheses
  - Active peptic ulcer disease
  - Psychiatric illness/social situations that would limit compliance with study requirements
- 3.2.18 Mean QT interval corrected for heart rate (QTc)  $\geq$ 470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction
- 3.2.19 Known HIV-positive participants are ineligible because these participants are at increased risk of lethal infections. Appropriate studies will be undertaken in participants receiving combination antiretroviral therapy when indicated.
- 3.2.20 Participants with known acute or chronic hepatitis B or hepatitis C.
- 3.2.21 Pregnant women are excluded from this study because tremelimumab and durvalumab have unknown effects on the developing fetus. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with tremelimumab or durvalumab, breastfeeding women are also excluded. Female subjects of child bearing potential must have a negative serum pregnancy test obtained prior to trial registration.

3.2.22 Participants who are involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

3.2.23 Participants who have undergone a pneumonectomy due to known potential for pulmonary toxicities and heightened risk for complications.

### **3.3 Inclusion of Women and Minorities**

Both men and women of all races and ethnic groups are eligible for this trial.

## **4. REGISTRATION PROCEDURES**

### **4.1 General Guidelines for DF/HCC Institutions**

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

### **4.2 Registration Process for DF/HCC Institutions**

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

## **5. TREATMENT PLAN**

### **5.1 Treatment Regimen**

One cycle is defined as 28 consecutive days. Participants will receive durvalumab and tremelimumab both via IV infusion on day 1 of each cycle. Participants will receive tremelimumab for up to 4 cycles (4 doses). Beginning with cycle 5 day 1, participants will continue to receive durvalumab alone (as monotherapy).

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in **Section 7**. Appropriate dose modifications are described in **Section 6**. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy, with the exception of palliative

radiation therapy or surgical resection to non-target lesions. Bisphosphonate use is permitted.

## 5.2 Duration of Treatment and Criteria for Retreatment

Participants who are tolerating durvalumab monotherapy without evidence of disease progression per modified RECIST criteria for mesothelioma may continue to receive durvalumab as monotherapy indefinitely or until other criteria for discontinuation are met (see **Section 5.6**).

Participants experiencing either confirmed or unconfirmed PD during the durvalumab monotherapy portion of the trial may undergo retreatment with tremelimumab (once only) if they meet the retreatment criteria below. The same treatment guidelines followed during the initial treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments, with the exception that participants undergoing retreatment are not required to undergo additional tumor biopsies.

1. The patient has not received any other anticancer treatments for their disease (with the exception of palliative radiation or surgical procedures as allowed per protocol).
2. The patient does not meet any of the other investigational product discontinuation criteria (**Section 5.6**).
3. Absence of clinical symptoms or signs indicating clinically significant disease progression.
4. No decline in ECOG performance status compared to baseline.
5. Absence of rapid PD or threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention.
6. All AEs while receiving initial therapy must have resolved to  $\leq$  Grade 1 or baseline. Must not have experienced a  $\geq$  Grade 3 AE, or pneumonitis or neurologic AE of any grade while receiving initial therapy. Note: Subjects with an endocrine AE of any grade are permitted to be retreated if they are stably maintained on appropriate replacement therapy and are asymptomatic.
7. Must not have used additional immunosuppression other than corticosteroids for the management of an AE, must not have experienced recurrence of an AE if rechallenged, and not currently requiring maintenance doses  $> 10$  mg prednisone or equivalent per day.
8. The patient has had a tumor imaging assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial treatment period (relative to the date of registration) until study treatment is stopped.

During the retreatment period, patients may resume tremelimumab dosing at 75 mg once every 4 weeks for 4 doses while continuing to receive durvalumab once every 4 weeks. Patients will then continue with durvalumab monotherapy at 1500 mg once every 4 weeks, beginning 4 weeks after the last dose of combination therapy.

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

with a confirmed progression receiving durvalumab plus tremelimumab cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy and progression occurs in a target lesion that has previously shown a confirmed response. Patients who the Overall PI (in communication with AstraZeneca) and/or the treating investigator determine may not continue treatment will enter follow-up.

Subjects should be made aware of the potential benefits and risks of continuing study regimens in the setting of confirmed or suspected PD leading to retreatment by providing separate written informed consent. Subjects will only be eligible for one retreatment opportunity.

### 5.3 Pre-Treatment Criteria

#### 5.3.1 Cycle 1, Day 1

Patients who completed screening assessments >72 hours prior to cycle 1 day 1 must have cycle 1 day 1 laboratory values that re-meet eligibility criteria. If screening assessments were completed ≤ 72 hours prior to cycle 1 day 1, laboratory tests do not need to be repeated on cycle 1 day 1 and the screening laboratory values can be used as the cycle 1 day 1 values.

If patients have cycle 1 day 1 labs performed, review of results by the treating investigator prior to dosing is required for the following tests: complete blood count with differential (CBC), blood urea nitrogen (BUN), serum creatinine, electrolytes, and liver function tests.

#### 5.3.2 Subsequent Cycles

Management of specific toxicities considered at least possibly related to tremelimumab and/or durvalumab are outlined in **Section 6**.

### 5.4 Agent Administration

<b>Table 1: Treatment Regimen Description</b>					
<b>Agent</b>	<b>Premedications/ Precautions</b>	<b>Dose</b>	<b>Route</b>	<b>Schedule</b>	<b>Cycle Length</b>
Tremelimumab	None	75 mg	IV over 1 hour (± 5 min)  Administer <b>prior to</b> durvalumab	Day 1 for 4 cycles	28 days (4 weeks)
Durvalumab	None	1500 mg	IV over 1 hour (± 5 min)  Begin infusion 1 hour <b>after</b>	Day 1	

			completion of tremelimumab ( $\pm$ 10 min)		
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#### 5.4.1 Tremelimumab

Tremelimumab will be administered first. Participants will receive 75 mg tremelimumab via IV infusion on day 1 of each cycle for up to 4 cycles (once every 4 weeks for up to 4 doses). Tremelimumab should be infused over 1 hour; there is a  $\pm$  5 minute infusion window. Tremelimumab will be administered at room temperature 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 using a 0.2 or 0.22- $\mu$ m in-line filter.

The IV line should be flushed with a volume of IV solution (0.9% 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.

#### 5.4.2 Durvalumab

Participants will receive 1500 mg durvalumab via IV infusion on day 1 of each cycle (once every 4 weeks). Durvalumab infusion will start 1 hour after the end of the tremelimumab infusion ( $\pm$ 10 minute window). Durvalumab should be infused over 1 hour; there is a  $\pm$  5 minute infusion window. Durvalumab will be administered at room temperature 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 using a 0.2 or 0.22- $\mu$ m in-line filter.

The IV line should be flushed with a volume of IV solution (0.9% 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.

#### 5.4.3 Post-Infusion Observation Period

A 1 hour observation period is required after the completion of the first infusions of both durvalumab and tremelimumab ( $\pm$ 10 minute window). If no clinically significant infusion reactions are observed during or after the first infusions, subsequent infusion observation periods can be at the treating investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

### 5.5 General Concomitant Medication and Supportive Care Guidelines

The treating 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.

#### 5.5.1 Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in **Section 5.5.2**.

#### 5.5.2 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 any stated protocol specified therapies. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy). Bisphosphonate use is permitted.
3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg per day, methotrexate, azathioprine, and TNF- $\alpha$  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, topical, ophthalmic, and intranasal corticosteroids is permitted, along with local steroid injections.
4. Live attenuated vaccines within 30 days of durvalumab and tremelimumab dosing (i.e., 30 days prior to the first dose, during treatment with durvalumab and tremelimumab, and for 30 days post discontinuation of durvalumab and tremelimumab). Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

#### 5.5.3 Highly Effective Methods of Contraception

Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must agree to use at least one highly effective method of contraception from the time of screening and must agree to continue using such precautions for 180 days after the last dose of investigational product. Male partners of a female subject must also agree to use male condom plus spermicide throughout this period.

Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 180 days after the last dose of investigational product. Female partners of a male subject must use a highly effective

method of contraception throughout this period.

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).

<b>Table 2: Highly Effective<sup>a</sup> Methods of Contraception</b>	
<b>Barrier/Intrauterine Methods</b>	<b>Hormonal Methods</b>
<ul style="list-style-type: none"> <li>• Copper T intrauterine device</li> <li>• Levonorgestrel-releasing intrauterine system (eg, Mirena<sup>®</sup>)<sup>b</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Etonogestrel implants: e.g. Implanon or Norplan</li> <li>• Intravaginal device: e.g. ethinylestradiol and etonogestrel</li> <li>• Medroxyprogesterone injection: e.g. Depo-Provera</li> <li>• Normal and low dose combined oral contraceptive pill</li> <li>• Norelgestromin/ethinylestradiol transdermal system</li> <li>• Cerazette (desogestrel)</li> </ul>

<sup>a</sup> Highly effective (i.e. failure rate of <1% per year)

<sup>b</sup> This is also considered a hormonal method

## 5.6 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely as described in **Section 5.2** or until one of the following criteria applies:

- Disease progression (exception for allowed retreatment as described in **Section 5.2**).
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

The research team will update the relevant Off Treatment information in OnCore.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Mark Awad MD, PhD at 617-632-3468.

