Clinical Study Protocol
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<< A Phase II multi-arm study to test the efficacy of immunotherapeutic agents in multiple sarcoma subtypes >>

Sponsor:

MD Anderson IND office

PROTOCOL SYNOPSIS

<< A Phase II multi-arm study to test the efficacy of immunotherapeutic agents in multiple sarcoma subtypes >>

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Study site(s) and number of subjects planned

Single site: University of Texas M D Anderson Cancer Center

Total number of subjects: ≤ 150

Study period		Phase of development
Estimated date of first subject enrolled	July 2016	Phase II
Estimated date of last subject completed	December 2017	Phase II

Hypothesis

Novel immunotherapeutic agents (including the combination of durvalumab and tremelimumab) will be safe, adequately tolerated, and will demonstrate clinical activity in

subjects with select sarcoma subtypes.

Study design

This study is a single-center phase II multi-arm study. This study will include patients (age ≥18 years) with recurrent/metastatic sarcoma, who have received at least one prior systemic therapy (if a standard therapy exists for the subtype), divided into the following categories/subtypes:

a. Adipocytic tumors (Well-differentiated/dedifferentiated liposarcoma, myxoid liposarcoma, pleomorphic liposarcoma)
b. Vascular tumors (leiomyosarcoma, angiosarcoma)
c. Undifferentiated pleomorphic sarcoma
d. Synovial sarcoma
e. Osteosarcoma
f. Other sarcomas.

Objectives

Primary Objective:	**Outcome Measure:**
To determine the progression-free survival (PFS) rate at 12 weeks after the initiation of the treatment in patients with relapsed/refractory sarcoma receiving novel immunotherapeutic agents	PFS at 12 weeks as defined by RECIST 1.1

Secondary Objective:	**Outcome Measure :**
To estimate the tumor response (irRC and RECIST) in patients with relapsed/refractory sarcoma receiving novel immunotherapeutic agents	irRC and RECIST response rate
To evaluate the safety and tolerability of receiving novel immunotherapeutic agents in patients with relapsed/refractory sarcoma	Toxicity rate (persistent grade 3 and/or 4 toxicity despite therapy) per treatment cohort
To estimate the PFS and overall survival (OS) in patients with relapsed/refractory sarcoma receiving novel immunotherapeutic agents	PFS and OS

Exploratory Objective:	**Outcome Measure :**
To determine expression of biomarkers (including but not limited to PD-1 and PD-L1) in pre & post tx samples.	Biomarker (PD-1/PD-L1) expression analysis (pre & post tx samples)
Quantification and characterization of the immune infiltrate (and other histologic and immunohistologic changes) from tissue samples prior to treatment initiation and post (treatment biopsy at week 6).	Tumor infiltrating lymphocytes (TILs) (pre & post tx samples)
Identification/quantification of immunologic changes (CD4+, CD8+, Teff, and Treg cells) in peripheral blood. Determining an immunoscore based on baseline tumor sample (identification of molecular response/resistance patterns/future therapy options)	

Target subject population

This study will include patients (age ≥18 years) with recurrent/metastatic sarcoma of the following subtypes, who have received at least one prior systemic therapy (if a standard therapy exists for the subtype). Patients with low-grade tumors are eligible if there is definite evidence of metastasis or progression (defined as 10% increase within a 3 month period).

Cohort 1: Adipocytic sarcomas-Well-diff/De-differentiated, Pleomorphic and Myxoid LPS
Cohort 2: Vascular sarcomas-Leiomyosarcomas, Angiosarcomas
Cohort 3: Undifferentiated Pleomorphic sarcomas (UPS)
Cohort 4: Synovial sarcomas
Cohort 5: Osteosarcoma
Cohort 6: Other sarcoma subtypes

Duration of treatment

The expected duration of a patient's participation in the trial is up to 15 months, including screening, treatment period (maximum of 12 months), and a follow-up visit at 1 month after last treatment and every 3 months after end of treatment (± 28 days) thereafter until progression or death. Patients who progress after completing 12 months of therapy in the observation period can be re-treated.

Investigational product dosage and mode of administration

Regimen 1 Dose:

Durvalumab 1500 mg and tremelimumab 75 mg every 4 weeks for 4 cycles followed by Durvalumab 1500 mg every 4 weeks for up to 8 additional cycles.

Mode of administration: Both agents will be administered by intravenous (IV) infusion. Tremelimumab will be administered first, and the infusion duration will be approximately 1 hour. The durvalumab (MEDI4736) infusion will start approximately 1 hour after the end of the tremelimumab infusion, and the infusion will be administered over approximately 1 hour. The combination of both agents shall be administered at Q4 week intervals for a maximum of 4 doses, after which the durvalumab will continue as a single agent at Q4 week intervals till progression or unacceptable toxicity for a maximum of 8 additional doses. If toxicity was noted with the combination, investigator can decide to continue durvalumab alone in case patient is having clinical benefit (SD or better).

Subjects enrolled who achieve and maintain disease control through the end of the treatment period will enter follow-up. During the first 12 months of follow-up, if the subject has progressive disease (PD), the subject may be re-administered durvalumab/tremelimumab for up to another 12 months with the same treatment guidelines followed during the initial 12-month period provided the subject does not meet any of the investigational product discontinuation criteria and fulfills the criteria for retreatment in the setting of PD, which include absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in Eastern Cooperative Oncology Group (ECOG) performance status compared to baseline; and absence of rapid disease progression or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

This study will not only allow us to evaluate the efficacy and safety of durvalumab and tremelimumab but provide the translational science to guide further development of novel immunotherapeutic agents in sarcomas.

Statistical methods

Sample Size: The planned sample size includes a maximum of 25 subjects in each cohort and less than or equal to 150 evaluable subjects in total for the combination of durvalumab and tremelimumab.

Design: The primary efficacy endpoint will be progression-free survival (PFS) at 12 weeks ($PFS_{12\ weeks}$). 12-week PFS is defined as evidence of stable disease or better 12 weeks after the initiation of therapy. In the meanwhile, we will also monitor the toxicity of the agent (Thall, 1996). Toxicity will be assessed within the first two cycles of the treatment (56 days). If there is a high probability that the $PFS_{12\ weeks}$ is unlikely to be at least 40% or that the unacceptable toxicity rate is likely to be greater than 30%, the drug would not be considered of interest for further study. Formally if $Pr(PFR_{12\ weeks} < 0.40 \mid Data) > 0.90$ or $Pr(\text{toxicity rate} > 0.30 \mid Data) > 0.90$, the corresponding cohort will be stopped. The assumed prior distribution for $PFS_{12\ weeks}$ is Beta (0.4, 0.6) and for toxicity is Beta (0.3, 0.7). The resulting prior means are 0.40 and 0.3 for $PFS_{12\ weeks}$ and toxicity rate, respectively, with one patient worth of information. Each of the disease cohorts will be monitored separately in cohorts of 5 patients after a minimum of 5 patients have been enrolled. For cohort 1, 2 and 6, since these include more than distinct subtypes, in order to assess anti-tumor activity of the treatment regimen within each histologic subtype, we will open enrollment simultaneously for each of the histologic subtypes but keep the maximum number of patients at 25 in each of these cohorts. Patients who are not evaluable for response to the treatment by 12 weeks post initiation of treatment will be considered a treatment failure.

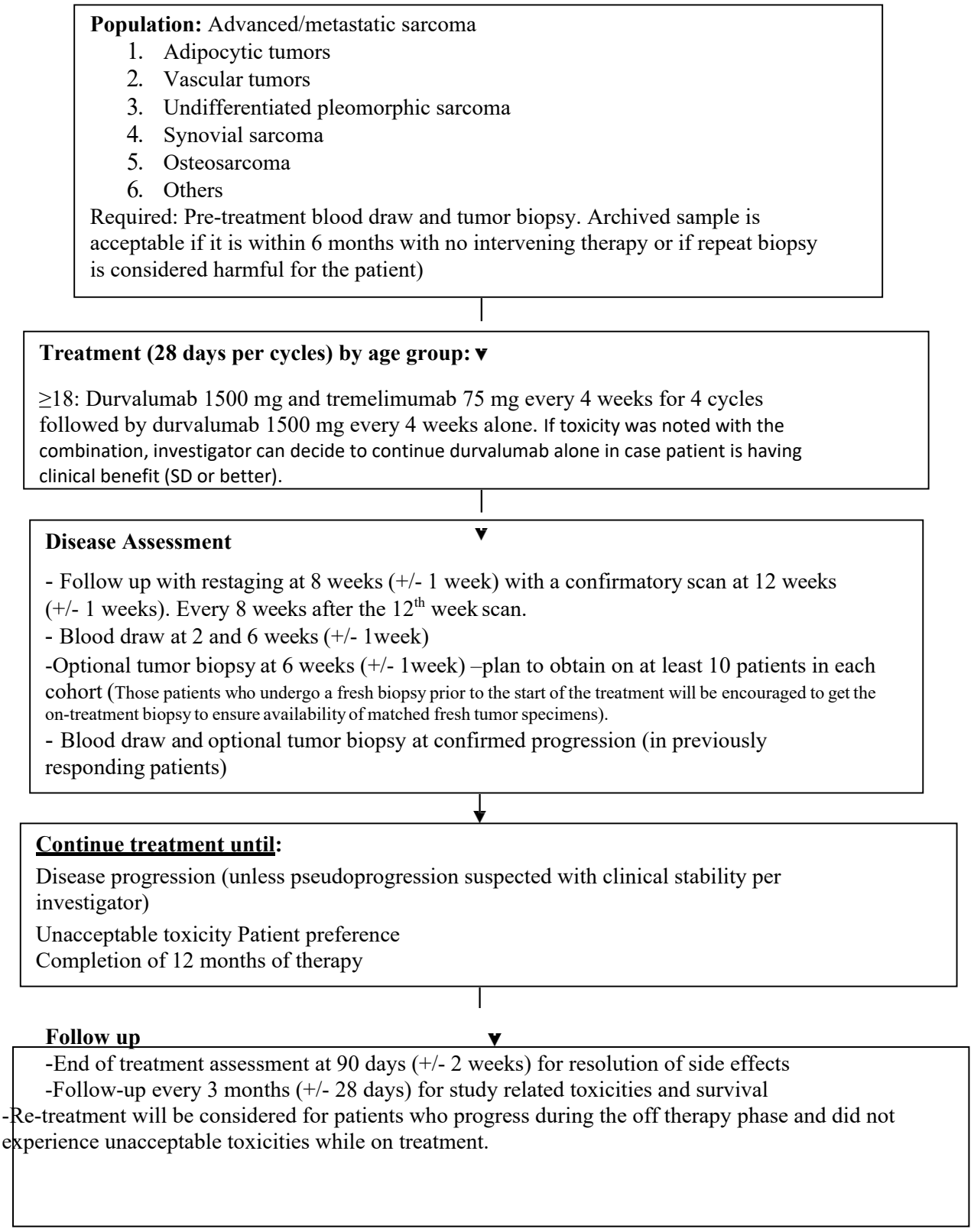
Analysis plan:

Efficacy: If a cohort is stopped early, this drug will not be considered of interest for future study for this cohort of patients. If all 25 patients are accrued, we will estimate the $PFS_{12\ weeks}$ and the corresponding 95% posterior credible interval. We will also apply a Bayesian hierarchical statistical model (Wathen, 2008) to analyze the data from all six cohorts to borrow information from each other. Response rate will be estimated along with 95% confidence interval. PFS and overall survival (OS) will be estimated using the Kaplan-Meier method (Kaplan,1958). Log-rank test (Mantel, 1966) will be performed to test the difference in survival between groups. Regression analyses of survival data based on the Cox proportional hazards model (Cox, 1972) will be conducted on PFS or OS.

Safety: Toxicity data will be summarized by frequency tables. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received. Toxicity rate will be estimated with 95% credible interval.

Correlatives: Exploratory data analysis and graphical methods will be applied to examine the distribution of the biomarker data, error checking, and outlier identification. T-test/ANOVA or their nonparametric countparts, Wilcoxon rank-sum test/Kruskal-Wallis test will be used to detect differences of the biomarkers between groups (1) Linear mixed effect models for repeated measures analysis (Liang, 1986) will be employed to assess the change of the biomarkers over time with multi-covariates including disease characteristics (tumor stage, site, pathology), and other prognostic factors. Appropriate transformation of the outcome assessment values will be used to satisfy the normality assumption of linear mixed effect model.

Figure 1 Schema



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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AE	Adverse event
CRF	Case Report Form (electronic/paper)
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of Investigational Product due to Adverse Event
DNA	Deoxyribonucleic acid
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IP	Investigational Product
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
LSLV	Last Subject Last Visit
OAE	Other Significant Adverse Event
PGx	Pharmacogenetic research
PI	Principal Investigator
SAE	Serious adverse event
WBDC	Web Based Data Capture

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Sarcomas are a rare collection of mesenchymal tumors with around 11,000 new cases diagnosed each year in the United States (2). While low-grade, localized disease may be amenable to surgical resection, patients with unresectable disease or metastasis have a high mortality rate. Currently, cytotoxic chemotherapy is the primary treatment modality for patients with unresectable/metastatic disease, and the most common front-line regimens include doxorubicin. While time to progression on doxorubicin-containing combinations has repeatedly been shown to be superior to that of doxorubicin alone, overall survival is not different in the same randomized studies (3). Furthermore, previous studies have shown an estimated median survival for these patients to be approximately 8 to 13 months from the start of first-line anthracycline-based chemotherapy, (4-7). Gemcitabine-docetaxel is most commonly used in the second line with specific activity against leiomyosarcomas and undifferentiated pleomorphic sarcoma. Recently, pazopanib, a multi-tyrosine kinase receptor inhibitor, received an FDA indication for use in soft tissue sarcomas on the basis of a 4.6-month progression-free survival (PFS), a 3-month improvement compared to placebo. Despite some of these advances there are still sub-types such as epithelioid sarcoma, clear cell sarcoma or well-differentiated liposarcomas for which we have no effective regimens beyond surgical resection.

In several solid tumor types, there are data to suggest that an antigen-specific adaptive immune response to cancer naturally exists in patients. In the tumor microenvironment, antigen presenting cells acquire and process peptides released from cell turnover during tumor growth. The most potent antigen presenting cells are dendritic cells (DCs). DCs then migrate to the draining lymph nodes where they sensitize and activate T cells against these peptide antigens. T cells, in particular antigen-specific, cytotoxic CD8 T cells, are then capable of eliminating antigen-expressing tumor cells found in the peripheral tissues. This process is restricted by the display of the antigen on the tumor cell surface in the context of an appropriate, matched major histocompatibility complex (MHC; e.g. human leukocyte antigen or HLA) molecule.

