conCOORDINATING CENTER: University of Maryland Greenebaum Cancer Center

1711GCCC: Neoadjuvant Anti-PD-L1 (Durvalumab/MEDI4736) Plus Anti-CTLA-4 (Tremelimumab) and Radiation for High Risk Soft-Tissue Sarcoma

Investigational Drug Substance(s):	Durvalumab (MEDI4736) and Tremelimumab
Trial Phase	Integrated Phase I/II
Externally Sponsored Research #:	ESR-16-11953
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Confidentiality Statement

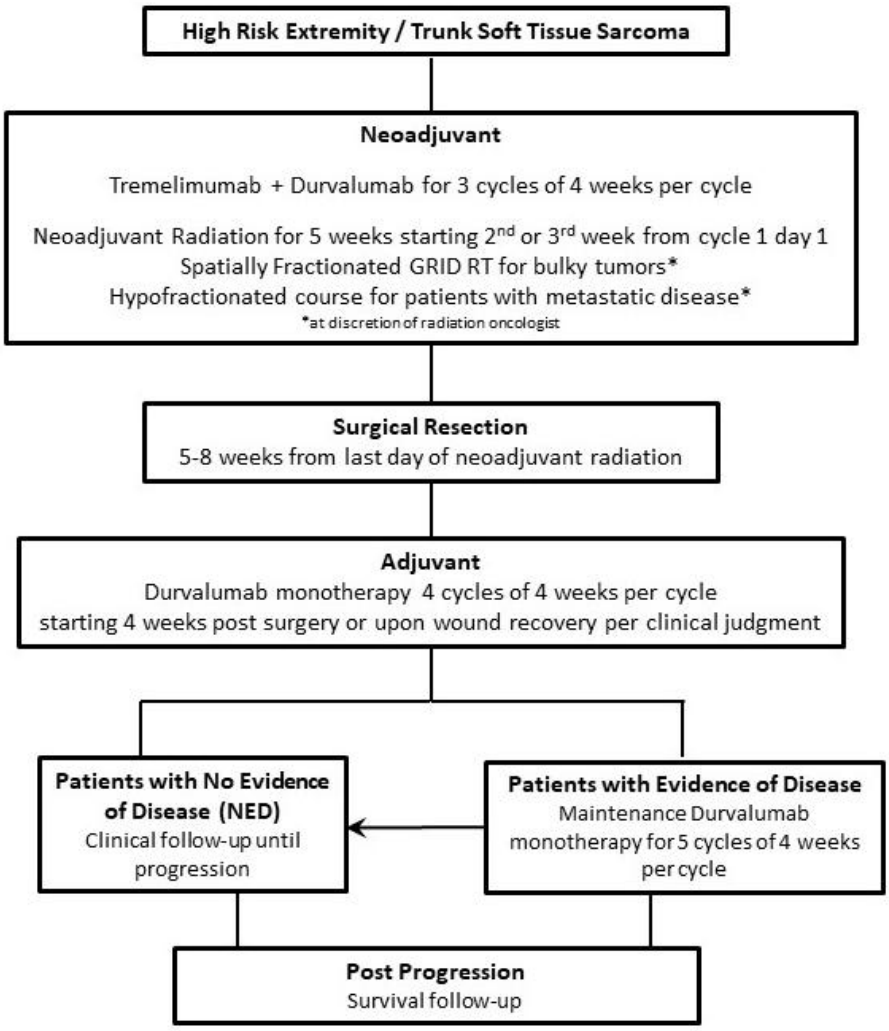
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PROTOCOL SYNOPSIS