### **5.7 Duration of Follow Up**

Participants will be followed until death after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.

### **5.8 Criteria for Taking a Participant Off Study**

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

The research team will update the relevant Off Study information in OnCore.

## **6. DOSING DELAYS**

Dose delays will be made as indicated in the following tables. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for dose delays. A copy of the CTCAE version 4.03 can be downloaded from the CTEP website:

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

For adverse events (AEs) that are considered at least partly due to administration of durvalumab or tremelimumab the following dosing 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.
- The maximum amount of time that durvalumab and tremelimumab can be held before a participant is permanently withdrawn from the study is 56 days.
- In the event that the treating investigator believes a toxicity to be related to tremelimumab and not to durvalumab, the treating investigator may opt to discontinue tremelimumab and continue with durvalumab as monotherapy once the toxicity has resolved to  $\leq$  Grade 1 or baseline. If tremelimumab is discontinued prematurely due to toxicity, it may not be reinstated.
- If tremelimumab dosing is held but toxicity does not necessitate discontinuation of the study agent, participants may receive the 4 total doses of tremelimumab (i.e. the tremelimumab infusion may be given upon acceptable resolution of the adverse event rather than omitted or skipped entirely).

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 delayed based on toxicities observed (see **Tables 3 - 6**). **Dose reductions of either durvalumab or tremelimumab 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 delay requirements and toxicity management guidelines for immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions are detailed in **Tables 3 - 6**.

In addition, reporting guidelines for adverse events of special interest (AESIs) and serious adverse events (SAEs) are detailed in **Sections 7.4, 7.5, 7.9, 7.10, and 7.11**.

## **6.1 Toxicity Management Guidelines**

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
<b>Pneumonitis / ILD</b>	<p>All participants should be monitored 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 clinically indicated.</p> <p>Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan as determined by the treating investigator.</p>		
	Grade 1	<p>No dose delay required.</p> <p>However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies.</p>	<p>Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated.</p> <p>Consider pulmonary and infectious disease consult.</p>
	Grade 2	<p>Hold study drug/study regimen dose.</p> <ul style="list-style-type: none"> <li>• If toxicity worsens then treat as Grade 3 or Grade 4</li> <li>• If toxicity improves to baseline then the decision to reinstate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment.</li> </ul> <p>Study drug/study treatment can be resumed at the next</p>	<p>Monitor symptoms daily and consider hospitalization as clinically appropriate.</p> <p>Promptly start systemic steroids (e.g., prednisone PO 1-2mg/kg/day [or equivalent] or IV equivalent).</p> <p>Reimage as clinically indicated.</p> <p>If no improvement within 5 days, additional work-up should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started (or equivalent).</p> <p>If still no improvement within 5 days despite IV methylprednisolone at 2-</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>scheduled dose once event stabilizes to grade <math>\leq 1</math> and at least 5 days have passed after completion of steroid taper.</p>	<p>4/g/kg/day (or equivalent), promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks or equivalent). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.</p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)<sup>45</sup>.</p> <p>Consider pulmonary and infectious disease consult.</p> <p>Consider as necessary discussing with Overall PI.</p>
	<p><math>\geq</math> Grade 3</p>	<p>Permanently discontinue study drug/study regimen.</p>	<p>Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.</p> <p>Obtain pulmonary and infectious disease consults as clinically indicated.</p> <p>Hospitalize the patient as clinically appropriate.</p> <p>Provide supportive care (oxygen,</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			<p>etc.).</p> <p>If no improvement within 5 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose or equivalent) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.</p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)<sup>45</sup>.</p>
<p><b>Diarrhea / Enterocolitis</b></p>			<p>All participants should be monitored 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).</p> <p>Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.)</p> <p>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.</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
<p>Use analgesics carefully; they can mask symptoms of perforation and peritonitis.</p>			
<p>Grade 1 diarrhea</p>			
<p>Grade 2 diarrhea</p>		<p>Hold study drug/study regimen</p> <ul style="list-style-type: none"> <li>• If toxicity worsens then treat as Grade 3 or Grade 4</li> <li>• If toxicity improves then treat at next scheduled treatment date</li> </ul> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> and at least 5 days have passed after completion</p>	<p>Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide or equivalent. Use of probiotics as per treating physician's clinical judgment.</p> <p>Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide or equivalents.</p> <p>Promptly start prednisone 1 to 2 mg/kg/day or equivalent.</p> <p>If event is not responsive within 5 days or worsens despite prednisone at 1-2 mg/kg/day or equivalent, consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		of steroid taper.	<p>with IV methylprednisolone 2-4mg/kg/day (or equivalent) started.</p> <p>If still no improvement within 5 days despite 2-4mg/kg IV methylprednisolone (or equivalent), promptly start immunosuppressives such as infliximab at 5mg/kg once every 2 weeks (or equivalent).            Caution: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.</p> <p>Consider consulting Overall PI if no resolution to <math>\leq</math> Grade 1 in 5 days.</p> <p>Once improving, gradually taper steroids over <math>\geq</math>28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p>
	Grade $\geq$ 3 diarrhea	Permanently discontinue study drug/study regimen	<p>Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent.</p> <p>Monitor stool frequency and volume and maintain hydration.</p> <p>Consider urgent GI consult and imaging and/or colonoscopy as appropriate.</p>

<b>Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions</b>			
<b>Toxicity</b>	<b>Grade of the Event (NCI CTCAE version 4.03)</b>	<b>Dose Modifications</b>	<b>Toxicity Management</b>
			<p>If no improvement within 5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). Caution: Rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.</p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals, and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p>
<b>Hepatitis (Elevated AST [SGOT], ALT [SGPT], and/or total bilirubin)</b>  <i>Note: Infliximab should not be used for management of Immune Related Hepatitis</i>	Grade 1	No dose delay required.  If it worsens, treat as Grade 2 event.	Monitor and evaluate liver function tests: AST, ALT, alkaline phosphatase (ALP) and total bilirubin as per protocol.  Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 2	Hold study drug/study regimen dose.  <ul style="list-style-type: none"> <li>• If toxicity worsens then treat as Grade 3 or Grade 4</li> <li>• If improves to baseline then treat at next</li> </ul>	Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations are improving or resolved.  If no resolution to $\leq$ Grade 1 or baseline in 2 days, discuss with the Overall PI.

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>scheduled treatment date.</p> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> or baseline and at least 5 days have passed after completion of steroid taper.</p>	<p>If event is persistent (&gt;5 days) or worsens, promptly start prednisone 1-2mg/kg/day or IV equivalent.</p> <p>If still no improvement within 5 days despite 1-2mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day or equivalent.</p> <p>If still no improvement within 5 days despite 2-4mg/kg/day of IV methylprednisolone or equivalent, promptly start immunosuppressives (mycophenolate mofetil<sup>1</sup> or equivalent). <b>Infliximab should NOT be used.</b></p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p>
	Grade 3	<p>For elevations in transaminases <math>\leq 8 \times</math> ULN, or elevations in bilirubin <math>\leq 5 \times</math> ULN:</p> <ul style="list-style-type: none"> <li>• Hold study drug/study regimen</li> </ul>	<p>Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.</p> <p>If still no improvement within 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent,</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>dose until resolution to <math>\leq</math> Grade 1 or baseline</p> <ul style="list-style-type: none"> <li>Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade <math>\leq</math> Grade 1 or baseline within 14 days</li> </ul> <p>Permanently discontinue study drug/study regimen if the elevations do not downgrade to <math>\leq</math> Grade 1 or baseline within 14 days.</p> <p>For elevations in transaminases <math>&gt; 8 \times</math> ULN or elevations in bilirubin <math>&gt; 5 \times</math> ULN, discontinue study drug/study regimen.</p> <p>Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT <math>&gt; 3x</math> ULN + bilirubin <math>&gt; 2x</math> ULN without initial findings of cholestasis [i.e. elevated alkaline P04] and in the absence of any alternative cause<sup>46</sup>).</p>	<p>promptly start treatment with immunosuppressive therapy (mycophenolate mofetil or equivalent). <b>Infliximab should NOT be used.</b></p> <p>Consider hepatology consult, abdominal work-up, and imaging as appropriate.</p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p>

<b>Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions</b>			
<b>Toxicity</b>	<b>Grade of the Event (NCI CTCAE version 4.03)</b>	<b>Dose Modifications</b>	<b>Toxicity Management</b>
	Grade 4	Permanently discontinue study drug/study regimen.	<p>Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.</p> <p>If still no improvement within 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil or equivalent). <b>Infliximab should NOT be used.</b></p> <p>Consider hepatology consult, abdominal work-up, and imaging as appropriate.</p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p>
<b>Nephritis or Renal Dysfunction (Elevated Serum Creatinine)</b>			<p>For elevations of serum creatinine of any grade, consider consulting with a nephrologist as clinically appropriate.</p> <p>Monitor for signs and symptoms that may be related to changes in renal function (e.g. elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalances, decrease in urine output, proteinuria, etc.).</p> <p>Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.).</p> <p>Steroids should be considered in the absence of clear alternative etiology even</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
for low grade events (Grade 2) in order to prevent potential progression to higher grade event.			