Multiple inhibitory mechanisms, however, may be responsible for the inability of the immune system to eliminate tumor cells. Inappropriate antigen presentation or lack of appropriate activation signals from DCs can result in the opposite effect, tolerance of T cells to the target antigen. Immunosuppressive cytokines (TGF-beta, IL-10) and alternate immune cell types (myeloid derived suppressor cells, regulatory T cells, tumor-associated macrophages) present at the tumor microenvironment may directly inhibit the anti-tumor immune response. Tumor

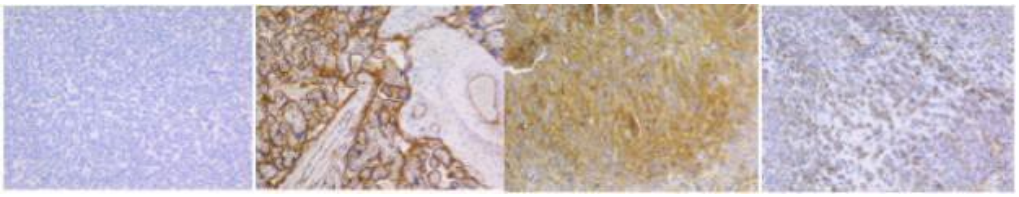
cells may lose expression of the target antigen and thus avoid detection. Activated T cells also express inhibitory signals known as immune checkpoint molecules, which arise naturally and dampen the immune response, to the advantage of tumor cells. Among the most extensively studied immune checkpoint molecules are CTLA4 and PD-1.

Immune-based therapies, offer the possibility of significant response and even durable complete responses for patients with cancers that are considered "incurable" (8, 9), but remain largely unexplored in sarcoma. Anti-CTLA-4 activity via ipilumumab has demonstrated survival benefits in melanoma and agents that target programmed death-1 (PD-1) have shown responses and potential survival benefits in various malignancies such as melanoma, non-small cell lung carcinoma, and renal cell carcinoma (9, 10). The presence of TILs and more importantly PD-L1 expression in the tumor have been correlated with objective response to the anti-PD-1 agent, nivolumab (9, 11).

High expression of PD-1/PD-L1 has also been reported in various subtypes of sarcoma and has been shown to be a negative prognostic marker for OS (12-14). Recent data also shows blockade of PD-1/PD-L1 interactions dramatically improves the function of osteosarcoma-reactive CTLs *in vitro* and *in vivo*, and results in decreased tumor burden and increased survival in the K7M2 mouse model of metastatic osteosarcoma (15). Combination immunotherapy with α-CTLA-4 and α-PD-L1 antibody blockade in the K7M2 mouse model of metastatic osteosarcoma resulted in complete control of tumors in a majority of mice as well as immunity to further tumor inoculation (16). Our preliminary clinical data also confirms the presence of PD-L1 expression in multiple sarcoma subtypes tested at MD Anderson (alveolar soft part sarcomas, chondrosarcomas, leiomyosarcomas, liposarcomas, undifferentiated pleomorphic sarcomas, osteosarcomas, and synovial sarcomas to name a few) (Figure 1). A majority of sarcomas also have a defined immunologic target (e.g. chromosomal fusion protein, cancer testis antigen, or mutation) and there is indeed a naturally-occuring immune infiltrate in multiple sarcomas. Previous studies, including one from our group has demonstrated the presence of TILs in certain sarcoma subtypes (17-19). The presence of a naturally-occurring immune infiltrate in many subtypes of sarcomas is encouraging and suggests that immunotherapy may potentially be beneficial in these patients. Interestingly, one of the earliest examples of immunotherapy from the late 19th century (Coley's toxin) was in fact, motivated by a sarcoma patient with tumor regression after clearance of a bacterial infection.

We believe checkpoint inhibitors will lead to clinical benefit in at least some of these sarcoma subtypes and lead to a survival benefit. This study will help us evaluate the clinical benefit in

multiple common sarcoma subtypes (selected on the basis of their higher mutation load, presence of TILs, and/or PD-L1 staining). This study will help us identify the immune markers of response or resistance in these sarcomas that will inform the future development of immunotherapy options for these patients. As part of this investigator-initiated study we intend to analyze blood and tissue specimens to help us select the next novel immunotherapeutic agent from the Medimmune pipeline that is likely to benefit these patients.



1A 1B 1C 1D

Figure 2 1A - U293 cell line (negative control); 1B - placenta (positive control); 1C - UPS; 1D - synovial sarcoma

1.2 Durvalumab and Tremelimumab Background

Durvalumab (MEDI4736) and tremelimumab are briefly described below. Refer to the current Investigator's Brochures for details.

1.2.1 Durvalumab Background

Durvalumab is a human immunoglobulin G (IgG)1 kappa mAb directed against human PD-L1. Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and cluster of differentiation (CD)80. The fragment crystallizable (Fc) domain of Durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (20).

1.2.2 Tremelimumab Background

Tremelimumab (formerly CP-675,206) is a human IgG2 mAb being investigated as a cancer immunotherapeutic agent. Tremelimumab is expressed in NS0 (murine myeloma) cells and has an overall molecular weight of approximately 149 kDa. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins. Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T-cell activation. Tremelimumab shows

minimal specific binding to Fc receptors, does not induce natural killer (NK) ADCC activity, and does not deliver inhibitory signals following plate-bound aggregation.

1.3 Summary of Nonclinical Experience

Nonclinical experience with durvalumab and tremelimumab are briefly described below. Refer to the current Investigator's Brochures for details.

1.3.1 Durvalumab Nonclinical Experience

Programmed cell death 1 (CD279) is a member of the immunoglobulin superfamily of molecules involved in regulation of T-cell activation. It is found on T cells, B cells, macrophages, NK cells, dendritic cells, and mast cells. It has also been described on peripheral tissues including cardiac endothelium, lung, small intestine, keratinocytes, islet cells of the pancreas, and syncytiotrophoblasts in the placenta as well as a variety of tumor cell types (21-32).

Programmed cell death ligand 1 (CD274, B7-H1) is constitutively expressed on many hematopoietic cells, but may be upregulated in hematopoietic and non-hematopoietic cells. Regulation of PD-L1 is mediated, in part, by type I and type II interferon (IFN). Programmed cell death ligand 2 (PD-L2; B7-DC) was identified in 2001 (25, 33). Its expression is far more restricted and is confined to hematopoietic cells.

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 (34-39);).

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

- Durvalumab binds to PD-L1 and blocks its interaction with PD-1 andCD80.
- Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation invitro.
- 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 free3 months after tumor implantation and demonstrated long-term immunity during

re-challenge.

- 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.
- Prevalence of PD-L1 expression on the surface of human tumors, ranging from approximately 0% to 35%, was demonstrated in a broad survey of samples derived from tumor types of interest.

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 programmed cell death ligand 1 (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 toxicology studies conducted in cynomolgus monkeys with durvalumab that were 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 antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry (IHC) study. Similar observations have been reported by MedImmune in cynomolgus monkeys administered human mAbs unrelated to durvalumab. 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. Interim audited data from the dosing phase of the pivotal 3-month GLP toxicity study with durvalumab 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. In addition to the in vivo toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues. Finally, in vitro cytokine release studies

showed that durvalumab and tremelimumab, either alone or in combination, did not induce cytokine release in blood from any donor.

1.3.2 Tremelimumab Nonclinical Experience

Cytotoxic T-lymphocyte-associated antigen 4 (CD152) is a cell-surface receptor expressed primarily on activated T cells. Cytotoxic T-lymphocyte-associated antigen 4 engagement on activated T cells inhibits cytokine synthesis and restricts cell proliferation (40-44) . Upon T-cell activation, CTLA-4 expression is upregulated and acts to dampen immune responses, modulating and eventually switching off T-cell activation. The natural ligands for CTLA-4 are CD80 and CD86, which are present on antigen-presenting cells (APCs). Binding of these ligands to CTLA-4 delivers a negative regulatory signal to T cells.

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 has the potential to be efficacious, the lower end of the potentially efficacious range being a plasma concentration of approximately 10 µg/mL and the target plasma concentration being 30 µg/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 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 hematologic systems. Clinical dose-limiting toxicity (DLT; eg, gastrointestinal effects) and non-DLT (eg, skin rash) were appropriately identified in a chronic toxicity study in monkeys. Most toxicities were reversible or showed a trend towards reversibility.

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

1.4 Summary of Clinical Experience

Clinical experience with durvalumab and tremelimumab are briefly described below. Refer to the current Investigator's Brochures for details.

1.4.1 Durvalumab Clinical Experience

MEDI4736 has been administered to subjects in 5 ongoing clinical studies (2 investigating MEDI4736 as monotherapy and 3 as combination therapy).

1.4.1.1 Monotherapy Studies

Study CD-ON-MEDI4736-1108:

Study CD-ON-MEDI4736-1108 is a Phase 1, first-time-in-human, multicenter, open-label, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose, safety, PK, immunogenicity, and antitumor activity of durvalumab in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. A total of 414 subjects with advanced solid tumors have been treated in Study CD-ON-MEDI4736-1108, where 393 of these subjects have received durvalumab at 10 mg/kg Q2W (either in the dose-escalation or dose-expansion phase of the study). In addition, 21 subjects have been enrolled in the following dose-escalation cohorts: 4 subjects in each of the 0.1, 0.3, and 1.0 mg/kg Q2W cohorts, 3 subjects in the 3.0 mg/kg Q2W cohort, and 6 subjects in the 15 mg/kg every 3 weeks (Q3W) cohort.

Of the 393 subjects treated with 10 mg/kg Q2W, 331 subjects (84.2%) had at least 1 AE (regardless of causality; Table 5.3.1.3-1). Overall, the most frequently reported (≥ 10% of subjects) AEs (all grades) were fatigue, nausea, dyspnea, decreased appetite, constipation, diarrhea, vomiting, cough, pyrexia, back pain, and rash. Approximately half (48.1%) of these AEs were Grade 1 to 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were noted in 141 of 393 subjects (35.9%). These events occurring in more than 1% of subjects were dyspnea (5.1%); increased gamma-glutamyltransferase (3.3%); fatigue, general physical health deterioration, increased aspartate aminotransferase, and back pain (2.3% each); anemia and dehydration (1.8% each); and abdominal pain, vomiting, sepsis, syncope, sepsis, and hypotension (1.3% each).

Treatment-related AEs were reported for 162 of 393 subjects (41.2%). The most frequently reported (≥ 2% of subjects) treatment-related AEs (all grades) were fatigue (13.5%); nausea (8.4%); diarrhea, decreased appetite, and rash (5.3% each); vomiting (4.8%); pruritus (4.1%);

dyspnea (3.8%); pyrexia (3.1%); hypothyroidism (2.8%); increased alanine aminotransferase, increased aspartate aminotransferase, and cough (2.5% each); myalgia (2.3%); and abdominal pain and dizziness (2.0% each). Treatment-related Grade 3 events that occurred in 2 or more subjects were fatigue (4 subjects), increased gamma-glutamyltransferase (3 subjects), and vomiting, increased alanine aminotransferase, increased aspartate aminotransferase, and arthralgia (2 subjects each). There were 2 subjects with treatment-related Grade 4 events (hypercalcemia, fatigue) and 1 subject with a treatment-related Grade 5 event (progression of disease [verbatim term]). However, the causality of the Grade 5 AE was changed to "not related" after the data cutoff date of 14Jul2014. According to the patient safety database, 1 subject in this study died due to treatment-related angiopathy (entry into the clinical database is pending).

A total of 229 SAEs (regardless of causality) have been reported in 123 of 393 subjects (31.3%) treated with 10 mg/kg MEDI4736 Q2W. The SAEs reported for 5 or more subjects were dyspnea, general physical health deterioration, pyrexia, abdominal pain, back pain, dehydration, pleural effusion, and sepsis. Eleven subjects (2.8%) had SAEs considered related to durvalumab by the investigator. A majority of these events were Grade 3 or higher in severity and recovered with or without sequelae.

Three subjects with treatment-related SAEs died. Two deaths due to progression of disease; pneumonitis was ongoing at the time of one of the subject's death but pleural effusion had resolved. The third death was due to treatment-related angiopathy.

Of the 414 subjects treated with durvalumab (all dose levels), 169 subjects were evaluable for response analysis, which included subjects who had at least 24 weeks of follow-up as of 14Jul2014 and had either at least 1 post-baseline tumor assessment or experienced clinical PD or death. Nineteen subjects (11.2%) had a best overall response of CR/PR (confirmed and unconfirmed). The DCR (CR + PR + SD $\geq$ 12 weeks) was 32% (54 of 169 subjects). Programmed cell death ligand 1 status (based on Ventana/MedImmune assay) was known for 143 of 169 evaluable subjects, of whom 30 were PD-L1 positive. A best overall response of CR/PR (confirmed and unconfirmed) was observed in 7 of 30 (23.3%) PD-L1-positive subjects and in 6 of 113 (5.3%) PD-L1-negative subjects.

Study D4190C00002 (Phase 1 Dose Escalation and Dose Expansion in Japanese Subjects with Advanced Solid Tumors)

Overall, 12 of 18 Japanese subjects (66.7%) who have been treated in Study D4190C00002 had at least 1 AE (Table 5.3.1.3-2). Treatment-related AEs were reported for 9 of 18 subjects (50.0%). The most frequent (≥ 2 subjects) treatment-related AEs (all grades) were constipation, stomatitis, fatigue, pyrexia, and pruritus (2 subjects each). In the majority of the subjects, the maximum severity of AEs was Grade 1 (6 of 12 subjects) or Grade 2 (5 of 12 subjects). These events were manageable by general treatment guidelines as described in the study protocol. Grade 3 or higher AEs were reported in 1 subject in the 10 mg/kg MEDI4736 Q2W cohort. The event for this subject was a Grade 3 treatment-related SAE of decreased free tri-iodothyronine. The SAE was ongoing at the time of the subject's death due to disease progression.

Limited efficacy data are available for Study D4190C00002. Twelve of 18 subjects had at least 1 post-baseline tumor assessment. One subject had a best overall response of PR (unconfirmed) and 6 subjects had SD as assessed by RECIST guidelines v1.1 (45).

Study D4191C00003 (ATLANTIC; Phase 2 Open Label in Subjects with NSCLC)
Fourteen subjects have been treated in Study D4191C00003. Subjects have received 1 to 4 doses of durvalumab (10 mg/kg Q2W). Only SAE data (from the patient safety database) are available. One of 6 subjects reported SAEs. The events were Grade 3 abnormal

liver function test, thrombotic stroke (severity unknown), Grade 3 asthenia, and Grade 3 ischemic cerebral infarction. The subject died due to asthenia and ischemic cerebral infarction. None of the SAEs were considered related to investigational product.