Clinical Protocol

Study Title: Neoadjuvant anti-PD-L1 (Durvalumab/MEDI4736) Plus anti-CTLA-4 (Tremelimumab) and Radiation for High Risk Soft-Tissue Sarcoma
Protocol Number: 1711GCCC/HP-00070749, ESR-16-11953
Clinical Phase: Integrated Phase I/II
Number of Centers: Multicenter (University of Maryland, University of Arizona, Allegheny Health Network)
Investigational Product(s) and Reference Therapy: Durvalumab is supplied in a glass vial containing 500 mg of durvalumab in liquid solution for intravenous (IV) infusion after dilution. The durvalumab solution is at a concentration of 50 mg/ml. Tremelimumab is supplied in a glass vial containing 400 mg of solution for intravenous (IV) infusion after dilution. The tremelimumab solution is at a concentration of 20 mg/mL.
Investigational Product(s), Dose, and Mode of Administration: (Part 1) Neoadjuvant Durvalumab (1500 mg) and Tremelimumab (75 mg) Neoadjuvant Combination Therapy, 3 cycles of 4 weeks per cycle in patients > 30 kg (Part 2) Adjuvant Durvalumab (1500 mg) Adjuvant Monotherapy, 4 cycles of 4 weeks per cycle in patients > 30 kg (Part 3) [**Maintenance Phase Arm ONLY**] Durvalumab (1500 mg) Monotherapy, 5 cycles of 4 weeks per cycle Weight-based dosing should be utilized for patients < 30 kg Durvalumab 20 mg/kg q4w and Tremelimumab 1 mg/kg q4w

Study Flowchart for Disease Treatment



Study Assessments and Criteria for Evaluation:

Safety Assessments:

CTCAE v4.0 (Common Terminology for Adverse Events)

RTOG Toxicity Criteria (Radiation Therapy Oncology Group)

Efficacy Assessments:

RECIST v1.1

irRC (Immune Related Response Criteria)

PERCIST (Positron Emission Tomography [PET] Response Criteria in Solid Tumors)

Clinical oncological outcomes

Histopathological Outcomes

Research Hypothesis

(1) The combination of Durvalumab, Tremelimumab and RT will demonstrate histopathologic response within the primary tumor upon surgical resection.

(2) The combination of Durvalumab, Tremelimumab and RT will demonstrate a beneficial effect by decreasing the size of the primary tumor.

(3) This neoadjuvant regimen of combination immunotherapy plus radiation will be well tolerated by even those patients who would be deemed poor candidates for cytotoxic chemotherapy.

(4) Patients harboring tumors with T-cell inflamed phenotypes will have a greater response to immunotherapy, but radiation will facilitate tumor-specific immune responses even in patients with a non-T-cell inflamed phenotype.

Objectives:

Primary Objectives:

(1) **Objectives:** Phase I component: To evaluate the safety and tolerability of neoadjuvant Durvalumab/Tremelimumab and radiation therapy in patients with high-risk STS. Phase II component: To evaluate the proportion of patients achieving an excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor regression) on histopathologic examination of the surgical specimen.

Secondary Objective(s):

(2) **Objective:** To evaluate the clinical outcomes of distant relapse, progression of disease, and disease-specific survival with neoadjuvant Durvalumab/Tremelimumab and RT followed by surgical resection.

(3) **Objective:** To evaluate the effect of neoadjuvant Durvalumab/Tremelimumab and radiation therapy on the primary tumor using RECIST v1.1 and the immune-related response criteria (irRC).

(4) **Objective:** To evaluate whether neoadjuvant Durvalumab/Tremelimumab and radiation therapy produces tumor-specific immune responses within the tumor, the infiltrative

margins and surrounding reactive zone, and in the peripheral blood, and whether the strength of these responses correlate with the extent of tumor microsatellite instability and mutagenic burden.

Exploratory Objective(s):

(5) **Objective:** To evaluate the effect of neoadjuvant Durvalumab/Tremelimumab and radiation therapy on the primary tumor using PERCIST criteria

Statistical Methods and Data Analysis:

[See section 11] This trial is a seamless phase I/II single-arm trial of a fixed dose of Durvalumab (D)/Tremelimumab (T) combined with a fixed schedule of radiation therapy (RT).

The phase I component establishes the safety and provides a provisional characterization of the toxicity profile of D/T/RT by continual assessment of high-grade toxicity in the first 12 cases enrolled on the trial. The phase I component uses a Pocock boundary to make a decision to stop or continue the trial after each patient evaluated with respect to early toxicity.