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> and at least 5 days have passed after completion of steroid taper.</p>	<p>If event is persistent (<math>&gt;5</math> days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent.</p> <p>If event is not responsive within 5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day (or equivalent) started.</p> <p>Once improving gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p> <p>When event returns to baseline or <math>\leq</math> grade 1, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.</p>
	Grade 3 or 4	Permanently discontinue study drug/study regimen	<p>Carefully monitor serum creatinine on a daily basis.</p> <p>Consider consulting a nephrologist and consider renal biopsy if clinically indicated.</p> <p>Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent.</p> <p>If event is not responsive within 3-5</p>

<b>Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions</b>			
<b>Toxicity</b>	<b>Grade of the Event (NCI CTCAE version 4.03)</b>	<b>Dose Modifications</b>	<b>Toxicity Management</b>
			<p>days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day (or equivalent) started.</p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p>
<b>Rash (excluding bullous skin formations)</b>	<p>All participants should be monitored for signs and symptoms of dermatitis (rash and pruritus).</p> <p><b>**IF THERE IS ANY BULLOUS FORMATION, THE OVERALL PI SHOULD BE CONTACTED AND STUDY DRUG DISCONTINUED**</b></p>		
	Grade 1	No dose delay.	Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	<p>For persistent (&gt;2 weeks) grade 2 events, hold scheduled study drug/study regimen until resolution to <math>\leq</math> Grade 1 or baseline.</p> <ul style="list-style-type: none"> <li>• If toxicity worsens then treat as Grade 3</li> <li>• If toxicity improves then resume</li> </ul>	<p>Obtain dermatology consult as clinically indicated.</p> <p>Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine or equivalents) and topical therapy (e.g., urea cream or equivalent).</p> <p>Consider moderate-strength topical steroid.</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>administration at next scheduled dose</p> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> or baseline and 7 days have passed after completion of steroid taper.</p>	<p>If no improvement of rash/skin lesions occurs within 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with Overall PI and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent.</p> <p>Consider skin biopsy if persistent for &gt;2 weeks or recurs.</p>
	Grade 3	<p>Hold study drug/study regimen until resolution to <math>\leq</math> Grade 1 or baseline.</p> <p>If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to <math>\leq</math> Grade 1 or baseline within 30 days, then permanently discontinue study drug/study regimen.</p>	<p>Consult dermatology as clinically indicated.</p> <p>Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.</p> <p>Consider hospitalization if clinically indicated.</p> <p>Consider skin biopsy (preferably more than 1) as clinically feasible.</p>
	Grade 4	Permanently discontinue study drug/study regimen	<p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p>

<b>Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions</b>			
<b>Toxicity</b>	<b>Grade of the Event (NCI CTCAE version 4.03)</b>	<b>Dose Modifications</b>	<b>Toxicity Management</b>
			Discuss with Overall PI.
<b>Endocrinopathy</b>  (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	<p>For patients experiencing endocrinopathy of any grade, consider consulting with an endocrinologist as clinically appropriate.</p> <p>All patients should be monitored patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness.</p> <p>Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.)</p> <p>Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy.</p> <p>If a patient experiences an AE of any grade that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.</p>		
	Grade 1  (including those with asymptomatic TSH elevation)	No dose delay.	<p>Monitor patient with appropriate endocrine function tests.</p> <p>If TSH &lt; 0.5X LLN, or TSH &gt;2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.</p>
	Grade 2	For endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is	<p>Initiate hormone replacement as needed for management.</p> <p>Evaluate endocrine function, and as clinically indicated, consider pituitary scan.</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>clinically stable.</p> <ul style="list-style-type: none"> <li>• If toxicity worsens then treat as Grade 3 or Grade 4</li> <li>• If toxicity improves to baseline then treat at next scheduled treatment date</li> </ul> <p>Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids.</p> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> and at least 5 days have passed after completion of steroid taper.</p> <p>Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen</p>	<p>For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones).</p> <p>Once improving, gradually taper steroids over <math>\geq 28</math> days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p> <p>For patients with normal endocrine work-up (lab or MRI scans), repeat labs/MRI as clinically indicated.</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>on the following conditions:</p> <ol style="list-style-type: none"> <li>1) The event stabilizes and is controlled</li> <li>2) The patient is clinically stable as per treating physician's clinical judgement</li> <li>3) Doses of prednisone are at less than or equal to 10mg/day or equivalent.</li> </ol>	
	Grade 3 or 4	<p>For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled.</p> <p>Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids.</p>	<p>Consult endocrinologist as clinically appropriate.</p> <p>Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.</p> <p>Administer hormone replacement therapy as necessary.</p> <p>For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity.</p> <p>Once improving, gradually taper immunosuppressive steroids over <math>\geq 4</math> weeks and consider prophylactic antibiotics, antifungals and anti PCP</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>Resume study drug/study regimen administration if controlled at the next scheduled dose.</p> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> and at least 5 days have passed after completion of steroid taper.</p>	<p>treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<sup>45</sup>.</p> <p>Discuss with Overall PI.</p>
<p><b>Immune-mediated Neurotoxicity</b>            (to include but not limited to limbic encephalitis, autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)</p>		<p>All patients with suspected immune-mediated neurotoxicity of any grade should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations). Utilize appropriate symptomatic treatment with neurological consult as indicated.</p> <p>All patients should be monitored for general symptoms (headache, nausea, vertigo, behavior change, or weakness).</p>	
	Grade 1	No dose delay.	See recommendations above.
	Grade 2	<p>For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to <math>\leq</math> Grade 1.</p> <p>For sensory</p>	<p>Discuss with the Overall PI.</p> <p>Obtain Neurology Consult as indicated.</p> <p>Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin,</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>neuropathy/ neuropathic pain, consider holding study drug/study regimen dose until resolution to <math>\leq</math> Grade 1.</p> <ul style="list-style-type: none"> <li>• If toxicity worsens then treat as Grade 3 or Grade 4</li> <li>• If toxicity improves to baseline then treat at next scheduled treatment date</li> </ul> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> and at least 5 days have passed after completion of steroid taper.</p>	<p>duloxetine, etc.).</p> <p>Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent.</p> <p>If no improvement within 5 days despite 1-2mg/kg/day prednisone or IV equivalent consider additional work-up and promptly treat with additional immunosuppressive therapy (e.g. IVIG or equivalent).</p>
	Grade 3	<p>Hold Study drug/study regimen dose until resolution to <math>\leq</math> Grade 1.</p> <p>Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to <math>\leq</math> Grade 1 within 30 days.</p>	<p>Discuss with Overall PI.</p> <p>Obtain Neurology Consult as indicated.</p> <p>Consider hospitalization as clinically appropriate.</p> <p>Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.</p>

<b>Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions</b>			
<b>Toxicity</b>	<b>Grade of the Event (NCI CTCAE version 4.03)</b>	<b>Dose Modifications</b>	<b>Toxicity Management</b>
			<p>If no improvement within 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG or equivalent).</p> <p>Once stable, gradually taper steroids over <math>\geq 4</math> weeks.</p>
	Grade 4	Permanently discontinue study drug/study regimen	<p>Discuss with Overall PI.</p> <p>Obtain Neurology Consult as indicated.</p> <p>Consider hospitalization as clinically appropriate.</p> <p>Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.</p> <p>If no improvement within 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG or equivalent).</p> <p>Once stable, gradually taper steroids over <math>\geq 4</math> weeks.</p>
<b>Immune-mediated peripheral neuromotor</b>	<p>The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly</p>		

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
<p><b>syndromes such as Guillain-Barre and Myasthenia Gravis</b></p>	<p>progressive weakness, and signs of respiratory insufficiency or autonomic instability.</p> <p>All patients experiencing signs or symptoms should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult.</p> <p>Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and “repetitive stimulation” if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.</p> <p>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 IVIG and followed by plasmapheresis if not responsive to IVIG.</p>		
	Grade 1	No dose delay.	<p>Discuss with the Overall PI.</p> <p>Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.</p> <p>Obtain a neurology consult unless the symptoms are very minor and stable.</p>
	Grade 2	Hold study drug/study regimen dose until resolution to $\leq$ Grade 1.	<p>Discuss with the Overall PI.</p> <p>Care should be taken to monitor patients for sentinel symptoms of a</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		<p>Permanently discontinue study drug/study regimen if it does not resolve to <math>\leq</math> Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.</p>	<p>potential decompensation as described above.</p> <p>Obtain a Neurology Consult as clinically indicated.</p> <p>Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.).</p> <p><i>MYASTHENIA GRAVIS:</i></p> <p>Steroids may be successfully used to treat Myasthenia Gravis. 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.</p> <p>Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.</p> <p>If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			<p>to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.</p> <p><i>GUILLAIN-BARRE:</i></p> <p>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 IVIG and followed by plasmapheresis if not responsive to IVIG.</p>
	Grade 3	<p>Hold study drug/study regimen dose until resolution to <math>\leq</math> Grade 1.</p> <p>Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to <math>\leq</math> Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability</p>	<p><b>For severe or life threatening events:</b></p> <p>Discuss with Overall PI.</p> <p>Recommend hospitalization.</p> <p>Monitor symptoms and obtain neurological consult as indicated.</p> <p><i>MYASTHENIA GRAVIS:</i></p> <p>Steroids may be successfully used to</p>