Study D4190C00007 (Phase 1 Dose Escalation and Dose Expansion in Subjects with Myelodysplastic Syndrome [MDS])
Two subjects have been treated in Study D4190C00007. Subjects have received 2 to 3 doses of durvalumab (10 mg/kg Q2W) and both subjects reported AEs. All of these events were Grade 1 or 2 in severity, with 3 events considered to be related to durvalumab. Nearly half of the events resolved. No DLTs have been reported.

Study D4191C00001 (PACIFIC; Phase 3 Randomized in Subjects with NSCLC)
One subject has been treated in Study D4191C00001. The subject received 6 doses of investigational product. The subject had events of Grade 1 dehydration and sinus tachycardia, Grade 3 shortness of breath, and Grade 3 hypotension (downgraded to Grade 2). The event of dehydration was considered related to investigational product. All of the events resolved, except for sinus tachycardia that was reported as ongoing.

1.4.1.2 Durvalumab and Tremelimumab Combination Study Experience

Study D4190C00006

Study D4190C00006 is a multicenter, open-label, dose-escalation, and dose-expansion study of durvalumab in combination with tremelimumab to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of durvalumab and tremelimumab in adult subjects with advanced NSCLC. In the dose-escalation phase up 102 patients were enrolled and received treatment. (46) Median follow up was 18.8 weeks (IQR 11 – 33). The maximum tolerated dose was exceeded in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg.

Overall, 82 of the 102 subjects (80%) reported a treatment-related AE (all grades,). See table 1 for details. The most common of these AEs included diarrhea in 33 patients (32%), fatigue in 24 patients (24%), and pruritus in 21 patients (21%). There was no dose dependency of the AEs noted in subjects with fixed dose of tremelimumab 1 mg/kg. Most of the Grade 1 and 2 AEs were manageable. Fifty-six subjects (55%) required treatment with immunosuppressants (corticosteroids, adalimumab, or infliximab) from all cohorts (102 patients). There were 15 (35%) of 43 patients that received one or more doses of the study regimen after the initiation of the first grade 3 or grade 4 treatment-related adverse event.

Forty-three of 102 subjects (42%) experienced grade 3/grade 4 treatment-related AEs. Thirty-seven of 102 subjects (36%) experienced a treatment-related SAE. See Table 2 for details. Twenty-nine of the 102 subjects (28%) discontinued the study as a result of treatment.

For the cohort of durvalumab 10 – 20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 1 mg/kg, the most common treatment-related hematologic grade 3/grade 4 toxicity was anemia in 3 subjects (5%). The most common treatment-related, non-hematologic grade 3/grade 4 toxicity was diarrhea in 4 subjects (7%). The most treatment-related, grade 3/4 laboratory abnormality was increased lipase in 5 subjects (9%).

There were 3 deaths (3%) related to treatment. One patient died from complications arising from myasthenia gravis (durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg). Another patient died of complications related to a pericardial effusion (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg). The last treatment-related death occurred due to a neuromuscular disorder (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg).

For the cohort of durvalumab 10 – 20 mg/kg every 2 weeks or 4 weeks plus tremelimumab 1

mg/kg, 6 patients of 26 evaluable patients (23%) experienced an objective response and 9 of 26 patients (35%) experienced disease control in patients with ≥ 24 weeks of follow up. PD-L1 status did not appear to select out for response (Antonia reference). This data represents information from patients gathered between October 28, 2013 and June 1, 2015.

Table 1 Treatment-related Adverse Events Summary, As-treated Population, Study D4190C00006

n (%)	D3 q4w T1 n=3	D10 q4w T1 n=3	D15 q4w T1 n=18	D20 q4w T1 n=18	D10 q2w T1 n=17	D10 q4w T3 n=3	D15 q4w T3 n=14	D20 q4w T3 n=6	D10 q2w T3 n=11	D15 q4w T10 n=9	All cohorts N=102
Safety summary											
Any AE	3 (100)	3 (100)	18 (100)	18 (100)	16 (94)	3 (100)	14 (100)	6 (100)	11 (100)	9 (100)	101 (99)
Any Grade 3/4 AE	0 (0)	2 (67)	13 (72)	11 (61)	9 (53)	3 (100)	11 (79)	6 (100)	9 (82)	8 (89)	72 (71)
Any deaths	0 (0)	1 (33)	6 (33)	6 (33)	2 (12)	0 (0)	3 (21)	2 (33)	1 (9)	1 (11)	22 (22)
SAE	1 (33)	2 (67)	13 (72)	10 (56)	6 (35)	2 (67)	10 (71)	6 (100)	8 (73)	8 (89)	66 (65)
AE leading to D/C	1 (33)	1 (33)	8 (44)	4 (22)	3 (18)	2 (67)	6 (43)	5 (83)	5 (45)	5 (56)	40 (39)
Related AE	1 (33)	3 (100)	13 (72)	11 (61)	14 (82)	3 (100)	13 (93)	5 (83)	11 (100)	8 (89)	82 (80)
Related Grade 3/4 AE	0 (0)	2 (67)	8 (44)	3 (17)	4 (24)	2 (67)	7 (50)	5 (83)	5 (45)	7 (78)	43 (42)
Related deaths	0 (0)	1 (33)*	0 (0)	1 (6)†	0 (0)	0 (0)	0 (0)	1 (17)‡	0 (0)	0 (0)	3 (3)
Related SAE	0 (0)	1 (33)	5 (28)	4 (22)	2 (12)	2 (67)	6 (43)	5 (83)	5 (45)	7 (78)	37 (36)
Related AE leading to	0 (0)	1 (33)	3 (17)	3 (17)	2 (12)	2 (67)	4 (29)	4 (67)	5 (45)	5 (56)	29 (28)

Table 2 Treatment-related Serious Adverse Events in Subjects Treated with Durvalumab Q4W/Tremelimumab Q4W, As-treated Population, Study D4190C00006

n (%)	D3 q4w T1 n=3	D10 q4w T1 n=3	D15 q4w T1 n=18	D20 q4w T1 n=18	D10 q2w T1 n=17	D10 q4w T3 n=3	D15 q4w T3 n=14	D20 q4w T3 n=6	D10 q2w T3 n=11	D15 q4w T10 n=9	All cohorts N=102
Preferred term											
Any related SAE	0 (0)	1 (33)	5 (28)	4 (22)	2 (12)	2 (67)	6 (43)	5 (83)	5 (45)	7 (78)	37 (36)
Colitis	0 (0)	0 (0)	1 (6)	1 (6)	0 (0)	1 (33)	2 (14)	1 (17)	3 (27)	2 (22)	11 (11)
Diarrhoea	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	3 (50)	1 (9)	3 (33)	8 (8)
Pneumonitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (14)	0 (0)	1 (9)	2 (22)	5 (5)
AST increased	0 (0)	1 (33)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	3 (3)
ALT increased	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	2 (2)
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (9)	1 (11)	2 (2)
Amylase increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (1)
Asthenia	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Blood alkaline phosphatase increased	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Decreased appetite	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Dehydration	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (1)

Depressed level of consciousness	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Dyspnoea	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Enteritis	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
GGT increased	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Headache	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Hypophysitis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (1)
Hypotension	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	0 (0)	0 (0)	1 (1)
Hypoxia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7)	0 (0)	1 (9)	0 (0)	2 (2)
Lipase increased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (1)
Myalgia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Myasthenia gravis	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (1)
Neck pain	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Neuromyopathy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (17)	0 (0)	0 (0)	1 (1)
Pancreatitis	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Pericardial effusion	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Platelet count decreased	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Polymyositis	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

Purpura	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	1 (1)
Rash maculo-papular	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (11)	1 (1)
Sepsis	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Thrombocytopenia	0 (0)	0 (0)	0 (0)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)

Study D4880C00010

Study D4880C00010 is a Phase 1, multicenter, open-label, dose-escalation and combination phase study of tremelimumab to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of tremelimumab monotherapy and tremelimumab in combination with durvalumab in adult Japanese subjects with advanced solid malignancies. As of the data cutoff date of 12Nov2014, a total of 11 subjects has been treated in the study with 8 subjects receiving tremelimumab monotherapy (4 subjects each at 3 and 10 mg/kg) and 3 subjects receiving 10 mg/kg tremelimumab in combination with 15 mg/kg Q4W durvalumab.

Eight (72.7%) of the 11 subjects had treatment-related AEs. The most frequently reported treatment-related AEs were: fatigue (4 subjects), diarrhea, decreased appetite, pruritus, maculo-papular rash (3 subjects each), and hypothyroidism (2 subjects).

Serious adverse events were reported in 4 of 11 subjects (36.4%), of whom 3 subjects (27.3%) had events that were considered related to treatment. One female subject with advanced thymoma received tremelimumab 10 mg/kg and durvalumab 15 mg/kg. She developed Grade 3 hypophysitis and Grade 4 muscular weakness after one dose. The subject developed worsening generalized muscle weakness requiring mechanical ventilation. The muscular weakness was eventually diagnosed as myasthenia gravis and considered related to treatment. The underlying diagnosis of thymoma likely increased the risk of developing myasthenia gravis. No treatment-related deaths have been reported in this study.

Study D4190C00010

Study D4190C00010 is a Phase 1, multicenter, open-label, dose-exploration, and dose-expansion study to evaluate the safety, tolerability, antitumor activity, PK, and immunogenicity of durvalumab in combination with tremelimumab in subjects with select advanced solid tumors. The study has enrolled 3 subjects in the dose exploration phase. Two subjects have been treated as of the data cutoff date of 12Nov2014.

Study D4190C00011

Study D4190C00011 is a multicenter, open-label, dose-exploration, and dose-expansion study to evaluate the safety, tolerability, antitumor activity, PK, and immunogenicity of durvalumab in combination with tremelimumab or tremelimumab alone in subjects with recurrent/metastatic SCCHN. As of the data cutoff date of 12Nov2014, 4 of 6 subjects who have been treated in this study reported at least 1 AE. With the exception of fatigue that was reported in 2 subjects, all

other preferred terms were reported in 1 subject each. A majority of the events were considered mild or moderate in severity and not related to tremelimumab.

Two of 6 subjects reported an SAE: systemic inflammatory response syndrome and worsening pleural effusion. The event of systemic inflammatory response syndrome was severe and considered related to initial treatment with tremelimumab. The subject died due to this event and only received tremelimumab therapy prior to developing the SAE. The event of worsening pleural effusion was considered to be moderate in severity and not related to tremelimumab.

D4191C00004

D4191C00004 is a Phase 3 open-label multi-center, global study in subjects with locally advanced or metastatic NSCLC (Stage IIIB-IV). The study will evaluate durvalumab used as monotherapy (10 mg/kg), tremelimumab (10 mg/kg) used as monotherapy and durvalumab used in combination with tremelimumab. This study was originally planned as a monotherapy study with durvalumab. The protocol was amended in August 2014 to include a tremelimumab combination arm as well as a tremelimumab monotherapy arm. No subjects have been enrolled in any portion of the study as of the data cutoff date of 12Nov2014.

1.4.2 Tremelimumab Clinical Experience

As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 9 are ongoing. Tremelimumab has been administered as monotherapy to 973 subjects (not including 497 subjects who have been treated in the blinded Phase 2b study, D4880C00003 [DETERMINE]) participating in 10 of the 22 sponsored clinical studies, 2 of which are ongoing. Most of these subjects had melanoma and received the tremelimumab 15 mg/kg every 90 days dosing regimen. In addition, 208 subjects with a variety of tumor types have received tremelimumab in combination with other anticancer agents in 12 of the 22 sponsored clinical studies, 7 of which are ongoing.

Across the clinical development program for tremelimumab a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this class of agents. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting months to years even in subjects with aggressive tumors, such as, refractory metastatic melanoma. Some subjects may have had progression of their disease early during treatment, with delayed tumor response or disease stabilization. Tremelimumab has been

tested in a Phase 3 study for advanced melanoma. Although the study failed to demonstrate improved overall survival (OS; primary endpoint) following a prespecified interim futility analysis, the final analysis showed a median OS of 12.6 months in the tremelimumab arm and 10.7 months in the dacarbazine/temozolomide arm. The ongoing Phase 2b study in recurrent pleural or peritoneal malignant mesothelioma is testing an alternative dosing schedule of tremelimumab with a dose of 10 mg/kg Q4W to maximize exposure to tremelimumab while managing safety according to the established anti-CTLA-4 AE management guidelines. The 10 mg/kg Q4W regimen is also being tested in an ongoing Phase 2 investigator-sponsored study in malignant mesothelioma (NCT01655888).

In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following IV infusion. The estimate of clearance, volume of distribution at steady state, and terminal-phase half-life is 1.132 mL/h/kg, 81.2 mL/kg, and 22.1 days, respectively. These values are consistent with those of natural IgG2.

Overall, 944 of the 973 subjects (97.0%) treated with tremelimumab monotherapy experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of subjects, were serious in 36.5%, were considered to be treatment related in 79.1% of subjects. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that seems to be confined to subjects with melanoma). Events reported in the tremelimumab monotherapy studies at a frequency > 5% and assessed by the investigator as treatment related were diarrhea (41.2%), rash (27.2%), pruritus (25.1%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite(11.3%), headache (7.2%), pyrexia (7.0%), abdominal pain (6.7%), and colitis (5.5%). The events of diarrhea, rash, and pruritus are considered as identified risks. Infusion-related side effects are rare. The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by adherence to current immune-related toxicity management guidelines.

As of the data cutoff date of 12Nov2014, 659 subjects (67.7%) who received tremelimumab monotherapy have died. Majority of the deaths were ascribed to the subject's underlying malignant disease (61.8%), only 5 deaths were caused by AEs considered by the investigator as related to tremelimumab (0.5%), whereas the remaining causes included other or unknown/missing (7.1%).

The frequency of any AEs and ≥ Grade 3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of subjects in the 10 mg/kg Q28D and 15 mg/kg

Q90D groups compared with the < 10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product, and deaths.