**Table 3: Dosing Modification and Toxicity Management Guidelines for Specific Immune-mediated Adverse Reactions**

Toxicity	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 4	Permanently discontinue study drug/study regimen	<p>treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist.</p> <p>Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG.</p> <p>If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.</p> <p><i>GUILLAIN-BARRE:</i></p> <p>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 IVIG and followed by plasmapheresis if not responsive to IVIG.</p>

**Table 4: Toxicity Management Guidelines for Immune-related Adverse Events not Otherwise Noted**

Adverse Event	Dose Modifications	Toxicity Guidance
<b>Immune-related Adverse Events not Otherwise Noted</b>	<p>In addition to the above criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (<b>Table 3</b>), <b>permanently discontinue</b> study drug/study regimen for the following conditions:</p> <ul style="list-style-type: none"> <li>• Inability to reduce corticosteroid to a dose of <math>\leq 10</math> mg of prednisone per day (or equivalent) <b>within 56 days</b> after last dose of study drug/regimen</li> <li>• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.</li> </ul>	<p>Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.).</p> <p><b>In the absence of a clear alternative etiology, all events should be considered potentially immune related.</b></p> <p>Symptomatic and topical therapy should be considered for low-grade events (Grade 1 or 2, unless otherwise specified).</p> <p>For persistent (greater than 5 days) low-grade (Grade 2) or severe (Grade <math>\geq 3</math>) events promptly start prednisone PO (or equivalent) 1-2mg/kg/day or IV equivalent.</p> <p>If symptoms recur or worsen during corticosteroid tapering (<math>&lt; 28</math> days of taper), increase the corticosteroid dose until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (<math>\geq 28</math> days of taper)</p> <p>More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) should be considered for events not responding to systemic steroids (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive).</p>
	<p>Grade 1: No dose delay.</p>	
	<p>Grade 2: Hold study drug/study regimen dose until resolution to <math>\leq</math> Grade 1 or baseline.</p> <ul style="list-style-type: none"> <li>• If toxicity worsens then treat as Grade 3 or Grade 4</li> <li>• If toxicity improves to baseline then treat at next scheduled treatment date</li> </ul> <p>Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq 1</math> or baseline and at least 5 days have passed after completion of steroid taper.</p> <p>Patients with endocrinopathies who may require prolonged or continued steroid</p>	

<b>Table 4: Toxicity Management Guidelines for Immune-related Adverse Events not Otherwise Noted</b>			
<b>Adverse Event</b>	<b>Dose Modifications</b>		<b>Toxicity Guidance</b>
		<p>replacement can be retreated with study drug/study regimen on the following conditions:</p> <ol style="list-style-type: none"> <li>1) The event stabilizes and is controlled</li> <li>2) The patient is clinically stable as per treating physician's clinical judgment</li> <li>3) Doses of prednisone are at less than or equal to 10mg/day or equivalent.</li> </ol>	<p>Note: Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient made by the treating investigator.</p>
	Grade 3	<p>Hold study drug/study regimen until resolution to <math>\leq</math> Grade 1 or baseline.</p> <p>For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen. If complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen.</p> <p>Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade <math>\leq</math> 1 or baseline and at least 5 days have passed after completion of steroid taper.</p>	
	Grade 4	<p>Permanently discontinue study drug/study regimen.</p> <p>For Grade 3 and above</p>	

<b>Table 4: Toxicity Management Guidelines for Immune-related Adverse Events not Otherwise Noted</b>		
<b>Adverse Event</b>	<b>Dose Modifications</b>	<b>Toxicity Guidance</b>
	asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen.	

<b>Table 5: Dosing Modification and Toxicity Management Guidelines for Infusion-Related Reactions</b>		
<b>Severity Grade</b>	<b>Dose Modifications</b>	<b>Toxicity Management</b>
<p><b>Management of any infusion-related reaction should be per institutional standard at the discretion of the treating investigator.</b></p> <p>Monitor all patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.).</p>		
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event.	<p>For Grade 1 or Grade 2:</p> <p>Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator.</p> <p>Consider premedication per institutional standard prior to subsequent doses.</p>
Grade 2	<p>The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event.</p> <p>Subsequent infusions may be given at 50% of the initial infusion rate.</p>	
Grade $\geq$ 3	Permanently discontinue study drug/study regimen.	Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

<b>Table 6: Dosing Modification and Toxicity Management Guidelines for Non-Immune Mediated Reactions</b>		
<b>CTC Grade/Severity</b>	<b>Dose Modification</b>	<b>Toxicity Management</b>
Note: dose delays are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant. At the treating investigator's discretion, study medication dosing may be held for toxicity considered unlikely related or unrelated to study treatment. In the event of a dosing delay for unrelated adverse events, the maximum amount of time either study medication may be held is 28 days.		
Grade 1	No dose adjustment	Treat accordingly as per institutional standard.
Grade 2	At the treating investigator's discretion, study drug/regimen may be held until resolution to $\leq$ Grade 1 or baseline.	Treat accordingly as per institutional standard
Grade 3	Hold study drug/study regimen until resolution to $\leq$ Grade 1 or baseline.  For AEs that downgrade to $\leq$ Grade 2 within 7 days or resolve to $\leq$ Grade 1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. Otherwise, discontinue study drug/study regimen.	Treat accordingly as per institutional standard
Grade 4	Discontinue Study drug/study regimen.  Note for grade 4 laboratory abnormalities, decision to discontinue would be based on accompanying clinical signs/symptoms and as per treating investigator's clinical judgment and in consultation with the Overall PI.	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.

**6.2 Overdose**

There are no known antidotes for over-dosage of tremelimumab or durvalumab. In the case of suspected overdose, monitor hematologic parameters, serum chemistries, vital signs, cardiac and pulmonary function, and provide supportive care as necessary. See reporting requirements in

## Section 7.9.

### 7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (**Section 7.1**) and the characteristics of an observed AE (**Sections 7.3, 7.4, 7.5, and 7.10**) will determine whether the event requires expedited reporting **in addition** to routine reporting.

#### 7.1 Expected Toxicities

##### 7.1.1 Adverse Event List for Durvalumab

Potential risks, based on the mechanism of action of durvalumab and related molecules, include immune-mediated reactions, such as colitis, pneumonitis, hepatitis/hepatotoxicity (elevations in ALT, AST, ALP, and/or total bilirubin), 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.

AEs that have occurred in durvalumab monotherapy trials and have been assessed to have at least a reasonable possibility of a causal relationship to durvalumab include:

- Very common (> 10/100)
  - Diarrhea
- Common (> 1/100 and <10/100)
  - ALT increased
  - AST increased
  - Pneumonitis
- Uncommon (> 1/1,000 to <1/100)
  - Colitis

The majority of diarrhea, ALT increased, AST increased, and pneumonitis events were reported to be mild to moderate in severity (CTCAE Grades 1/2), while for colitis the majority of events were reported to be moderate to severe (Grades 2/3). Please also refer to the Investigator's Brochure (IB).

##### 7.1.2 Adverse Event List for Tremelimumab

Immune-mediated reactions, also considered to be adverse events of special interest or immune related adverse events (irAEs), are important risks of immune checkpoint inhibitors such as tremelimumab that can result in an inflammatory response in any organ or tissue including the liver, gastrointestinal tract, thyroid glands, pancreas, skin, nervous system, hematopoietic system, respiratory tract, kidney, and adrenal glands.

Potential immune-mediated reactions associated with tremelimumab include the following:

- Gastrointestinal events including colitis, 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 hyper- 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, Guillain-Barre and myasthenia gravis (the latter reported with combination of tremelimumab and durvalumab)
- Cytopenias including thrombocytopenia, anemia and neutropenia

Additional risks that are common to any immunoglobulin include infusion-related reactions, anaphylaxis, and serious acute IgE-mediated allergic reactions. These reactions may occur, may be severe, and may result in death.

Other potential risks identified with tremelimumab include headache, fatigue, and pyrexia. Please also refer to the IB.

### 7.1.3 Adverse Event List for Durvalumab and Tremelimumab Combined

Common (>10 % of subjects) treatment-related AEs of any grade occurring among subjects treated with the combination of durvalumab and tremelimumab include:

- Diarrhea
- Fatigue
- Increased amylase and pruritus
- Rash
- Colitis
- Increased lipase

## 7.2 Definition of Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an adverse event (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. The term disease progression should not be reported as an AE or serious adverse event (SAE), however, medically significant individual events and/or laboratory abnormalities associated with disease progression (see definition of disease progression below) that fulfill the AE or SAE definition should be reported. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (e.g., renal failure, hematuria) not the laboratory abnormality (e.g., elevated creatinine, urine red blood cell increased).

AEs may be treatment emergent (i.e., occurring after initial receipt of investigational product) or non-treatment emergent. A non-treatment-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 non-serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

### **Adverse Events Associated with Disease Progression**

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of a new metastasis or progression of existing metastasis related to the primary cancer under study should not be considered an AE. Death clearly resulting from disease progression should NOT be reported as an SAE (see reporting guidelines in **Section 7.4**).

### **New Cancers**

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the investigational product and have been identified after the subject's inclusion in the study. New metastatic lesion(s) of the subject's known cancer should NOT be reported as a new cancer.

## **7.3 Adverse Event Characteristics**

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

#### 7.4 Serious Adverse Events

A serious adverse event (SAE) is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject 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.

#### 7.5 Time Period for Collection of Adverse Events

Adverse events will be collected from the time treatment, , throughout the treatment period and including the follow-up period of 30 days after the last dose of durvalumab and tremelimumab, or at the start of a new treatment

Serious adverse events will be recorded from the time treatment through 30 days after the last dose of durvalumab and tremelimumab or the start of new treatment.

#### 7.6 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 AEs or SAEs occurring in former study subjects after the 90-day safety follow-up period. 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 the investigational product, the investigator should notify the Overall PI and AstraZeneca or its

representative.

## 7.7 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are to be followed by the investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

## 7.8 Reporting of Serious Adverse Events to AstraZeneca

Investigators must report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment.

The Overall PI is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH guidelines and/or local regulatory requirements. The Overall PI may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the Overall PI or AstraZeneca/MedImmune as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying the Overall PI and MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to both the Overall PI and MedImmune Patient Safety within 24 hours of learning of the new information.

## 7.9 Other Events Requiring Immediate Reporting

### 7.9.1 Overdose

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

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event** to AstraZeneca/MedImmune Patient Safety or designee using the Safety Fax Notification Form (see **Section 7.8** for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF. 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 7.4** and **Section 7.9**).

### 7.9.2 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to AstraZeneca/MedImmune are defined as any increase in ALT or AST to greater than  $3 \times$  institutional ULN and concurrent increase in bilirubin to greater than  $2 \times$  ULN (i.e., Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE. Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" **within 24 hours of knowledge of the event** to the Overall PI and AstraZeneca/MedImmune representative(s) as an SAE (see **Section 7.9**). The investigator will review the data with AstraZeneca/MedImmune. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by AstraZeneca/MedImmune. If the etiology of the event remains unconfirmed and/or is considered related to investigational product, a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune safety review committee (or equivalent) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the MedImmune safety review committee (or equivalent) is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities including IRBs/IECs will be notified of any actions taken with the study.

### 7.9.3 Pregnancy

If pregnancy occurs in a female subject who has received investigational product, the investigator or other site personnel must inform the Overall PI as well as the appropriate AstraZeneca/MedImmune study representative(s) **within 24 hours** of when he or she becomes aware of it.

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 MedImmune Patient Safety or designee after outcome.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product this should be reported **within 24 hours of knowledge of the event** to MedImmune Patient Safety or designee using the Safety Fax Notification Form (see **Section 7.8** for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

#### 7.9.4 Pneumonitis

Adverse events of pneumonitis are required to be reported **within 24 hours of knowledge of the event** to the Overall PI and MedImmune Patient Safety or designee using the Safety Fax Notification Form (see **Section 7.9** for contact information).

### 7.10 Expedited Adverse Event Reporting

7.10.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after informed consent, during treatment, or within 90 days of the last dose of treatment on the local institutional SAE form.

#### 7.10.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

### 7.11 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

Any reports filed with the FDA should also be sent to AstraZeneca/MedImmune (see **Section 7.9** for contact information).

### 7.12 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

### 7.13 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

## 8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in **Section 7.1**.

### 8.1 Durvalumab

#### 8.1.1 Description

Durvalumab (laboratory code MEDI4736) is a human IgG1 $\kappa$  monoclonal antibody (mAb) selected from a panel of hybridomas secreting human antibodies recognizing human PD-L1. The antibody-coding deoxyribonucleic acid (DNA) sequence was recovered from a selected hybridoma and engineered by recombinant DNA technology to introduce a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to complement protein C1q and the Fc $\gamma$  receptors involved in triggering effect or function. Functional binding properties of the modified antibody were confirmed. An expression plasmid was prepared for durvalumab production in Chinese hamster ovary (CHO) cells. Durvalumab is selective for human PD-L1 and blocks the binding of human PD-L1 to the human PD-1 and CD80 receptors.

#### 8.1.2 Form

Durvalumab is formulated at 50 mg/mL. The investigational product is supplied as a 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. 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.

#### 8.1.3 Storage and Stability

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiration date on the label.

#### 8.1.4 Compatibility

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

#### 8.1.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

### 8.1.6 Availability

Durvalumab is an investigational product that will be provided by AstraZeneca.

### 8.1.7 Preparation

The dose of durvalumab for administration must be prepared by the Investigator's or site's designated investigational product (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.

A dose of 1500 mg durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22- $\mu$ m in-line filter. Remove 30 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30 mL of durvalumab (i.e., 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

### 8.1.8 Administration

Durvalumab infusion will start 1 hour after the end of the tremelimumab infusion ( $\pm$ 10 minute window). Durvalumab should be infused over 1 hour; there is a  $\pm$  5 minute infusion window. Durvalumab will be administered at room temperature 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 using a 0.2 or 0.22- $\mu$ m in-line filter.

The IV line should be flushed with a volume of IV solution (0.9% 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. Please see **Section 5**.

### 8.1.9 Ordering

Drug supply will be ordered from AstraZeneca or its designee by site pharmacy personnel.

### 8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

### 8.1.11 Destruction and Return

Expired supplies of durvalumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. At the end of the study, unused supplies of durvalumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## 8.2 Tremelimumab

### 8.2.1 Description

Tremelimumab is a human IgG2 mAb directed against CTLA-4. Tremelimumab has an overall molecular weight of approximately 149 kDa including oligosaccharides. CTLA-4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to CD80 and CD86 ligands on antigen-presenting cells, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to CD80/86, leading to prolongation and enhancement of T-cell activation and expansion.

Tremelimumab is produced in accordance with current Good Manufacturing Practices. Tremelimumab is expressed in a NS0 (murine myeloma) cell line. It is purified using 3 chromatography steps, a virus inactivation step, and a virus reduction filtration step.

### 8.2.2 Form

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 dehydrate, pH 5.5.

The Drug Product is supplied as a sterile liquid solution containing 400 mg (nominal) tremelimumab per vial. The nominal fill volume is 20.0 mL.

### 8.2.3 Storage and Stability

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab must be used within the individually assigned expiry date on the label.

#### 8.2.4 **Compatibility**

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed.

#### 8.2.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

#### 8.2.6 **Availability**

Tremelimumab is an investigational product provided by AstraZeneca.

#### 8.2.7 **Preparation**

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 2°C-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 30 minutes prior to administration.

Tremelimumab does not contain preservatives and any unused portion must be discarded.

Doses of 75 mg tremelimumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.1 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 (i.e., 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/mL to 10 mg/mL (IV bag volumes 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

#### 8.2.8 **Administration**

Tremelimumab should be infused over 1 hour; there is a ± 5 minute infusion window. Tremelimumab will be administered at room temperature 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 using a 0.2 or 0.22- $\mu$ m in-line filter.

The IV line should be flushed with a volume of IV solution (0.9% 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. Please see **Section 5**.

### 8.2.9 **Ordering**

Drug supply will be ordered from AstraZeneca or its designee by site pharmacy personnel.

### 8.2.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

### 8.2.11 **Destruction and Return**

Expired supplies of tremelimumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form. At the end of the study, unused supplies of tremelimumab should be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

## **9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES**

### **9.1 Tumor Tissue Collection**

#### 9.1.1 Archival Tissue

Baseline archival tissue will be collected from all patients enrolling to the trial. Patients who do not have archival tissue available or who do not have sufficient tissue for analysis may be enrolled at the treating investigator's discretion.

A minimum of 10 unstained slides should be obtained for analysis. Slides should be labeled with the protocol number and study subject number and sent to:

Belfer Center for Applied Cancer Science  
Dana-Farber Cancer Institute  
360 Longwood Ave, LC4210

Boston, MA 02215

### 9.1.2 Fresh Tumor Biopsies

Mandatory pre- and on-treatment fresh tumor biopsies will be obtained from patients enrolling to the trial. In the event the biopsy is not clinically feasible in the opinion of the treating investigator or interventionalist performing the procedure, exceptions to one or both fresh biopsy requirements are possible after discussion with the principal investigator.

The pre-treatment biopsy should be obtained following consent and prior to the first dose of any study medication (prior to Cycle 1 Day 1). The on-treatment biopsy may be obtained anytime between Cycle 2 Day 1 (after completion of the study medication infusions) to Cycle 2 Day 8.