1.5 Rationale for study design and dosing

1.5.1 Rationale for study design

Sarcoma is a heterogeneous group of diseases that includes more than 50 subtypes. Traditionally, due to the rarity of sarcomas they have been lumped together in clinical trials even though response to treatment is quite variable among the different subtypes. This has slowed the progress in identifying novel effective therapies that might be relevant for specific sarcoma subtypes. Options for treatment for patients with advanced / recurrent or metastatic disease are quite limited. This study is designed to evaluate the efficacy of check-point inhibitors in the multiple sarcoma subtypes divided into cohorts that will be individually analysed. The first five cohorts were selected on the basis of their higher frequency, the mutational load and reported presence of PD-L1 positivity in prior studies. The 6th cohort will allow enrollment of subjects with other sarcoma subtypes not included in the first 5. The goal of this trial is not only to test the efficacy and safety of the check-point inhibitor combination farthest along in development (anti-PDL-1 and anti-CTLA4) but have the correlative studies to help guide us regarding the biomarkers for activity or lack thereof and inform us in prioritizing the novel immunotherapeutic agents for the next trial.

1.5.2 Rationale for endpoints

Response to systemic therapy in metastatic/refractory disease is low and is less meaningful if not correlated with improvement in survival. For this reason, PFS has become an acceptable metric in the measurement of efficacy in sarcomas with refractory disease or in sarcomas with primary resistance to anthracycline-based chemotherapies. The objective data to support use of PFS as a primary end point in sarcomas was derived from a review of the EORTC sarcoma database by van Glabbeke *et al* in 2002 (46). In the EORTC analysis, which involved 12 clinical trials, patients with no prior treatment received experimental agents were compared to those with prior systemic treatment who were received experimental agents. In a multivariate analysis, patients with prior therapy obtained an improved PFS with active agents compared to inactive agents. For previously treated patients, an **active agent** was associated with a PFS of at least 39% and 14% at 3 months and 6 months, respectively. **Inactive agents** were associated with a PFS of 21% and 8% at 3 months and 6 months, respectively.

Hence PFS has been used as the primary end-point to determine if the investigational agents being tested are active in the sarcoma subtypes. Secondary endpoints include safety, response rate by RECIST and irRC and OS.

1.5.3 Rationale for pre-treatment and on treatment biopsy

In addition to evaluating the efficacy of these novel immunotherapeutic agents in sarcoma, the unique strength of this study is the translational science that can not only help us understand the rationale for response and resistance but also guide us with the selection of appropriate sarcoma subtypes and also the right combination of immunotherapeutic agents for the next planned studies. All patients will require to have baseline tissue available from a resection or biopsy (archived samples are acceptable if they are recent within 6 month with no intervening treatment including radiation to the biopsied lesion). Exceptions to the baseline biopsy will be made only on a case-to-case basis after discussion with the PI. For example, if a biopsy attempt was unsuccessful or if the risk was felt to be unduly high. On-treatment biopsy at 6 weeks will be optional but we hope to acquire at least 10 patient biopsies in each cohort. Patients who got baseline fresh biopsy will be encouraged to get an on-treatment biopsy so we can get paired samples in at least 10 patients in each cohort. The pre-treatment biopsy and on-treatment biopsy for 10 patients in each cohort is key in order to maximize the potential of this collaboration with Medimmune and strategically access their novel immunotherapeutics pipeline to benefit sarcoma patients. We will need to understand the immune-microenvironment of the tumors and the patient characteristics that lead to response or resistance. The biomarkers from tissue and blood acquired as part of this prospective trial will be analyzed in real-time by the correlative science team headed by Dr. Wistuba and Dr. Lazar, so the results can inform the next phase of the sarcoma immunotherapy studies. Blood for correlative testing including flow cytometry (under Dr. Bernatchez) will be obtained at baseline, 2 weeks, 6 weeks and at the time of confirmed progression. Patients who are part of this trial but do not experience benefit from the combination of durvalumab and tremelimumab might be eligible for future combinations based on their tumor immunoprofile.

1.5.4 Rationale for dosing of durvalumab and Tremelimumab

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 ≤ 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; (47). The population PK model indicated minor impact of body weight on PK of tremelimumab (coefficient of ≤ 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 fixed dosing regimen.

Similar findings have been reported by others (48-51). 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 (49). 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 (50). 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. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	**Outcome Measure:**
To determine the progression free survival (PFS) rate at 12 weeks after the initiation of the treatment in patients with relapsed/refractory sarcoma receiving check-point inhibitors (anti-CTLA-4 and anti-PD-L1).	PFS at 12 weeks as defined by RECIST 1.1

2.2 Secondary objectives

Secondary Objective:	**Outcome Measure:**

To estimate the tumor response (irRC and RECIST) in patients with relapsed/refractory sarcoma receiving receiving check-point inhibitors (anti-CTLA-4 and anti-PD-L1).	irRC and RECIST response rate
To evaluate the safety and tolerability of check-point inhibitors in patients with relapsed/refractory sarcoma	Toxicity rate (persistent grade 3 and/or 4 toxicity despite therapy) per treatment cohort
To estimate the PFS at 24 weeks and overall survival (OS) in patients with relapsed/refractory sarcoma receiving check-point inhibitors (anti-CTLA-4 and anti-PD-L1).	PFS at 24 weeks and OS

2.3 Exploratory objectives

Exploratory Objective:	**Outcome Measure :**
To determine PD-1/PD-L1 expression analysis (pre & post tx samples).	PD-1/PD-L1 expression analysis (pre & post tx samples)
Quantification and characterization of immune infiltrate (and other histologic and immunohistologic changes) from tissue samples prior to treatment initiation and post treatment (biopsy at week 6).	Tumor infiltrating lymphocytes (TILs) (pre & post tx samples)

3. STUDY DESIGN

3.1 Description of the Study

This is a single center, open-label, phase II study to evaluate the antitumor activity, safety, tolerability and immunogenicity of durvalumab in combination with tremelimumab in subjects with advanced/metastatic sarcomas. This study will include patients (age ≥12 years) with recurrent/metastatic sarcoma, who have received at least one prior systemic therapy (if a standard therapy exists for the subtype), divided into the following categories/subtypes:

1. Adipocytic tumors (Well-differentiated/dedifferentiated liposarcoma, myxoid liposarcoma, pleomorphic liposarcoma)

2. Vascular tumors (leiomyosarcoma, angiosarcoma)
3. Undifferentiated pleomorphic sarcoma
4. Synovial sarcoma
5. Osteosarcoma
6. Other sarcomas

A Bayesian design will be used to analyze data in each of the cohorts.

3.1.1 Treatment Regimen

Durvalumab 1500 mg IV and tremelimumab 75 mg IV every 4 weeks for 4 cycles followed by durvalumab 1500 mg every 4 weeks for up to 8 additional cycles. If toxicity was noted with the combination, investigator can decide to continue durvalumab alone in case patient is having clinical benefit (SD or better).

Cycle duration: 28 days

Mode of Administration**:** Tremelimumab will be administered first and the infusion duration will be approximately 1 hour. The durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion and the infusion will be administered over approximately 1 hour. Both agents will be administered by intravenous (IV) infusion Q4W for 4 doses, after which durvalumab will continue to be administered Q4W (up to 8 additional doses).

Subjects enrolled who achieve and maintain disease control through the end of the 12-month treatment period will enter follow-up. During the first 12 months of follow-up, if the subject has progressive disease (PD), the subject may be re-administered durvalumab/tremelimumab (4 doses of combination followed by single agent durvalumab) and continue treatment as long as they do not meet any of the investigational product discontinuation criteria (Section 4.6). Inthe setting of PD, they need to meet criteria for continuation in the setting of PD; which include absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in Eastern Cooperative Oncology Group (ECOG) performance status compared to baseline; absence of rapid disease progression or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention; and continuing benefit in the opinion of the investigator and PI.

3.1.2 Management of study related toxicities

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, the occurrence of irAEs that are either overlapping or greater than each of these drugs when used as monotherapy is possible. Potential irAEs may be similar to those seen with the use of ipilimumab, nivolumab, or the combination thereof and may include immune-

mediated enterocolitis, dermatitis, pneumonitis, hepatitis (hepatotoxicity), neuropathy, and

endocrinopathies (8-10, 52). Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, pneumonitis, dermatitis, hepatitis, neuropathy, and endocrinopathy. In addition to the treatment modifications shown in Table 3.1.5-1, it is recommended that management of irAEs follow the guidelines outlined for ipilimumab (53). These guidelines recommend the following:

1. Subjects should be evaluated to identify any alternative etiology.
2. In the absence of a clear alternative etiology, all events of an inflammatorynature should be considered to be immune-related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab, mycophenolate, etc).

Treatment modifications will not be required for AEs that are clearly not attributed to durvalumab or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Dose reductions of durvalumab or tremelimumab are not permitted.

Treatment modifications may be required for durvalumab and tremelimumab in the event of treatment-related toxicity. General guidelines regarding treatment modification are provided in Table 3. All toxicities will be graded according to NCI CTCAE v4.03. If toxicity requires discontinuation of check-point inhibitor therapy and was experienced while receiving the combination, the investigator has the option to continue single agent durvalumab if safe and if clinical benefit is noted (SD or better).

Table 3 Immunotherapy (durvalumab and Tremelimumab) Treatment Modification Due to Toxicity and Supportive Care Guidelinesfor Immune-Related Adverse Events (irAEs)

GRADE 1 - Immunotherapy Related Toxicities

For endocrinopathy irAEs

- Do not hold immunotherapy (Durvalumab and/or Tremelimumab)
- Obtain labs pertinent to specific endocrinopathy

For dermatologic irAEs

- Do not hold immunotherapy (Durvalumab and/or Tremelimumab)
- Start medium potency topical steroid Antihistamine
- Reassess verbally in 72 hours
- If responds continue same directions for 7 days then taper off
- If no relief advance to wet dressings and consult dermatology.

For gastrointestinal irAEs

- Do not hold immunotherapy (Durvalumab and/or Tremelimumab)
- Fluid replacement (2-3 liters/day)
- If patient has lab abnormalities or dehydrated consider outpatient IV fluids with
- electrolyte replacement for a total of 2-3 liters x 48 hours)
- Anti-diarrheals
- Reassess verbally in 24 hours
- If responds, continue same directions for 72 hours then taper
- If no relief, proceed to grade 2 management

For hepatitis (ALT, AST and/or bilirubin) irAEs

- Continue immunotherapy (Durvalumab and/or Tremelimumab)
- Consider increased LFT monitoring

For pneumonitis irAEs

- Continue immunotherapy (Durvalumab and/or Tremelimumab) if clinically stable
- Monitor symptoms every 2-3 days
- Repeat Chest X-ray in 2 weeks

For Uveitis/Episcleritis irAEs

- Consider ophthalmology consultation
- Topical steroids (1% prednisolone acetate suspension)

For infusion-related reactions:

- The infusion rate of Durvalumab or Tremelimumab may be decreased by 50% or temporarily interrupted until resolution of the event. In subjects experiencing Grade ≤ 2 infusion related reaction, subsequent infusions may be infused at 50% of the initial rate.
- Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator.
- Consider premedication prior to subsequent doses.

For all other irAEs:

- No treatment adjustment is required.

GRADE 2 - Immunotherapy Related Toxicities

For endocrinopathy irAEs

- Hold treatment (Durvalumab and Tremelimumab or Durvalumab alone)
- When endocrinopathy is controlled, resume treatment (Durvalumab and Tremelimumab or Durvalumab alone)

For dermatologic irAEs

- Do not hold Tremelimumab and/or Durvalumab
- Start medium potency topical steroid Antihistamine

- Reassess verbally in 72 hours
- If responds continue same directions for 7 days then taper off
- If no relief advance to wet dressings and consult dermatology.

For gastrointestinal irAEs

- Hold immunotherapy (Tremelimumab and/or Durvalumab)
- Fluid replacement (2-3 liters/day)
- If patient has lab abnormalities or dehydrated consider outpatient IV fluids with electrolyte replacement for a total of 2-3 liters x 48 hours
- Anti-diarrheals
- Reassess verbally in 24 hours
- If responds, continue same directions for 72 hours then taper
- If persists after 24 hours:
- Hold immunotherapy until less than grade 1
- Prednisone oral 1 mg/kg/day
- Consult gastroenterology
- Obtain CT scan of abdomen & pelvis +/- colonoscopy
- If immune mediated colitis is confirmed by biopsy, proceed to grade 3/grade 4 management
- If patient is benefiting from treatment per imaging then PI discretion on length of time study drugs can be held.
- Allow time for steroid taper.

For Pneumonitis irAEs

- Hold immunotherapy (Tremelimumab and/or Durvalumab) until improvement to ≤ Grade 1
- HospitalAdmission
- Monitor symptomsdaily
- Obtain chest imaging (CT chest is preferred)
- Evaluate for disease progression
- Pulmonary & Infectious Disease Consultations
- Rule out other etiologies (infectious, autoimmune, etc.)
- Prednisone PO 1 mg/kg/day
- If no improvement, treat as grade 3/grade 4 pneumonitisirAE.

For Hepatitis (ALT, AST and/or bilirubin)irAEs

- Hold Tremelimumab and/or Durvalumab until less than grade 1
- Monitor LFTs every 72 hours (3 days)
- Evaluate for disease progression
- If this does not improve, monitor LFTs daily, and initiate prednisone oral 1 mg/kg/day
- If improvement to ≤ Grade 1 does not occur within 30 days, discontinue treatment.

For Uveitis/EpiscleritisirAEs

- Considerophthalmology consultation
- Topical steroids (1% prednisolone acetatesuspension)

For infusion-related reactions:

- The infusion rate of Durvalumab or Tremelimumab may be decreased by 50% or temporarily interrupted until resolution of the event. In subjects experiencing Grade ≤ 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate.
- Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator.
- Consider premedication prior to subsequent doses.

For all other irAEs

- Hold treatment (Durvalumab and Tremelimumab or Durvalumab alone) until improvement to ≤ Grade 1 or baseline.
- If improvement to ≤ Grade 1 does not occur within 60 days, discontinue treatment (Tremelimumab and/or Durvalumab).

Grade 3 - Immunotherapy Related Toxicities

Forendocrinopathy irAEs

- Hold treatment (Tremelimumab and/or Durvalumab)
- Considerhospitaladmission
- Monitor labs pertinent to endocrinopathy
- Endocrinology consultation
- Evaluate for disease progression
- Initiate high-dose steroids (1 mg/kg/day)
- Replace deficient hormones (hypophysitis)
- When endocrinopathy is controlled, resume treatment (Tremelimumab and/or Durvalumab) administration at next scheduled dose.

For Dermatologic irAEs

- Hold treatment (Tremelimumab and/or Durvalumab) until improvement to ≤ Grade 1 or baseline
- Dermatology consult
- High potency topical steroids Prednisone oral 0.5-1 mg/kg/day Antihistamine
- Reassess verbally in 72 hours
- If responds continue same directions for 7 days and then taper off
- If no relief, proceed to grade 4 management.
- If improvement to ≤ Grade 1 or baseline does not occur within 30 days, discontinue treatment (Tremelimumab and/or Durvalumab)

For Gastrointestinal irAEs

- Discontinue immunotherapy (Tremelimumab and/or Durvalumab)
- Hospital Admission Bowel Rest – NPO
- Methylprednisolone IV 2 mg/kg/day
- Gastroenterology consult
- Obtain CT scan of abdomen & pelvis +/- colonoscopy to evaluate for immune- mediated colitis
- Evaluate for perforation
- If perforation is suspected, obtain a surgical consultation immediately and do not start anti-diarrheals, steroids, and Infliximab
- Consider Infliximab IV 5 mg/kg; may repeat in 2 weeks (if no contraindication).
- If resolution occurs, slow taper steroid over greater than 4 weeks.

For Hepatitis (ALT, AST, and/or bilirubin) irAEs

- Discontinue immunotherapy (Tremelimumab and/or Durvalumab)
- Hospital Admission
- Monitor LFTs daily and consult gastroenterology/hepatology
- Initiate Methylprednisolone IV 2 mg/kg/day
- If persistent, add immunosuppressant (tacrolimus, antithymocyte globulin)
- For elevations in transaminases ≤ 8 times ULN, hold treatment (Tremelimumab and/or Durvalumab) until improvement to ≤ Grade 1 or baseline.
- If elevations downgrade to ≤ Grade 2 within 7 days or to ≤ Grade 1 or baseline within 28 days, resume treatment (Tremelimumab and/or Durvalumab administration at next scheduled dose. Otherwise, discontinuetreatment (Tremelimumab and/or Durvalumab)
- For elevations in transaminases > 8 times ULN, discontinue treatment (Tremelimumab and/or Durvalumab)
- For elevations in total bilirubin ≤ 5 times ULN, hold treatment (Tremelimumab and/or Durvalumab) until improvement to ≤ Grade 1 or baseline. If elevations downgrade to ≤ Grade 2 (< 3 Å~ ULN) within 7 days or improve to ≤ Grade 1 or baseline within 28 days, resume treatment (Tremelimumab and/or Durvalumab) administration at next scheduled dose. Otherwise, discontinue treatment (Tremelimumab and/or Durvalumab)
- For elevations in total bilirubin > 5 times ULN, discontinue treatment (Tremelimumab and/or Durvalumab)
- If resolution occurs, slow taper systemic steroid over greater than4 weeks.

For pneumonitis irAEs

- Discontinue immunotherapy (Tremelimumab and/or Durvalumab)
- HospitalAdmission
- Monitor symptomsdaily
- Methylprednisolone IV 2 mg/kg/day
- Evaluate for disease progression
- Pulmonary and Infectious Disease consultation
- Bronchoscopy and BAL analysis is stronglyrecommended.
- If resolves, slow taper steroids over greater than 4 weeks.

For Uveitis/EpiscleritisirAEs

- Discontinue immunotherapy (Tremelimumab and/or Durvalumab) permanently
- Ophthalmology consultation
- Topical steroids (1% prednisolone acetatesuspension)
- Consider oral prednisone 1 mg/kg/day with at least a 30-day taper.

For hypersensitivity and infusion-related reactions

- Discontinue treatment (Tremelimumab and/or Durvalumab)

For all other irAEs

- Hold treatment (Tremelimumab and/or Durvalumab) until improvement to ≤ Grade 1 or baseline.
- For AEs that downgrade to ≤ Grade 2 within 7 days or improve to ≤ Grade 1 or baseline within 14 days, resume treatment (Tremelimumab and/or Durvalumab) administration at next scheduled dose. Otherwise, discontinue treatment (Tremelimumab and/or Durvalumab)

Grade 4 - Immunotherapy Related Toxicities

For endocrinopathy irAEs

- Same as management for grade 3 endocrinopathy irAEs.

For dermatologic irAEs

- Discontinue immunotherapy (Tremelimumab and/or Durvalumab)
- Hospital admission
- IV hydration; especially if large BSA of denuded skin
- Dermatology consult
- Monitor closely for sepsis, respiratory symptoms
- Prednisone IV 2 mg/kg/day
- Oral care & eye care as indicated
- If resolves, slow taper systemic steroid over at least 4 weeks to prevent recurrence.

For gastrointestinal irAEs

- Same as management for grade 3 gastrointestinal irAEs.

For hepatitis irAEs

- Same as management for grade 3 hepatitis irAEs.

For pneumonitis irAEs

- Same as management for grade 3 pneumonitis irAEs.

For Uveitis/Episcleritis irAEs

- Same as management for grade 3 episcleritis/uveitis.

For all other irAEs

- Discontinue treatment (Durvalumab and/or Tremelimumab).

3.2 Cohort enrollment

3.2.1 Describe Bayesian design and monitoring of patients

Within each cohort, we will treat up to 25 patients. The primary efficacy endpoint will be progression-free survival at 12 weeks ($PFS_{12\ weeks}$). 12-week PFS is defined as evidence of stable disease or better 12 weeks after the initiation of therapy. In the meanwhile, we will also monitor the toxicity of the agent. Toxicity will be assessed within the first two cycles of the treatment. If there is a high probability that the $PFS_{12\ weeks}$ is unlikely to be at least 40% or that the unacceptable toxicity rate (as described in section 3.2.2 below) is likely to be greater than 30%, the drug would not be considered of interest for further study. The cohort will be monitored in cohorts of 5 patients after a minimum of 5 patients have been enrolled.

3.2.2 Unacceptable toxicity

All toxicities will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. Toxicities will be managed per section 3.1.2. In each cohort if the unacceptable toxicity rate as described below is greater than 30%, then further enrollment in that cohort will stop. Patients already on therapy will continue on treatment as per protocol.

Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition.

- Any Grade 4 immune-related adverse event (irAE)
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × upper limit of normal (ULN) or total bilirubin 5 × ULN
- Any≥ Grade 3 non-irAE
- The following will not be considered as unacceptable toxicity:
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
    - Grade 3 inflammatory reaction attributed to a local antitumor response (eg,

inflammatory reaction at sites of metastatic disease, lymph nodes, etc)

- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days.
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

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

4. SUBJECT SELECTION, ENROLLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

4.1 Number of Subjects

Approximately 5 to 25 subjects in each of the six cohorts and up to 150 subjects in total will be enrolled. All eligibility criteria should occur according to timeframes listed within Table 4, Section 5 of the protocol.

4.2 Inclusion criteria

4.2.1 Age: >/= 18 years of age

4.2.2 Histologically or cytologically confirmed sarcoma that fall into one of the following categories Patients with low-grade tumors are eligible if there is definite evidence of metastasis or progression (defined as at least a 10% increase in the cumulative sum of the longest diameters within a 3 month period):

1. Adipocytic tumors (Well-differentiated/dedifferentiated liposarcoma, myxoid liposarcoma, pleomorphic liposarcoma)
2. Vascular tumors (leiomyosarcoma, angiosarcoma)
3. Undifferentiated pleomorphic sarcoma
4. Synovial sarcoma

5. Osteosarcoma
6. Other sarcoma histologies

4.2.3 Must have received and have progressed, are refractory or intolerant to standard therapy appropriate for the specific sarcoma subtype, if there is a standard therapy for the subtype (i.e. Progressing well-differentiated liposarcoma, clear cell sarcoma etc do not require prior therapy).

4.2.4 Subjects must have at least 1 lesion that is measurable by irRECIST

a. A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable per irRECIST, and has clearly progressed.
b. Subjects undergoing fresh tumor biopsies must have additional non-target lesions that can be biopsied at acceptable risk as judged by the investigator or if no other lesion suitable for biopsy, then an irRECIST target lesion used for biopsy must be ≥ 2 cm in longest diameter.

4.2.5 Subjects must consent to provide archived tumor specimens for correlative biomarker studies. Tumor tissue must be identified and availability confirmed prior to initiation of study therapy. In the setting where archival material is unavailable or unsuitable for use, or there have been multiple intervening therapies subjects must consent and undergo fresh tumor biopsy. A tumor lesion planned for biopsy must not be an irRECIST target lesion unless there are no other lesions suitable for biopsy and lesion used for biopsy is ≥ 2 cm in longest diameter.

4.2.6 ECOG performance status of 0 or 1

4.2.7 Adequate organ function as determined by (lymphocyte count):

a. Hematological (without growth factor or transfusion support):
   i. Absolute neutrophil count ≥ 1.5 x 109/L ($1{,}500/mm^3$)
   ii. Platelet count ≥ 90×10^9 /L ($100{,}000/mm^3$)

iii. Hemoglobin ≥ 8.0 g/dL within first 2 weeks prior to first dose of investigational product

b. Renal:
   i. Calculated creatinine clearance (CrCl) or 24-hour urine CrCl > 50 mL/min Cockcroft-Gault formula (using actual body weight) will be used to calculate CrCl, except for pts with Osteosarcoma who will be allowed to participate with an estimated creatinine clearance (CrCl) of > 40 mL/min, as calculated by the Cockroft-Gault equation.

c. Hepatic:
   i. Total bilirubin ≤ 1.5 × ULN; for subjects with documented/suspected Gilbert's disease, bilirubin ≤ 3 × ULN
   ii. AST and ALT ≤ 2.5 × ULN; for subjects hepatic metastases, ALT and AST ≤ 5 × ULN

4.2.8 Females of childbearing potential who are sexually active with a nonsterilized male partner must use a highly effective method of contraception from the time of screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product.

4.2.9 Life expectancy of at least 6 months.

4.2.10 Ability to understand the purposes and risks of the study and has signed a written consent form approved by the investigator's IRB/Ethics Committee.

4.3 Exclusion criteria

4.3.1. Prior therapy with anti-PD1, anti-PD-L1 or anti-CTLA-4 antibody

4.3.2. Active or prior documented autoimmune disease (including inflammatory bowel disease, celiac disease, Wegener syndrome) within the past 2 years. Subjects with childhood atopy or asthma, vitiligo, alopecia, Hashimoto syndrome, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

4.3.3. Untreated central nervous system metastatic disease, leptomeningeal disease, or cord compression. Subjects previously treated central nervous system metastases that are radiographically and neurologically stable for at least 6 weeks and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to first dose of durvalumab and tremelimumab are permitted to enroll.

4.3.4. Concurrent enrollment in another clinical study, unless it is an observational

(non-interventional) clinical studyor the follow-up period of an interventional study.

4.3.5. Receipt of any conventional or investigational anticancer therapy not otherwise specified above within 28 days o r 5 hal f - l i ves of t he agent prior to the first dose of durvalumab and tremelimumab.

4.3.6. Any concurrent chemotherapy, IMT, or biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. In addition, local treatment (eg, by local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable beyond the first cycle with prior consultation and in agreement with the PI.

4.3.7. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 Grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by any of the investigational products may be included (eg, hearing loss) after consultation with the study chair.

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

a. Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection).

b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.

c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).

4.3.9. History of primary immunodeficiency, solid organ transplantation, or previous clinical diagnosis of tuberculosis.

4.3.10. True positive test results for human immunodeficiency virus (HIV) or hepatitis B or C.

4.3.11. Receipt of live, attenuated vaccine within 28 days prior to the first dose of

investigational products (NOTE: Subjects, if enrolled, should not receive live vaccine during the study and 180 days after the last dose of investigational products).

4.3.12. Major surgery (as defined by the investigator) within 4 weeks or thoracotomy

for pulmonary metastases within 2 weeks prior to first dose of treatment or if still recovering from prior surgery. Local surgery of isolated lesions for palliative intent is acceptable.

4.3.13. Other invasive malignancy within 2 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in situ of the breast that has/have been surgically cured.

4.3.14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from durvalumab or tremelimumab, or compromise the ability of the subject to give written informed consent.

4.3.15. Any condition that, in the opinion of the investigator or sponsor, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.

4.3.16. Patients with a history of pneumonitis or interstitial lung disease.

4.4 Subject enrollment

Study participation begins (ie, a subject is "enrolled") once written informed consent is obtained. Once informed consent is obtained, and the patient is enrolled an accession number will be assigned, and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The accession number will be used to identify the subject during the screening process and throughout study participation, if applicable. A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria), including the reason(s) for screening failure. Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not receive investigational product. There can be no exceptions to this rule. Subjects who are screening failures should be withdrawn from the study.

4.5 Withdrawal from the Study

Subjects are at any time free to withdraw from the study without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse

events will be followed up by the investigator for as long as medically indicated.

4.5.1 Withdrawal from Treatment

If a subject withdraws consent to further treatment, they will not receive any further investigational product(s), but may continue with further study observation. Subjects who decline to return to the site for evaluations will be offered follow-up by phone according to the schedule in Section 4.2.3 as an alternative. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.5.2 Withdrawal of Consent

If consent is withdrawn, the subject will not receive any further investigational product(s) or further study observation. Note that the subject may be offered additional tests.

4.5.3 Lost to Follow-up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at that time. Subjects, who refuse continued participation in the study, including phone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

4.6 Discontinuation of investigational product

An individual subject will not receive any further investigational product (durvalumab and tremelimumab) if any of the following occur in the subject in question:

1. Withdrawal of consent from further participation in study
2. Lost to follow-up
3. An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing. If toxicity was noted with the combination, investigator can decide to continue durvalumab alone in case patient is having clinical benefit (SD or better).
4. Subject experienced unacceptable toxicity as defined in Section 3.2.2
5. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational product dosing might constitute a safety risk
7. Pregnancy or intent to become pregnant
8. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (eg, refusal to adhere to scheduled visits)
9. Initiation of alternative anticancer therapy including another investigational agent

10. Confirmation of PD and retreatment criteria in the setting of PD are not met (absence of clinical symptoms or signs indicating clinically significant disease progression; no decline in Eastern Cooperative Oncology Group (ECOG) performance status compared to baseline; and absence of rapid disease progression or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.

4.6.1 Replacements of subjects

Nonevaluable subjects who withdraw consent prior to any study related treatment or are unable to begin treatment will be replaced.

4.6.2 Withdrawal of consent for data and biological samples

Study data are protected by the use of an accession number, which is a specific number for each subject. The investigators are in control of the information that is needed to connect a study sample to a subject. A subjects consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn any samples collected prior to that time may still be used but no additional data or samples will be collected unless specifically required to monitor safety of a subject.

5. SCHEDULE OF STUDY PROCEDURES

All patients will have history/physical examinations & laboratory assessments during the screening phase (day -30 to day -1) and prior to each drug administration every four weeks. Laboratory assessments for toxicity will be every 2 weeks for the first four months then the frequency will change to every 4 weeks. Patients with grade 3 or 4 immune-related adverse events (irAEs) will receive immunosuppressive treatment with systemic corticosteroids as per protocol.