An additional optional biopsy at the time of disease progression will also be offered to patients if deemed clinically feasible by the treating investigator. In patients undergoing re-treatment with tremelimumab, the time of progression biopsy may be obtained either prior to the initiation of re-treatment or upon progression following re-treatment. Preferably, time of progression biopsies should be obtained prior to the initiation of another cancer treatment. However, in the event that it is not possible to perform the biopsy before another treatment is begun, the biopsy can be obtained up to 60 days after the last dose of study medication.

Pre- and on-treatment core biopsy samples a minimum of 2 cores should be collected, if clinically feasible. A 16-18 gauge needle are preferable, but a 20 gauge core needle biopsy is also acceptable. For more information, please refer to the Thoracic Oncology Program 16-549 Biopsy Collection Guidelines. In the event that not enough tissue is obtained, priority should go to immune profiling.

If a core biopsy is judged to be too unsafe or difficult for the participant in the opinion of the treating investigator, a fine needle aspirate (FNA) or cytology sample can also be collected. The goal for a thoracentesis or paracentesis procedure will be 500 – 1000 mL collected in a standard collection tube. The goal for an FNA will be three distinct passes. Less than the goal amount of tissue is acceptable for any of the biopsy collection methods, and should be based upon the clinical judgment of the treating investigator and the clinician performing the procedure.

All tumor biopsy samples should be labeled with the protocol number, study subject number, date of collection, and identified as either “pre-treatment,” “on-treatment,” or “time of progression.”

Samples should be sent to:

Belfer Center for Applied Cancer Science  
Dana-Farber Cancer Institute  
360 Longwood Ave, LC4210

Boston, MA 02215

For time of progression core biopsy samples:

- Two (2) biopsy samples should be formalin-fixed and paraffin embedded per institutional standards for NGS.
- Two (2) should be placed in media (DMEM + 10% FBS) on wet ice (4°C) and delivered to the immuno-oncology laboratory at the Belfer Center for Applied Cancer Science for immune profiling.

In the event that not enough tissue is obtained, priority should go to providing the samples for NGS.

Immune samples should be sent to:

Belfer Center for Applied Cancer Science  
Dana-Farber Cancer Institute  
360 Longwood Ave, LC4210  
Boston, MA 02215

Samples for NGS should be sent to the Center for Advanced Molecular Diagnostics (CAMD) at Brigham and Women's Hospital.

For cytology samples:

- Cytology samples should be made into paraffin blocks per institutional standards.

## **9.2 Laboratory Correlative Studies**

Peripheral blood mononuclear cell (PBMC) samples will be collected at baseline (on Cycle 1 Day 1 prior to the first dose of study medication), on Cycle 2 Day 1, at visits following restaging scans, and at the off study visit. Samples collected on days where study medication dosing will occur can be collected anytime pre-dosing.

Collection and Shipping Procedure:

1. Blood samples should be labeled with the protocol number, study subject number, date of the draw, visit day (i.e. "C1D1" or "C2D1"), and labeled as "PBMC."
2. Draw venous blood into four 10 mL EDTA tubes and immediately gently invert the tube 3-4 times.
3. Send tubes to the CIO lab for processing within 6 hours of blood draw (tubes sent outside of this window due to shipping or scheduling difficulties will not be considered protocol violations but every effort should be made to get the samples to the laboratory within 6 hours of draw time):

ATTN: CIO Laboratory Manager  
Center for Immuno-Oncology Laboratory  
Jimmy Fund Building Room 406  
1 Jimmy Fund Way  
Boston, MA 02115

## **10. STUDY CALENDAR**

Baseline evaluations are to be conducted within two weeks prior to start of protocol therapy, with the exception of the informed consent and baseline imaging which must be done  $\leq 4$  weeks prior to the start of therapy.

**Assessments must be performed prior to administration of any study agent.**

**Table 7: Study Calendar**

	Pre-Study	Cycle 1 Day 1	Cycle 1 Day 15 <sup>H</sup>	Cycle 2 Day 1 <sup>I</sup>	Cycle 3 Day 1 <sup>I</sup>	Cycle 4 Day 1 <sup>I</sup>	Day 1 of Each Subsequent Cycle (after Cycle 4) <sup>I</sup>	Off Treatment <sup>J</sup>	Every 3 Months after Discontinuing <sup>K</sup>
Tremelimumab <sup>A</sup>		X		X	X	X			
Durvalumab <sup>A</sup>		X		X	X	X	X		
Informed consent	X								
Demographics	X								
Medical history	X								
Concurrent meds	X	X-----X						X	
Tumor Biopsy <sup>B</sup>	X			X				X	
Physical exam	X	X	X	X	X	X	X	X	
Vital signs <sup>C</sup>	X	X	X	X	X	X	X	X	
Height	X								
Weight	X	X	X	X	X	X	X	X	
ECOG Performance status	X		X	X	X	X	X	X	
CBC w/diff. plts	X	X	X	X	X	X	X	X	
Serum chemistry <sup>D</sup>	X	X	X	X	X	X	X	X	
Urinalysis (with microscopy)	X								
EKG <sup>E</sup>	X								
Serum β-hCG <sup>F</sup>	X								
Adverse event evaluation	X	X-----X						X	
Tumor measurements	X	Tumor measurements are repeated every 8 weeks, there is a ± 7 day window. Documentation (radiologic) must be provided for participants removed from study for progressive disease.						X	
Radiologic evaluation	X	CT or MRI imaging of any disease-involved site. Radiologic measurements should be performed every 8 weeks, there is a ± 7 day window.						X	
Blood immune analysis <sup>G</sup>		X		X	X		As indicated in footnote G.	X	



**Table 7: Study Calendar**

	Pre-Study	Cycle 1 Day 1	Cycle 1 Day 15 <sup>H</sup>	Cycle 2 Day 1 <sup>I</sup>	Cycle 3 Day 1 <sup>I</sup>	Cycle 4 Day 1 <sup>I</sup>	Day 1 of Each Subsequent Cycle (after Cycle 4) <sup>I</sup>	Off Treatment <sup>J</sup>	Every 3 Months after Discontinuing <sup>K</sup>
Telephone or Care Provider Contact									X
<p>A. As described in <b>Section 5</b>.</p> <p>B. Fresh tumor biopsy to be performed at baseline, anytime between cycle 2 day 1 (following study medication administration) and cycle 2 day 8, and at the off study visit as described in <b>Section 9.1</b>. Off study biopsy should be collected prior to the initiation of another anticancer treatment whenever feasible, or within 60 days of the last dose of study medication. Biopsy time points should be followed from C1D1 regardless of drug holds or delays.</p> <p>C. Vital signs to consist of heart rate, respiratory rate, blood pressure, temperature, and oxygen saturation (O<sub>2</sub> sat). On infusion days, vital signs are to be collected anytime pre-infusion (exact time of vital signs should be recorded). May be repeated as clinically indicated.</p> <p>D. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase, and TSH.</p> <p>E. Triplicate EKG to be performed at baseline. EKGs should be obtained after participant has been resting for a minimum of 5 minutes. Each EKG of the triplicate should be separated by at least one minute and not more than 5 minutes. Subsequent EKGs to be performed as clinically indicated.</p> <p>F. Serum pregnancy test for women of childbearing potential. Childbearing potential defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal (defined as ≥ 12 months with no menses without an alternative medical cause).</p> <p>G. Blood immune analysis as described in <b>Section 9.2</b>. Samples to be collected prior to the administration of either of the study medications on Cycle 1 Day 1, Cycle 2 Day 1, at visits following restaging scans (e.g. cycle Cycle 3 Day 1, Cycle 5 Day 1, and so on), and at the Off Study visit.</p> <p>H. A ± 3 day scheduling window exists for Cycle 1 Day 15 to accommodate adverse weather, vacations, clinic schedule, or holidays.</p> <p>I. A +7 day window exists for day 1 of each subsequent cycle following cycle 1 to accommodate adverse weather, vacations, clinic schedule, or holidays.</p> <p>J. Off-treatment evaluation. Note: follow-up visits or other contact are required in order to identify SAEs during the 90 days following the end of study treatment.</p> <p>K. Participants will be followed until death or withdrawal of consent after removal from protocol therapy. This follow up will be performed by review of the medical record, contact with care providers, and/or telephone contact as needed every 3-4 months.</p>									

## 11. MEASUREMENT OF EFFECT

### 11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for mesothelioma (version 1.1).<sup>44</sup>

Tumor thickness perpendicular to the chest wall or mediastinum is measured in two positions at three separate levels on transverse cuts of a CT scan. The sum of the six measurements defines a pleural unidimensional measure. Transverse cuts at least 1 cm apart and related to anatomical landmarks in the thorax are chosen to allow reproducible assessment at later time points. If measureable tumor is present, transverse cuts in the upper thorax, above the level of division of the main bronchi are preferred. At reassessment, pleural thickness is measured at the same position at the same level. This is not necessarily the greatest tumor thickness at that level. Nodal, subcutaneous and other bidimensionally measurable lesions are measured unidimensionally as per the RECIST 1.1 criteria. Unidimensional measurements are added to obtain the total tumor measurement.