Baseline imaging studies (CT-scans and/or MRI-scans) should be within 30 days prior to treatment initiation. The first restaging assessment will be performed at week 8 (+/- 1 week) with a confirmatory scan at 12 weeks (+/- 1 week). Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and Immune Response Evaluation Criteria in Solid tumors (iRECIST) will be used to measure response to treatment. Thus, the patient will continue on treatment until confirmed disease progression, unacceptable toxicities, or unless the patient chooses to withdraw consent for study participation.

Baseline biopsies will be obtained prior to treatment initiation (archived sample is acceptable if it is within 6 months with no intervening therapy including radiation to the biopsied lesion). In

each cohort we hope to have at least 10 patients that undergo a repeat biopsy at 6 weeks (+/- 1 week). Those patients who undergo a fresh biopsy prior to the start of the treatment will be encouraged to get the on-treatment biopsy to ensure availability of matched fresh tumor specimens for correlative analysis. Those patients with an increased risk from repeat biopsy as determined by the PI and the IR physician will be exempt. These biopsies would be obtained through interventional radiologic techniques with exception to superficial tumors that are accessible by punch biopsy. Blood work obtained for correlative studies would be performed at baseline, week 2, and week 6 (+/- 1 week for all time points). Blood draw for correlative biomarkers should coincide with the biopsy date when feasible. Optional biopsy and a blood draw for correlative studies will be performed at the time of confirmed progression in patients with prior evidence of response.

5.1 Enrollment/screening period (Day-30 to Day 1):

Table 4 All procedures to be conducted at the screening visit.

Procedure	Screening/Baseline
	Days -30 to Day 1
Written informed consent/assignment of an accession number	X
Verifyeligibility criteria	X
Tumor and disease assessments	
History of prior cancer treatment	X
Disease assessment by irRECIST (CT / MRI / (PET/CT), including evaluation for brain metastases	X
Study procedures and examinations	
Demographics (including date of birth, sex, race, ethnicity)	X
Medical history	X
Physical examination, height, weight	X
ECOG performance status	X
12-lead ECG[a]	X
Vital signs	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Laboratory tests	
Serumchemistry	X
Hematology	X
Thyroid function tests (TSH, free T3, and free T4)	X
Urinalysis	X
Serum pregnancy test	X
Hepatitis B and C; HIV[b]	X
Other laboratory tests and assays	
Archival tumor sample (if one obtained within the past 6 months is available with no intervening treatment including radiation to the biopsied lesion)	X
Fresh tumor biopsy (if no recent archival sample available as above)	X
Correlative laboratory assays (5 purple-top tubes, 8-10 ml per tube)	X

AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; MRI = magnetic resonance imaging; PET= positron emission tomography; SAE = serious adverse event; SID = subject identification; TSH = thyroid-stimulating hormone.

[a] At screening, ECGs will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart).

[b] Do not need to be repeated if negative result obtained within the last 3 months with no intervening symptoms or exposures.

5.2 Treatment period

Procedures to be conducted during the treatment period are presented in Table 5 for Weeks 0 to 44 and in Table 6 for Week 45 through end of treatment.

All samples are collected predose unless otherwise indicated.

Table 5 Schedule of Treatment Period Study Procedures Weeks 0 to 44

Study Period												
Week/Day	**W0 D1**	**W 2 D1**	**W4 D1 ± 3D**	**W6 D1 ± 3D**	**W 8 D1**	**W1 0 D1**	**W12 D1 ± 3D**	**W14 D1 ± 3D**	**W1 6 D1**	**W20 D1 ± 3D**	**W2 4 D1**	**W28,W32,W36 , W40, W44 D1 ± 3D**
Procedure/Study Day	**1**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**141**	**169**	
Durvalumabadministration **(Q4W dosing schedule)**	X		X		X		X		X	X	X	X
Tremelimumabadministration **(Q4W dosing schedule)**	X		X		X		X					
Tumor and disease assessments												
Disease assessment by irRECIST (CT /(PET)CT/ MRI) [a]					X		X			X		X
Fresh tumor biopsy				X [b] ± 7D								
Study procedures and examinations												
Physical examination, weight[f]	X		X		X		X		X	X	X	X
ECOG	X[c]		X		X		X		X	X	X	X
Vital signs [d]	X		X		X		X		X	X	X	X
12-lead ECG [e]	X											
Assessment of AEs/SAEs	X		X		X		X		X	X	X	X

Concomitant medications	X		X		X		X		X	X	X	X
Laboratory tests												
Serumchemistry [g]	X	X	X	X	X	X	X	X	X	X	X	X
Hematology [g]	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid function tests (TSH, free T3, free T4)	X		X		X		X		X	X	X	X
Urinalysis	X											
Urine or serum pregnancy test	X											
Correlative laboratory assays (5 purple-top tubes, 8-10 ml per tube)												
Flowcytometry		X		X								
PBMCcollection		X		X								
miRNA/mRNAcollection(whole blood PAXgene RNA tube)		X		X								

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; miRNA = micro ribonucleic acid; MRI = magnetic resonance imaging; mRNA = messenger ribonucleic acid; PBMC = peripheral blood mononuclear cell; Q4W = every 4 weeks; RNA = ribonucleic acid; SAE = serious adverse event; TSH = thyroid-stimulating hormone; W =week

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of MEDI4736/tremelimumab unless otherwise indicated. Tremelimumab will be administered first and the infusion duration will be approximately 1 hour. The MEDI4736 infusion will start approximately 1 hour post EOI of tremelimumab and the infusion will be administered over approximately 1 hour.

a. All Imaging time points have a window of +/- 1 week. After W12, restaging scans will be obtained every 8 weeks.

b. Optional on-treatment biopsy at 6 weeks (+/- 1 week). We plan to biopsy at least 10 patients in each of the 6 cohorts on-treatment. Those patients who undergo a fresh biopsy prior to the start of the treatment will be encouraged to get the on-treatment biopsy to ensure availability of matched fresh tumor specimens. Those patients with an increased risk from repeat biopsy as determined by the PI and the IR physician will be exempt.

c. If physical examination or safety laboratory tests are performed within 3 days prior to Dose 1, they do not need to be repeated.

d. Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on MEDI4736/tremelimumab treatment days. Vital signs will be measured prior to the start of tremelimumab and durvalumab administration, during and at the end of infusion per institutional guidelines. For the first day of administration of investigational product, an additional 60 minutes (± 15 minutes) post MEDI4736 infusion period of observation will be required.

e. On Day 1, ECGs will be obtained in triplicate (all 3 within a 5-minute time period) within 30 minutes prior to start of tremelimumab infusion.

f. Weight and height will be assessed (at screening only)

g. Week 2, 6, 10, and 14 labs window +/- 7 days

5.3 Follow-up period

Table 6 shows all procedures to be conducted during the end of treatment visit and follow-up period. For subjects who 12 months of therapy, the last dosing visit within the 12-month period is considered to be the end of treatment visit. Subjects who discontinue before 12 months will complete the end of treatment visit at the time the decision is made to discontinue treatment. Patient will complete all 12 cycles of treatment if meets all criteria per protocol even if greater than 12 months.

All subjects are to complete the end of treatment visit, all follow-up visits and be contacted for survival status in accordance with the Schedule of Assessments. However, if a subject discontinues from treatment and moves onto alternative anticancer treatment, the follow-up visits will no longer be required; however, survival follow-up assessments would be required as indicated in the Schedule of Assessments unless the subject withdraws consent for further survival follow-up. Survival follow-up will continue until the end of study as defined in Section 5.4.1.

Table 6 Schedule of Follow-up Procedures

Study Period	**Follow-up Period**		
Procedure / Study Day or Month	**EOT** [a]	**Day 30 ± 2 Weeks**	**Every 3 Months after end of treatment ± 28 Days**
Disease assessments			
Disease assessment by irRECIST (CT, MRI, or PET/CT) [b]	X		X
Fresh tumor biopsy	X [c]		
Subsequent anticancer therapy		X	X
Survival status		X	X
Study procedures and examinations			
Physical examination,	X	X	
ECOG	X	X	
Vital signs	X	X	
Assessment of AEs/SAEs	X	X	

Concomitant medications	X	X	
Laboratory tests			
Serumchemistry	X	X	
Hematology	X	X	
Thyroid function tests (TSH, free T3, free T4)	X		
Correlative laboratory assays (5 green-top tubes, 8-10 ml per tube)			
Flowcytometry	X[d]		
PBMCcollection	X[d]		
miRNA/mRNA collection (whole blood PAXgene RNA tube)	X[d]		

AE = adverse event; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment;

irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; TSH = thyroid-stimulating hormone

[a] For subjects who complete the 12-month treatment period, the last dosing visit within that period is considered to be the EOT visit. Subjects who discontinue before 12 months will complete the EOT visit at the time the decision is made to discontinue treatment.

[b] If a subject discontinues treatment due to confirmed PD, only the EOT disease assessment is required.

[c] Optional tumor biopsy collected once upon confirmed PD.

[d] Blood for correlative markers will also be obtained at EOT

After 90 days, subjects with investigational product-related SAEs will continue to be followed until resolution as determined by the treating physician for safety.

5.4 Efficacy assessments

5.4.1 Efficacy

Tumor assessments will be based on irRC (54) and will be performed according to the schedule presented in Section 5. Investigators are required to assess the subjects based on irRC and irRECIST. Antitumor activity will a l s o be assessed by RECIST guidelines v1.1 during central review of scans. After end-of-treatment subjects will be followed for progression and survival every 3 months (± 28 days) thereafter (according to the schedule in Table 6) through the end of the study (defined as 5 years after the final subject is enrolled or when all data points to assess the end-points of this study have been collected).

Tumor assessments may include the following evaluations: physical examination (with photograph and measurement of skin lesions as applicable); cross-sectional imaging using CT, positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis, and CT or MRI scan of the brain. Computed tomography or MRI scan of the brain will be performed if the subject is neurologically symptomatic. The preferred method of disease assessment is CT with contrast. The same method is preferred for all subsequent tumor assessments. If PET/CT imaging is utilized, the metabolic changes (alterations in FDG avidity) will be noted, but these changes alone will not guide therapy unless the treating investigator deems it to be necessary and it is approved by the principal investigators.

5.4.1.1 Physical examination

Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesion.

5.4.1.2 Computed tomography scan with contrast of the chest, abdomen, and pelvis (optional scan of pelvis unless known pelvic disease is present at baseline)

Computed tomography scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

5.4.1.3 Magnetic resonance imaging scans

Magnetic resonance imaging of the chest, abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. Computed tomography or MRI scan of the brain will be performed only at screening or if the subject is neurologically symptomatic. If possible, the same imaging modality should be used for serial

evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

5.4.1.4 Positron Emission Tomography – Computed Tomography

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 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.

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.

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

5.4.2 Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the

slice thickness and a minimum of 10 mm).

- 10 mm caliper measurement by clinical exam (when superficial).
- Malignant lymph nodes are considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as all other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

- **Target Lesions -** At baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. 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.

- **Non-target Lesions -** It is possible to record multiple non-target lesions involving the same organ as a single item (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

- **New Lesions -** If measurable, new lesions will be measured and included as target lesions. Up to 3 additional target lesions (maximum of 2 additional lesions per organ) may be added in this way. Other new lesions will be included as non-target lesions.

5.4.3 Evaluation of Tumor Response by irRC

Tumor response will be assessed by the irRC and irRECIST (54). irRECIST and irRC are a reconciliation of RECIST guidelines v1.1 with the original irRC (55). The latter standard incorporated principles important for assessment of IMT for cancer, but fundamentally differed from RECIST in using 2-dimensional tumor assessment. In contrast, irRECIST is based on 1- dimensional tumor measurement, but it differs from RECIST guidelines v1.1 in the following key ways:

- Under RECIST guidelines v1.1, the appearance of new lesions indicates PD. Under irRECIST, new measurable lesions are incorporated in the tumor burden, which is used

to determine immune-related progressive disease (irPD), immune-related partial response, and immune-related complete response (irCR). New nonmeasurable lesions preclude irCR.

- Under RECIST guidelines v1.1, there is no confirmation for PD. In addition, responses and irPDs must be confirmed by consecutive scans at least 4 weeks apart, assuming no clinical deterioration.

The following sub-sections describe irRECIST in more detail.

5.4.3.1 Tumor Burden

At baseline, the tumor burden is the sum of single diameters (short axis for nodal lesions, longest diameter for other lesions) for the target lesions. In subsequent scans, the diameters of new measurable lesions are added to the tumor burden. If a subject is retreated, then up to 5 target lesions (perhaps different from the original lesions) will be selected and a new baseline tumor burden will be established.

5.4.3.2 Overall Response at a Single Time Point

Table 7 shows the disease response will be determined at a single assessment based on irRECIST.

Table 7 Immune-related Response Evaluation Criteria in Solid Tumors: Overall Response

Tumor Burden (Baseline and New)	Non-Target Lesions (Baseline and New)	Response
Disappearance of non-nodal lesions. All pathologic lymph nodes < 10 mm (short axis)	Disappearance of non-nodal lesions. All pathologic lymph nodes < 10 mm (short axis)	irCR [a]
≥ 30% decrease from baseline	Any	irPR [a]
≥ 20% increase from nadir and at least 5 mm	Any	irPD [a]
Neither sufficient decrease to qualify for PR, nor sufficient increase to qualify for PD	Any	irSD
Disappearance of all non-nodal lesions. All pathologic lymph nodes < 10 mm	Any other than disappearance of all non-nodal lesions and reduction of pathologic lymph nodes < 10 mm	irPR [a]
Not all evaluated [b]	Any	irNE

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irNE = immune-related not evaluable; irSD = immune-related stable disease; PD = progressive disease; PR = partial response.

[a] Selection as best overall response requires confirmation by 2 consecutive measurements at least 4 weeks apart.

[b] If some lesions are measured, response may be inferred from available measurements. For example, growth in evaluated target lesions may be sufficient for irPD regardless of status of non-evaluated lesions.

5.5 Safety assessments

The following laboratory variables will be measured:

5.5.1 Laboratory Safety Variables

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically concerning abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

The following clinical laboratory tests will be performed according to the schedules of procedures in Sections 5.1, 5.2 and 5.3.

Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (ALP)
- Total bilirubin
- Thyroid stimulating hormone (TSH), free T4, free T3
- Amylase
- Lipase
- Gamma glutamyltransferase
- Lactic dehydrogenase
- Uric acid
- Creatinine
- Blood urea nitrogen
- Glucose
- Albumin
- Total protein
- Indirect bilirubin – not required for week 10 or 14

Note for serum chemistries: Tests for AST, ALT, ALP, indirect bilirubin and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology

- White blood cell count with differential
- Hemoglobin
- Prothrombin time/ International Normalized Ratio
- Platelet count
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration

Urinalysis

- Color
- Appearance
- Specific gravity
- Glucose
- Ketones
- Blood

- pH
- Protein
- Bilirubin

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin
- Serum beta-human chorionic gonadotropin (at screening only)

Other Safety Tests

- Hepatitis B surface antigen, hepatitis C antibody
- Human immunodeficiency virus (HIV) antibodies

5.5.2 Physical examination

Physical examinations will be performed according to institutional guidelines on study days noted in Sections 5.1, 5.2 and 5.3, and weight and height will be assessed (at screening only). Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the prestudy grade or below.

5.5.3 ECG

Electrocardiograms (12-lead) will be recorded on study days as noted in Sections 5.1 and 5.2. Electrocardiograms recorded on Day 1 will be obtained in triplicate (all 3 within a 5-minute time period). In case of clinically significant ECG abnormalities, including an ECG that demonstrates a QT corrected using Fridericia's formula (QTcF) value > 500 millisecond, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation.

5.5.4 Vital signs

Vital signs (temperature, blood pressure [BP], pulse rate, and respiratory rate) will be measured on study days noted in Sections 5.1, 5.2 and 5.3.

5.6 Other assessments

5.6.1 Biomarker analysis

Sample collection and processing. Both diagnostic and research tissue collection activities will be performed by members of the MD Anderson Cancer Center Institutional Tissue Bank (ITB) supervised by specialized pathologists. Tissue, cell and blood specimens will be processed immediately after procurement in order to preserve the qualityof tissue, cells and analytes. All

biospecimens will be collected using the *Biorepository NCI Best Practices*, and standard operating procedures (SOPs). All specimens and derivatives are given de-identified numbers.

Translational studies to be performed on tissue and blood will be detailed in a separate manual. A brief description of each type of specimen collection and processing is included below:

1) Core needle biopsy (CNB) samples: At least 5 cores will be obtained from the CNB procedure, and if possible, fine needle aspiration (FNA) specimens will be collected. Whenever possible additional passes to obtain fresh tissue for flow cytometry will be done. The CNB cores (~6-8 mm in length) will be processed as FFPE and fresh frozen specimens. The FNA samples will be placed on 4-6 smears and fixed in alcohol-based fixative immediately after collection, and if possible, a cell-block specimen will be prepared. The CNB and FNA specimens will be examined for quality control and pathological characterization before being utilized for immune-profiling, as well as for DNA, RNA, protein extractions and flow. These samples will be stored at -80°C.

2) Tissue collection from surgically resected tumors (during or prior to start of therapy): Fresh frozen and formalin-fixed and paraffin-embedded (FFPE) specimens will be obtained. For fresh frozen and FFPE collections, at least two specimens, tumor and adjacent normal tissue will be removed from removed from the surgically resection immediately. The fresh specimens if obtained will be used for: a) fresh tissue for flow cytometry and other procedures that require fresh tissue samples; b) "snap" frozen in liquid nitrogen; c) RNA "later"; d) OCT embedded; and, e) fixation in formalin. Samples will be stored at -80°C for subsequent isolation of nucleic acids and protein. For all fresh tissue samples, corresponding FFPE tissues will be available, including tumor and normal tissue specimens. The tissue specimens will be examined for quality control and pathological characterization before being utilized for immune-profiling, as well as for DNA, RNA and protein extractions.

3) Peripheral blood specimens: Blood will be collected at baseline, week 2, week 6 and at confirmed progression (5 green-top tubes, 8-10 ml per tube at each time point) per patient. Of those, plasma and peripheral blood mononuclear cells (PBMCs) will be immediately obtained, aliquoted and stored at -80°C.

Pathological evaluation and quality control (QC). All tissue specimens collected will be reviewed by a reference pathologists. At least, three types of QC activities for specimens collected will be performed: a) histology/cytology examination of the tissues and cells; b) tissue quality assessment of fresh specimens for extraction of DNA, RNA and proteins, and to prepare histology specimens such as whole sections for immunohistochemistry and

immunofluorescence; and, c) quality assessment of DNA, RNA and protein extracted. All histology stained samples will be scanned and digital images will be available.

Nucleic acids and protein extraction. All blood, tumor and corresponding normal tissue samples will be subjected to DNA, RNA and protein extraction using standard methods. DNA and RNA quantity and integrity will be assessed using NanoDrop 1000 spectrophotometer (Nanodrop technologies) and Pico-green analysis. Also, protein lysate will be extracted using standard methods.

Immuno-profiling: Fresh frozen and FFPE tissues will be used for analysis of immune markers. For immunohistochemistry (IHC) and immunofluorescence (IF) analyses, histology sections obtained from both type of tissue specimens will be will be utilized. IHC and IF will be performed on autostainers or manually. All antibodies used will be optimized for IHC/IF by examination of positive and negative controls and testing of the antibodies standard methods, including Western blotting. All pathology slides will be scanned into a digital image scanner and analyzed using image analysis software, including among others the Aperio Image Toolbox™ (Leica Biosystems) and Inform™ (Perkin-Elmer). For quantification of immune markers (immune cells infiltrates, immune checkpoints and other proteins) whole tissue sections or five randomly selected one-mm square areas within the tumor region will be selected for analysis. In selected cases, peritumoral and intratumoral areas will be examined. The expression of markers in malignant cells will be evaluated using image analysis to determine the percentage of positive cells (0 to 100) and intensity (0 to 3+), with a total score ranging from 0 to 300 (H-score system). The expression of protein markers and inflammatory cells will be examined using an infiltrate density score established by the number of cells expressing a determined marker by tissue area. The data and digital images will be deposited in a central database for review of pathology collaborators. For muliplex IF analysis, we will use the specialized microscopes such as the Vectra system (Perkin-Elmer) which includes the Nuance software. Among other markers, we will study the expression of the following PD-L1, PD-1, FOXP3, CD3, CD4, CD8 CD20, CD45Ro, CD57, CD68, and Granzyme B; additional markers will be selected according the results of the initial analysis.

As additional exploratory analysis, we will consider to perform tumor DNA genotyping by next-generation sequencing and other methodologies to identify mutations, copy number variations and translocations, as well as to perform clonal analysis of T and B cells. Gene expression analysis of immune and other relevant signatures using RNA sequencing, microarray and other methodologies (e.g., RNA-sequencing, Nanostring™, HTG EdSeq™, in situ hybridization, etc.) will be also used as exploratory methodologies to identify expression of gene(s) associated to

outcome of patients. Finally, protein analysis of tissues' lysates may be performed applying protein arrays (e.g., RPPA, multiplex ELISA, etc.), mass spectrometry and other techniques to identify protein(s) correlated with patients' outcome.

5.6.2 Storage, re-use and destruction of biological samples

If the patient agrees, the remaining biomarker samples (tumor, blood) may be stored for up to 15 years and further analyzed to address scientific questions related to MEDI4736 and tremelimumab, findings related to the drug class or disease, as well as reagent and assay availability.

5.6.3 Withdrawal of Informed Consent for donated biological samples

Studydata are protected by the use of a SID number, which is a specific number for each subject. The investigators are in control of the information that is needed to connect a study sample to a subject. A subjects consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn any samples collected prior to that time maystill be used but no additional data or samples will be collected unless specifically required to monitor safety of a subject.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

6.1 Definition of Adverse Event

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

6.1.1 Unexpected Adverse Event

An AE is "unexpected" when its nature (specificity), severity, or frequency are not consistent with (a) the known or foreseeable risk of AE associated with the research procedures described in the protocol, informed consent form or the investigator brochure.

6.1.2 Serious Adverse Event (SAE)

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

When there is doubt regarding an AE meeting the criteria for an SAE, the investigator should default to reporting the AE as an SAE.

There are special circumstances in which an SAE reporting form is used to communicate important clinical trial safety observations that may not constitute an SAE.

1. Pregnancy: Although pregnancy is not considered an SAE and is instead a normal human experience, all pregnancies reported in the month before or month after last investigational treatment must be reported to sponsor.

1. Overdose: An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. For reporting purposes, an overdose will be considered, regardless of adverse outcome, as an important medical event. All cases of overdose must be reported immediately to the sponsor.

6.1.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eyeskin, haematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis.
- In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.
- Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

6.2 Adverse Event Severity

All AEs will be evaluated according to the NCI CTCAE v4.03 (2010)

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. For AEs not listed in this reference scale, severity will be assessed by the investigator according to the criteria in Table 8.

Table 8 Adverse Event Severity Assessment

Grade 1 (Mild)	Requires minimal or no treatment and do not interfere with the patient's daily activities.
Grade 2 (Moderate)	Results in a low level of inconvenience or concern and may interfere with the patient's functioning.
Grade 3 (Severe)	Interrupts a patient's usual daily activity, may be incapacitating and may require systemic drug therapy or other treatment.

Grade 4 (Life threatening)	Places the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death.
Grade 5 (Death)	Death

Changes in the severity of an AE should be documented to enable an assessment of the duration of the event at each level of intensity. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

6.3 Relationship to Investigational Drug

The relationship between an AE and the study treatment will be determined by the investigator on the basis of his or her clinical judgment and the definitions in Table 9.

Table 9 Assessment of Relationship

Definitely related	AEs clearly attributable to study treatment administration
Probably related	AEs for which there is a reasonable possibility of causal association to study treatment
Possibly related	AEs for which there is confounding by comorbidities, medications or other considerations but for which it is not unreasonable that the AE may have been caused by study treatment It is not appropriate to invoke "you can't rule it out."
Not related	AEs that are clearly not causally related to study treatment, or for which there is a clear alternative explanation

AE = adverse event

If there is any question whether or not an AE is possibly, probably or definitely related, the investigator should default to conservatism in categorization. Similarly, the investigator should default to conservatism by calling an AE an SAE if there is doubt regarding the serious nature of an AE.

6.4 Adverse Event Collection Period

All enrolled patients will have periodic assessment of clinical and laboratory AEs. Please see Section 6.5 for guidelines on AE Reporting.

6.5 Adverse Event Reporting

At each study visit (including unscheduled visits), the investigator, or designee, will determine whether any AEs have occurred. Any AE that is possibly, probably or definitely related to study drug (section 6.3) will be reported in the patient's medical record and on the AE CRF page and each will be classified according to the criteria in Section 6.2 and 6.3. Any AEs that are grade 3 and above (section 6.2) regardless of relationship, will be reported in the patient's medical record and on the AE CRF page and each will be classified according to the criteria in Section 6.2 and 6.3. If known, the diagnosis should be recorded, in preference to the listing of individual signs and symptoms. Adverse event reporting for each patient starts when the patient signs the ICF and continues at all subsequent visits through the end-of-treatment visit. Any pre-existing conditions that are detected as part of the initial screening procedures will need to be reported in the medical history and not as an AE. However, pre-existing conditions that worsen after enrollment should be reported as an AE. Adverse events will be reported to FDA in accordance with the requirements outlined in 21 CFR 312.32. AESI's will be expedited to regulatory authorities, study investigators and DMC.

Each AE will also be assessed for meeting the criteria for a serious adverse event. If the AE meets the criteria of a SAE, expedited reporting must occur.

6.6 Serious Adverse Event Reporting

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

If a SAE occurs and is deemed related or possible related (expected and unexpected), Medimmune will be notified within 5 days of awareness of the event. In particular, if the SAE

is fatal, Medimmune must be notified within 24 hours, irrespective of the extent of available AE information. In the rare event that the investigator or designee does not become aware of the occurrence of a SAE immediately, the investigator or designee must report the event within 5 days (non-fatal SAE's) or 24 hours (fatal SAE's) of their awareness and document the time of when his/her first awareness occurred. Institutional guidelines for SAE reporting will be followed in addition to the above.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

6.7 Pregnancy

Sexually active men and FCBP must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized. Before enrolling FCBP in this clinical trial, all FCBP must be advised of the importance of avoiding pregnancy during trial

participation and the potential risk factors for an unintentional pregnancy. All patients (men and women) must sign an informed consent form documenting this discussion.

All FCBP must have a negative pregnancy test within 3 days prior to the study treatment initiation. If the pregnancy test is positive, the subject must not be enrolled in the study.

In addition, all FCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If following initiation of study treatment, it is subsequently discovered that a trial subject is pregnant or may have been pregnant within one month before or after study treatments will be permanently discontinued and the patient will be followed as possible by the investigator or designated health care professional to determine pregnancy outcomes for both mother and baby. If a male patient enrolled in study has a female sexual partner who becomes pregnant after initiation of study, then the study subject should be asked permission for the investigator (or designated health care professional) to approach his partner for permission to follow-up with the pregnant partner to determine outcomes for both mother and baby.

6.8 Overdose

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

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 reported as an SAE. The investigator will use clinical judgment to treat any overdose.

6.9 Protocol Deviations

A protocol deviation is any change, divergence or departure from the study design or procedures defined in the protocol such as the accidental destruction of a tissue biopsy sample intended for phenotyping to characterize the subject's type of tumor in order to determine study eligibility, or an accidental misread of a laboratory value as being within the reference range when it actually is sufficiently abnormal to preclude study participation by the subject.

Important protocol deviations are a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect

a subject's rights, safety or well being such as the PI prescribing or administering the wrong treatment, or the study subject being scheduled to return for follow-up intervention outside the protocol-dictated window as a convenience to the patient or study staff.

The investigator is responsible for complying with and adhering to IRB procedures for reporting protocol deviations and violations. All protocol deviations should be documented and forwarded to Medimmune or its authorized representative on a yearly basis. All protocol violations will be reported as per MD Anderson's institutional guidelines.

Protocol deviations will be collected during the study, and reported to the IRBs yearly in the annual report.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

7.1.1 Durvalumab

Investigational Product: Durvalumab is a human immunoglobulin (Ig)G1κ mAb directed against PD-L1, with reduced binding to C1q and the Fcγ receptors. Durvalumab is selective for human PD-L1 and blocks the binding of human PD-L1 to the human PD-1 and CD80 receptors. Medimmune is the manufacturer of durvalumab.

Therapeutic Indication: Durvalumab is being developed for the treatment of patients with advanced sarcomas.

7.1.2 Tremelimumab

Investigational Product: Tremelimumab is a human immunoglobulin (Ig)G2 monoclonal antibody (mAb) specific for human cytotoxic T lymphocyte-associated 4 (CTLA-4; cluster of differentiation [CD] 152). Tremelimumab has no cross-reactivity to related human proteins, or to mouse, hamster, rat, or rabbit CTLA-4, but it does demonstrate cross-reactivity to cynomolgus monkey CTLA-4. Medimmune is the manufacturer of tremelimumab.