#### 11.1.1 Definitions

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

Evaluable Non-Target Disease Response. Participants 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 re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

#### 11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension of at least 10 mm in diameter or thickness with CT scan, MRI, or 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 might or might not be



considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be  $\geq 15$  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  $\geq 10$  to  $< 15$  mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered 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 participant, 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.

### 11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers,

or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and  $\geq 10$  mm in 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 thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- (a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- (b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial

abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

MIBG (meta-iodobenzylguanidine). The following is recommended, to assure high quality images are obtained.

Patient preparation: Iodides, usually SSKI (saturated solution of potassium iodide), are administered to reduce thyroidal accumulation of free radioiodine, preferably beginning the day prior to injection and continuing for 3 additional days (4 days total). For infants and children, one drop t.i.d. is sufficient, for adolescents 2 drops t.i.d., and for adults 3 drops t.i.d. Participants and/or parents are asked about exposure to potential interfering agents. If none is noted, an indwelling intravenous line is established. The dose of MIBG is administered by slow intravenous injection over 90 seconds.

Images from the head to the distal lower extremities should be obtained.

I-123MIBG scintigraphy is performed to obtain both planar and tomographic images.

Planar: Anterior and posterior views from the top of the head to the proximal lower extremities are obtained for 10 minutes at 24 hours and occasionally at 48 hours following injection of 10 mCi/1.7 square meters of body surface area (~150 µCi/kg, maximum 10 mCi). Anterior views of the distal lower extremities are adequate. A large field of view dual head gamma camera with low energy collimators is preferred.

**SPECT:** Most participants receiving I-123 MIBG also undergo SPECT at 24 hours, using a single or multi-headed camera with a low energy collimator. The camera is rotated through 360 degrees, 120 projections at 25 seconds per stop. Data are reconstructed using filtered back projections with a Butterworth filter and a cut off frequency of 0.2-0.5. SPECT/CT may be performed at institutions with this capacity.

**Ultrasound.** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

**Endoscopy, Laparoscopy.** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

**Tumor markers.** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

**Cytology, Histology.** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

#### 11.1.4 Response Criteria

##### 11.1.4.1 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 total tumor measurement.

Progressive Disease (PD): At least a 20% increase in the total tumor measurement, 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.

#### 11.1.4.2 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 tumor markers are initially above the upper normal limit, they 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 tumor marker level above the normal limits.

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).

#### 11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered. Timing of the follow up evaluation should be performed at the discretion of the treating investigator and no more than 8 weeks following the date of the imaging that identified the potential new lesion.

#### 11.1.4.4 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 Participants with Measurable Disease (i.e., Target Disease)

<b>Table 8: Criteria for Participants with Measurable Disease</b>				
<b>Target Lesions</b>	<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>	<b>Best Overall Response when Confirmation is Required</b>
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	
* 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.				
<u>Note:</u> Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “ <i>symptomatic deterioration.</i> ” Every effort should be made to document the objective progression even after discontinuation of treatment.				

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

<b>Table 9: Criteria for Participants with Non-Measurable Disease</b>		
<b>Non-Target Lesions</b>	<b>New Lesions</b>	<b>Overall Response</b>
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

#### 11.1.5 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

#### 11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

#### 11.1.7 Response Review

Evaluation of scans will be done centrally at the DFCI using the Tumor Imaging Metrics Core.

## 12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in **Section 7** (Adverse Events: List and Reporting Requirements).

## **12.1 Data Reporting**

### **12.1.1 Method**

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

### **12.1.2 Responsibility for Data Submission**

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

## **12.2 Data Safety Monitoring**

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

## **13. STATISTICAL CONSIDERATIONS**

We will employ a Simon's 2-stage design to test the hypothesis that durvalumab and tremelimumab improve response rates in this patient population to 35%, compared to a historical control rate of 16%. In the first stage we will enroll 19 patients, and if 4 or more patients among those 19 respond to therapy (with either a complete or partial response), we will open the 2nd stage of accrual to enroll an additional 21 patients, making a total sample size of 40 patients. If fewer than 4 patients experience a response in the first stage then the study will be stopped. In order to declare study success, a total of 10 or more responses must be observed among all 40 study participants. This design has a 0.64 probability of stopping early under the null, and has 90% power while maintaining an overall one-sided type I error rate of 0.08.

### *Statistical Analysis Plan for Correlative Studies:*

Data from correlative studies will be summarized using descriptive statistics. Associations

between immune cell subsets, immune marker expression, and the characteristics of the PBMCs will be compared to clinical outcome, will be summarized by descriptive methods, and may be explored graphically.

We assume that 80% of patients (n=32) will be successfully biopsied at multiple time points and have tumors that yield valid results from the laboratory.

When comparing baseline, on-treatment, and time of progression genomic and immune results, it is of interest to identify new alterations that were not present at baseline. Initial analyses of these data will utilize tests for association comparing the frequency of a particular genomic or immune aberration at baseline, on-treatment, and at progression (for example, using McNemar's test) and association between alterations and baseline characteristics (for example, using Fisher's exact test). For non-normal distributions (% T-cell infiltrate), we will explore associations with the presence or absence of a genomic or immune feature using non-parametric analysis for subgroup comparisons (Wilcoxon rank-sum or Kruskal-Wallis). Fisher's exact test will be used for discrete comparisons of categorical immune and clinical variables (such as PD-L1 positive vs. negative). More sophisticated analyses may include multivariable logistic regression modeling and/or competing risks analysis, however it is expected that analyzable results will not be obtained from all patients (either due to things like assay failure, inability to biopsy at progression due to poor patient health, etc).

With at least 32 patients included in the correlative analysis, this sample size provides 84% power to detect differences in the rate of another binary variable (such as baseline characteristics or abnormality) with frequencies of 8% and 60%, respectively, while testing with a one-sided 0.10-level Fisher's exact test; this also assumes that the underlying prevalence of the genomic marker is 50%, thus splitting the cohort into two groups with 16 patients in each. It is worth noting that the Fisher's test for association between the presence/absence of baseline samples and resistant samples assumes independence between those samples. Given what is known about tumor heterogeneity, the likelihood that the cancer may be altered genomically over time and due to therapy, and the low chance that the same area of a patient's tumor will be biopsied at both time points, this seems like a reasonable assumption.

### 13.1 Study Design/Endpoints

#### *Primary Efficacy Measure:*

- Investigate the ORR in patients with malignant pleural mesothelioma.

#### *Secondary Efficacy Measures:*

- Evaluate the safety and tolerability of tremelimumab in combination with durvalumab.
- Determine the OS, PFS, and DoR in patients with malignant pleural mesothelioma.

#### *Exploratory Endpoints:*

- Investigate the immunologic determinants of primary response and resistance to tremelimumab in combination with durvalumab in malignant pleural mesothelioma
- Investigate the immunologic mechanisms of acquired resistance to tremelimumab in

- combination with durvalumab
- Investigate genomic correlates of response to tremelimumab in combination with durvalumab

### 13.2 Sample Size, Accrual Rate and Study Duration

The planned total sample size is 40 patients in this single-arm, phase 2 study of durvalumab and tremelimumab in patients with malignant pleural mesothelioma. The planned accrual rate is approximately 5 patients per quarter. Up to an additional year of follow-up will be required on the last participant accrued to observe the patient’s response and survival following study therapy, for a total study length of approximately three years.

<b>Table 10: Accrual Targets</b>					
<b>Ethnic Category</b>	<b>Sex/Gender</b>				
	<b>Females</b>		<b>Males</b>		<b>Total</b>
Hispanic or Latino	1	+	3	=	4
Not Hispanic or Latino	9	+	27	=	36
<b>Ethnic Category: Total of all subjects</b>	10 (A1)	+	30 (B1)	=	40 (C1)
<b>Racial Category</b>					
American Indian or Alaskan Native	0	+	0	=	0
Asian	1	+	2	=	3
Black or African American	1	+	2	=	3
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	8	+	26	=	34
<b>Racial Category: Total of all subjects</b>	10 (A2)	+	30 (B2)	=	40 (C2)

(A1 = A2)                      (B1 = B2)                      (C1 = C2)

### 13.3 Analysis of Primary and Secondary Endpoints

The primary and secondary analyses will include all eligible patients who started assigned therapy. The exception to this includes the planned analysis of toxicity data, which will include all patients who received study drug regardless of eligibility. Response will be assessed using the modified RECIST criteria for mesothelioma; toxicity will be graded using CTCAE v. 4.03.

For the analysis of the response efficacy measures, participants will be censored if they are alive and without disease progression at the date of the last disease evaluation. In the case of OS, participants will be censored if they are living at the date last known alive.

Time-to-event data, such as PFS and OS, will be estimated using the Kaplan-Meier method, and Cox proportional hazards models will be used to estimate hazard ratios. Comparisons of groups will be made using the logrank test and Cox modeling.