Therapeutic Indication: Tremelimumab is being developed for the treatment of patients with advanced sarcomas.

7.1.3 Summary

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	1500 mg Q4 weeks	MedImmune
Tremelimumab	75 mg Q4 weeks	MedImmune

7.2 Dose and treatment regimens

The dose of durvalumab will be 1500 mg every 4 weeks, and the dose of tremelimumab will be 75 mg every 4 weeks. Both agents will be administered by intravenous (IV) infusion. Tremelimumab will be administered first, and the infusion duration will be approximately 1 hour. The durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion, and the infusion will be administered over approximately 1 hour. The combination of both agents shall be administered at Q4 week intervals for 4 doses, after which the durvalumab will continue to be at Q4 week intervals (up to 8 additional doses). If toxicity was noted with the combination, investigator can decide to continue durvalumab alone in case patient is having clinical benefit (SD or better).

7.3 Labelling

7.3.1 Durvalumab

Liquid formulation: Durvalumab is formulated at 50 mg/mL. The investigational product is supplied as a vialed liquid solution in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 500 mg (nominal) of active investigational product at a concentration of 50 mg/mL.
Mode of Administration: The reconstituted solution (for lyophilized product) or liquid product is to be diluted with 0.9% (w/v) saline for IV infusion.

7.3.2 Tremelimumab

Tremelimumab will be supplied by AstraZeneca either as a 400-mg or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

7.4 Storage

Durvalumab: Unopened vials of durvalumab lyophilized or liquid Drug Product must be stored at 2°C to 8°C (36°F to 46°F).

Tremelimumab: Unopened vials of Tremelimumab must be stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. This product should be protected from light when not in use.

7.5 Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

7.6 Accountability

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune authorized depot or disposed of upon authorization by MedImmune.

7.7 Concomitant and other treatments

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the treatment phase of the study (EOT visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the patient's medical record.

7.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 7.7.2. Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management [including palliative radiotherapy, etc]) should be used when necessary for all subjects. Opioids can be used but with caution and under medical control after discussion with the study chair.

7.7.2 Prohibited Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator to make sure they are permitted on the trial. The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy
2. Monoclonal antibodies against CTLA-4, PD-1, or PD-L1 through 90 days post last dose during the study
3. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), IMT, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Temporary uses of corticosteroids for concurrent illnesses (eg, food allergies, CT scan contrast hypersensitivity, etc) are acceptable upon discussion with the Principal Investigators
5. Live attenuated vaccines during the study through 180 days after the last dose of investigational product
6. Inactivated vaccinations ± 30 days around any dose of investigational product
7. Herbal and natural remedies should be avoided

8. STATISTICAL ANALYSES

8.1.1 Statistical considerations

Response to systemic therapy in metastatic/refractory disease is low and is less meaningful if not correlated with improvement in survival. For this reason, PFS has become an acceptable metric in the measurement of efficacy in sarcomas with refractory disease or in sarcomas with primary resistance to anthracycline-based chemotherapies. The objective data to support use of PFS as a primary end point in sarcomas was derived from a review of the EORTC sarcoma database by van Glabbeke *et al* in 2002 (46). In the EORTC analysis, which involved 12 clinical trials, patients with no prior treatment received experimental agents were compared to those with prior systemic treatment who were received experimental agents. In a multivariate analysis, patients with prior therapy obtained an improved PFS with active agents compared to inactive agents. For previously treated patients, an **active agent** was associated with a PFS of

at least 39% and 14% at 3 months and 6 months, respectively. **Inactive agents** were associated with a PFS of 21% and 8% at 3 months and 6 months, respectively.

A concern with the use of PFS at 3 months as a primary endpoint for this study is whether response assessment at 3 months will fail to capture patients who may have delayed benefit from check-point inhibitors, however it has been shown that the majority of patients with response to anti-PD-1 therapy obtained response within 12 weeks of drug initiation (9).

The goal of this trial is to assess the efficacy of MEDI4736 in combination with tremelimumab by evaluating progression-free rate at 12 weeks for each cohort.

Design and sample size/power

For cohort 3, 4 and 5, we will treat up to 25 patients within each cohort. The primary efficacy endpoint will be progression-free survival at 12 weeks ($PFS_{12\ weeks}$). 12-week PFS is defined as evidence of stable disease or better 12 weeks after the initiation of therapy. In the meanwhile, we will also monitor the toxicity of the agent (56). Toxicity will be assessed within the first two cycles of the treatment. If there is a high probability that the $PFS_{12\ weeks}$ is unlikely to be at least 40% or that the unacceptable toxicity rate (as described in section 3.2.2) is likely to be greater than 30%, the drug would not be considered of interest for further study. Formally if $Pr(PFR_{12\ weeks} < 0.40 \mid Data) > 0.90$ or $Pr(\text{toxicity rate} > 0.30 \mid Data) > 0.90$, the corresponding cohort will be stopped. The assumed prior distribution for $PFS_{12\ weeks}$ is Beta (0.4, 0.6) and for toxicityis Beta (0.3, 0.7). The resulting prior means are 0.40 and 0.3 for $PFS_{12\ weeks}$ and toxicity rate, respectively, with one patient worth of information. Each of the disease cohorts will be monitored separately in cohorts of 5 patients after a minimum of 5 patients have completed two cycles, a summary will be submitted to the IND Office Medical Monitor after each cohort of 5 patients. All patients who receive at least one study related treatment will be included in the analysis. Patients who are not evaluable for response to the treatment by 12 weeks post treatment initiation will be considered treatment failure. Patients who withdraw consent or become ineligible prior to receiving any study related treatment (full or partial dose) will be replaced. Consideration will be given to stop the cohort according to the following stopping boundaries.

Table 10 Stopping boundaries for $PFS_{12\ weeks}$ futility monitoring or for excessive toxicity monitoring within each cohort

# Patients (Inclusive)	# 12-week PFS (Inclusive)	# Toxicities (Inclusive)
5	0	4-5
10	0-2	6-10
15	0-3	8-15
20	0-5	9-20
25	Always stop with this many patients	Always stop with this many patients

Table 11 Operating characteristics for the stopping rules for $PFS_{12\ weeks}$ futility monitoring or for excessive toxicity monitoring in the expansion phase

True Progression-Free Rate	True toxicity Rate	Probability Stop Early	Average number of patients treated
0.20	0.15	0.86	11.8
0.20	0.30	0.88	11.4
0.20	0.45	0.95	10.0
0.20	0.50	0.97	9.3
0.40	0.15	0.25	21.3
0.40	0.30	0.35	20.1
0.40	0.45	0.71	15.7
0.40	0.50	0.83	13.8
0.60	0.15	0.02	24.6
0.60	0.30	0.16	23.1
0.60	0.45	0.62	17.5

0.60	0.50	0.77	15.2

For cohort 1, 2 and 6, since these include more than distinct subtypes, in order to assess anti-tumor activity of the treatment regimen within each histologic subtype, we will open enrollment simultaneously for each of the histologic subtypes but keep the maximum number of patients at 25 in each of these cohorts. The stopping boundaries for PFS_{12} weeks futility monitoring or for excessive toxicity monitoring in Table 10 will be applied within each histologic subtype. For example, enrollment to vascular sarcomas-Leiomyosarcomas will be stopped if none of the first 5 patients with vascular sarcomas-Leiomyosarcomas were progression-free at12 weeks or 4 or more patients had the unacceptable toxicity. With 5 patients enrolled within each histologic subtype, the probabilities of observing one or more patients with 12-week PFS are 67.2%, 92.2% and 99% if the true 12-week PFS are 20%, 40%, and 60% while the probabilities of observing four or more patients with toxicities are 0.2%, 3.1% and 18.8% if the true toxicity rate are 15%, 30%, and 50%. If 10 patients with the same histologic subtype have been enrolled, the probabilities of observing three or more patients with 12-week PFS are 32.2%, 83.3% and 98.8% if the true 12-week PFS are 20%, 40%, and 60% while the probabilities of observing six or more patients with toxicities are 0.1%, 4.7% and 37.7% if the true toxicity rate are 15%, 30%, and 50%.

8.2 Sample size estimate

The study consists of 6 cohorts arranged by histologic classifications. Within each cohort, a minimum of 5 patients (in cohorts 3, 4 and 5), 10 patients (cohort 2), 15 patients (cohort 1) and 25 (cohort 6) will be enrolled. The maximum number of patients in all the cohorts will be 25 patients. Therefore, the minimum patients to be enrolled onto this trial will 65 patients and the maximum is 150 patients.

8.3 Definitions of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis.

8.3.1 Efficacy analysis set

All patients who have received at least one dose of treatment (durvalumab and/or tremelimumab) and have disease reassessed will be considered evaluable for response. Patients who drop out the study due to drug-related toxicity and/or death before the time of first response assessment will be included in the denominator for the estimation of PFS at 12 weeks and response rate.

8.3.2 Safety analysis set

All patients who received at least 1 full or partial dose of durvalumab in combination with tremelimumab.

8.4 Outcome measures for analyses

Primary Endpoint is PFS at 12 weeks.

Seondary endpoints include 1) response rate (CR,PR) assessed by irRC and RECIST; 2) toxicities; 3) PFS and OS.

Correlative endpoints include PD-1/PD-L1, immune panels including AIC, CD4, CD8 et al measured in tumor as well as in blood samples over time.

8.5 Methods for statistical analyses

8.5.1 Analysis of the primary variable(s)

If a cohort is stopped early, this drug will not be considered of interest for future study for this cohort of patients. If all 25 patients are accrued, we will estimate both the PFS at12 weeks and toxicity rate and the corresponding 95% posterior credible intervals. We will also apply a Bayesian hierarchical statistical model (57) to analyze the data from all six cohorts to borrow information from each other.

8.5.2 Analysis of the secondary variable(s)

PFS is defined as the time from treatment onset to either disease progression as defined by RECIST or death from any cause, whichever occurs first. OS is defined as the time from treatment onset to death. For events that have not occurred by the time of data analysis, times will be censored at the last contact at which the patient was known to be progression-free for PFS, or the last time the patient was known to be alive for OS. PFS and OS will be estimated using the Kaplan-Meier method (58). Log-rank test (59) will be performed to test the difference in survival between groups. Regression analyses of survival data based on the Cox proportional hazards model (60) will be conducted on PFS or OS. The proportional hazards assumption will be evaluated graphically and analytically, and regression diagnostics (e.g., martingale and Shoenfeld residuals) will be examined to ensure that the models are appropriate.

Toxicity data will be summarized by frequency tables. For the toxicity endpoint, per-treated analysis will be used to include any patient who received the treatment regardless of the eligibility nor the duration or dose of the treatment received. Toxicity rate will be estimated with 95% credible interval.

Exploratory data analysis and graphical methods will be applied to examine the distribution of the biomarker data, error checking, and outlier identification. Range check and consistency check will be applied to ensure the data quality. Standard distribution plots such as the histogram and box-plot will be applied. A more versatile BLiP plot will be used to facilitate the plotting

of both discrete and continuous data. Since PD-1/PD-L1 IHC expression and the immune correlates will be measured at baseline and multiple post treatment time points. T-test/ANOVA or their nonparametric countparts, Wilcoxon rank-sum test/Kruskal-Wallis test will be used to detect differences of the biomarkers between groups (1) Linear mixed effect models for repeated measures analysis (61) will be employed to assess the change of the biomarkers over time with multi-covariates including disease characteristics (tumor stage, site, pathology), and other patient prognostic factors. Appropriate transformation of the outcome assessment values will be used to satisfy the normality assumption of linear mixed effect model.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first subject is entered into the study, the Principal Investigator via site Initiation Meeting will review and discuss the requirements of the Clinical Study Protocol with investigational research staff. Also, Principal Investigator will train investigational research staff in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a Delegation of Authority log.

9.2 Data and Safety Monitoring

The Principal Investigators will be responsible for monitoring the safety and efficacy of the trial, and complying with all reporting requirements. This will be accomplished under the oversight of the IND office of MD Anderson Cancer Center (MDACC).

The MDACC IND office is responsible for monitoring data quality and patient safety for all interventional investigator-initiated trials (IIT's). The MDACC IND office will have oversight of this protocol. Also, the IIT will be audited by the IND Clinical Research Quality Specialist at least once a year.

The IND reviews all IRB reportable serious adverse events, monitoring/ auditing reports, and protocol deviations and has the authority to recommend closure and/or suspension for trials on which there are safety or trial conduct issues and may submit recommendations for corrective actions. All IRB reportable serious adverse events, monitoring/ auditing reports will be reviewed by the IND. The Sarcoma Clinical Trials Center will forward the SAE

event report to the IRB using the eSAE (electronic Serious Adverse Event) reporting system and they will then be reviewed by the IND Office.

9.3 Data Collection and storage

Electronic and hard copy CRF's will be provided for the recording of data. Will be using the REDCap database for data entry and tracking. With the exception of hard copy case report forms utilized for expedited reporting requirements as described in section 6.6 Reporting of SAE's, the remainder of patient data will be collected and submitted via electronic CRFs. All data should be substantiated by clinical source documents organized within a patient research record. ICH Good Clinical Practices are to be followed.

Federal law requires that an Investigator maintain all study records for two years after the investigation is discontinued.

9.4 Study Timetable and End of Treatment

An individual subject will be considered to have completed the study if the subject was followed through the on-treatment evaluation period or the subject completed at least 1 on-treatment disease evaluation regardless of the number of doses of investigational product that was received.

The end of the treatment ("study completion") is 5 years after the final subject is enrolled or the date the study is closed as all data-points have been collected, whichever occurs first.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

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

10.2 Subject data protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

In exceptional circumstances, however, certain individuals might see the personal identifiers of a subject. For example, in the case of a medical emergency, a medical monitor or an

investigator might know a subject's identity and also have access to his or her medical information.

10.3 Ethics and regulatory review

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

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

MedImmune will provide regulatory authorities, IRB/IEC, and principal investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

Each principal investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the principal investigator so that he/she can meet these reporting requirements.

10.4 Informed consent

The principal investigator(s) will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the MD Anderson Cancer Center Investigator(s) and MedImmune.

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

The amendment is to be approved by the IRB/IEC and if applicable, before implementation.

10.6 Recruitment procedure

All patients referred to or seeking treatment for advanced stage soft tissue sarcoma and meet the eligibility criteria will be offered this trial.

Women and men will be recruited, and are anticipated to be equally represented in the trial.

Minority participation will be encouraged.

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