Categorical data, such as response rates (CR+PR) and toxicity, will be compared using Fisher's exact tests with a one-sided type I error rate of 10%; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes. Though none are currently planned, any continuous outcomes will be analyzed using Wilcoxon rank sum test, and multivariable linear regression models may be used to adjust for multiple associations with outcome.

Modeling procedures will implement backward selection; variables significant at the 0.10 level in the univariate setting will be chosen for inclusion in an initial full model, and at each step the least significant variable will be removed from the model. Only those covariates with  $p < 0.05$  will remain in any final models, unless there are factors identified by the study team as crucial to model interpretation.

Point estimates of all endpoints will be accompanied by the corresponding two-sided 80% confidence intervals. The method of Atkinson and Brown will be used for the estimation of the confidence interval for response.

In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned because we do not anticipate an excess of missing data.

Subset analyses are planned for all known prognostic factors, such as performance status, age, sites of metastases, gender, etc. Subset analyses of all variables, including correlatives, are considered to be exploratory in nature.

## **13.4 Reporting and Exclusions**

### **13.4.1 Evaluation of Toxicity**

All participants will be evaluable for toxicity from the time of their first dose of study medication.

### **13.4.2 Evaluation of the Primary Efficacy Endpoint**

All eligible participants included in the study will be assessed for response, even if there are major protocol therapy deviations. Each participant should be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.

#### **14. PUBLICATION PLAN**

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

## REFERENCES

1. Vogelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2003;21(14):2636-2644.
2. Stebbing J, Powles T, McPherson K, et al. The efficacy and safety of weekly vinorelbine in relapsed malignant pleural mesothelioma. *Lung cancer*. 2009;63(1):94-97.
3. Zauderer MG, Kass SL, Woo K, Sima CS, Ginsberg MS, Krug LM. Vinorelbine and gemcitabine as second- or third-line therapy for malignant pleural mesothelioma. *Lung cancer*. 2014;84(3):271-274.
4. Evan A, Molife RL, Santoro A, et al. Clinical safety and efficacy of pembrolizumab (MK-3475) in patients with malignant pleural mesothelioma: Preliminary results from KEYNOTE-028 [abstract]. *Cancer Research*. 2015;75(15s).
5. Mansfield AS, Roden AC, Peikert T, et al. B7-H1 expression in malignant pleural mesothelioma is associated with sarcomatoid histology and poor prognosis. *Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer*. 2014;9(7):1036-1040.
6. Stewart R, Mullins S, Watkins A, Morrow M. Preclinical modelling of immune checkpoint blockade (P2012). Vol 190. *The Journal of Immunology*2013.
7. Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. *Med Oncol*. 2011;28(3):682-688.
8. Hirano F, Kaneko K, Tamura H, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. *Cancer Res*. 2005;65(3):1089-1096.
9. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proc Natl Acad Sci U S A*. 2002;99(19):12293-12297.
10. Okudaira K, Hokari R, Tsuzuki Y, et al. Blockade of B7-H1 or B7-DC induces an anti-tumor effect in a mouse pancreatic cancer model. *Int J Oncol*. 2009;35(4):741-749.
11. Bennett F, Luxenberg D, Ling V, et al. Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses. *J Immunol*. 2003;170(2):711-718.
12. Carter L, Fouser LA, Jussif J, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. *Eur J Immunol*. 2002;32(3):634-643.
13. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunol Rev*. 2008;224:166-182.
14. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*. 2000;192(7):1027-1034.
15. Nurieva R, Thomas S, Nguyen T, et al. T-cell tolerance or function is determined by combinatorial costimulatory signals. *EMBO J*. 2006;25(11):2623-2633.
16. Saunders PA, Hendrycks VR, Lidinsky WA, Woods ML. PD-L2:PD-1 involvement in T

- cell proliferation, cytokine production, and integrin-mediated adhesion. *Eur J Immunol*. 2005;35(12):3561-3569.
17. Tarhini AA, Kirkwood JM. Tremelimumab (CP-675,206): a fully human anticytotoxic T lymphocyte-associated antigen 4 monoclonal antibody for treatment of patients with advanced cancers. *Expert Opin Biol Ther*. 2008;8(10):1583-1593.
  18. Wang E, Kang D, Bae KS, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamic analysis of tremelimumab in patients with metastatic melanoma. *J Clin Pharmacol*. 2014;54(10):1108-1116.
  19. Korn EL, Liu PY, Lee SJ, et al. Meta-analysis of phase II cooperative group trials in metastatic stage IV melanoma to determine progression-free and overall survival benchmarks for future phase II trials. *J Clin Oncol*. 2008;26(4):527-534.
  20. Kirkwood JM, Lorigan P, Hersey P, et al. Phase II trial of tremelimumab (CP-675,206) in patients with advanced refractory or relapsed melanoma. *Clin Cancer Res*. 2010;16(3):1042-1048.
  21. Ribas A, Kefford R, Marshall MA, et al. Phase III randomized clinical trial comparing tremelimumab with standard-of-care chemotherapy in patients with advanced melanoma. *J Clin Oncol*. 2013;31(5):616-622.
  22. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-264.
  23. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455-2465.
  24. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.
  25. Hassan R, Thomas A, Patel M, et al. Avelumab (MSB001071BC; anti-PD-L1) in patients with advanced unresectable mesothelioma from the JAVELIN solid tumor phase Ib trial: Safety, clinical activity, and PD-L1 expression. [Abstract]. *Journal of Clinical Oncology*. 2016;34(suppl; abstr 8503).
  26. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med*. 2013;369(2):122-133.
  27. Antonia S, Gettinger S, Chow L, Juergens R, Borghaei H, Shen Y. Nivolumab (anti-PD-1; BMS-936558; ONO-4538) and ipilimumab in first-line NSCLC: interim phase I results [abstract]. *Journal of Clinical Oncology*. 2014;32(5s).
  28. Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. *Pharm Res*. 2006;23(6):1275-1284.
  29. Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. *J Clin Pharmacol*. 2009;49(9):1012-1024.
  30. Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. *J Clin Pharmacol*. 2012;52(1):18-28.
  31. Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon- $\alpha$  monoclonal antibody, in systemic lupus erythematosus. *Clin Pharmacokinet*. 2013;52(11):1017-1027.
  32. Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. *J Clin Oncol*. 2015;33(17):1889-1894.

33. Hodi FS, Sznol M, Kluger HM, et al. Long-term survival of ipilimumab-naive patients (pts) with advanced melanoma (MEL) treated with nivolumab (anti-PD-1, BMS-936558, ONO-4538) in a phase I trial [abstract]. *Journal of Clinical Oncology*. 2014;32(5s).
34. Drake C, McDermott D, Sznol M, et al. Survival, safety, and response duration results of nivolumab (Anti-PD-1; BMS-936558; ONO-4538) in a phase I trial in patients with previously treated metastatic renal cell carcinoma (mRCC): Long-term patient follow-up [abstract]. *Journal of Clinical Oncology*. 2013;31.
35. Brahmer J, Horn L, Gandhi L, et al. Nivolumab (anti-PD-1, BMS-936558, ONO-4538) in patients (pts) with advanced non-small-cell lung cancer (NSCLC): Survival and clinical activity by subgroup analysis [abstract]. *Journal of Clinical Oncology*. 2014;32(5s).
36. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *J Clin Oncol*. 2014;32(10):1020-1030.
37. Herbst R, Gordon M, Fine G, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors [abstract]. *Journal of Clinical Oncology*. 2013;31(15s).
38. Lawrence MS, Stojanov P, Mermel CH, et al. Discovery and saturation analysis of cancer genes across 21 tumour types. *Nature*. 2014;505(7484):495-501.
39. Garraway LA, Lander ES. Lessons from the cancer genome. *Cell*. 2013;153(1):17-37.
40. Awad MM, Hammerman PS. Durable Responses With PD-1 Inhibition in Lung and Kidney Cancer and the Ongoing Search for Predictive Biomarkers. *J Clin Oncol*. 2015;33(18):1993-1994.
41. Meng X, Huang Z, Teng F, Xing L, Yu J. Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy. *Cancer Treat Rev*. 2015;41(10):868-876.
42. Nagaraj S, Youn JI, Weber H, et al. Anti-inflammatory triterpenoid blocks immune suppressive function of MDSCs and improves immune response in cancer. *Clin Cancer Res*. 2010;16(6):1812-1823.
43. Cornelissen R, Heuvers ME, Maat AP, et al. New roads open up for implementing immunotherapy in mesothelioma. *Clin Dev Immunol*. 2012;2012:927240.
44. Byrne MJ, Nowak AK. Modified RECIST criteria for assessment of response in malignant pleural mesothelioma. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2004;15(2):257-260.
45. Postow MA. Managing immune checkpoint-blocking antibody side effects. *Am Soc Clin Oncol Educ Book*. 2015:76-83.
46. FDA. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009; <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>. Accessed May 13, 2016.

**APPENDIX A PERFORMANCE STATUS CRITERIA**

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature ( <i>e.g.</i> , light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

**APPENDIX B COCKCROFT-GAULT EQUATION FOR CREATININE CLEARANCE**

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