The phase II component uses a Simon two-stage design with excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor regression) on histopathologic examination as the endpoint for the phase II component. 33 patients will have been enrolled at the end of the second stage. All patients enrolled during the phase I component will be evaluable with respect to efficacy as well. A full analysis of toxicity and efficacy, including clinical efficacy endpoints, will be conducted in the full trial population using the intention to treat principle.

Sample Size Determination:

[See sections 11.1.1 and 11.1.2] It is important for the validity and practical implementation of this strategy that the sequence of patients entered into the study is strictly recorded and preserved. Ideally, the design assumes that the outcome, i.e. the incidence of excessive toxicity among the first i patients is known when entering patient i+1. However, the accrual rate is expected to be around 1-2 patients per month and the time window for observing early toxicity in a patient is pragmatically defined as the time during and within two weeks after the completion of RT; therefore, insisting on complete observations before entering the next patient will slow down accrual considerably. Instead, we will allow staggered entry of cases. For patient safety reasons, no more than 4 patients will be allowed to be on active neoadjuvant treatment at any point during the phase I portion of the trial.

The primary objective of the Phase I portion of trial is to evaluate the safety and tolerability of neoadjuvant Durvalumab/Tremelimumab and radiation therapy in patients with high-risk STS. All patients entered during the phase I component are evaluable with respect to efficacy. The efficacy endpoint of the Phase II portion of trial is an excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor regression) on histopathologic examination. Based

on the literature review (Stacchiotti S et al, 2009; Chen et al, 2013; Hermann et al, 2012; Canter et al, 2010; Donahue et al, 2010; Eilber et al, 2001; Evilevitvh et al, 2008; Shah et al, 2012) for cytotoxic chemotherapy, we propose that if the excellent response rate is lower than 20% the combination is not superior to existing modalities in this regard, whereas a response rate of 40% will be seen as promising for further development.

Simon's two-stage design will be used (Simon R, *Controlled Clinical Trials*). The null hypothesis that the true response rate is 20% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these patients, the study will be stopped. Otherwise, 15 additional patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more responses are observed in 33 patients. This design yields a type I error rate of 4.5% and power of 80% when the true response rate is 40%.

Study Design: Integrated phase I/II clinical trial investigating the combination of IgG2 mAb anti-CTLA-4 Tremelimumab and IgG1κ mAb anti-PD-L1 Durvalumab/MEDI4736 as a neoadjuvant with radiation therapy, followed by surgical resection, in patients with high risk Soft Tissue Sarcomas.

Study Duration: 24 months

Number of Subjects: 35

Study Population: Patients with a biopsy-proven adult-type high-risk STS in the pelvis or extremities will be included. High-risk STS will be defined as tumors greater than or equal to 5 cm, intermediate or high grade according to FNCLCC criteria, and a location deep or superficial to fascia. Intermediate or high-grade tumors that are locally recurrent, metastatic or have had prior inadequate resections will also be included as high risk. Histologies will include the most common adult-type STS such as undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, fibrosarcoma, synovial sarcoma, angiosarcoma, epithelioid sarcoma and malignant peripheral nerve sheath tumor. Patients must have measurable disease as defined by RECIST v1.1. Their ECOG performance status must be < 2 and have adequate organ and marrow function. Patients must be ≥18 years old. Patients who have had prior cytotoxic chemotherapy or targeted systemic therapy (ex: Pazopanib, Trabectidin) will be included as long as it is greater than 4 weeks prior to the start of Durvalumab. Patients with surgically unresectable primary lesions will not be included.

Inclusion Criteria:

1. Written informed consent and any locally-required authorization (e.g., HIPAA) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
2. Patients with a biopsy-proven adult-type high-risk soft tissue sarcoma (STS) in the trunk (non-retroperitoneal) or extremities. Histologies will include the most common adult-type STS such as undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, fibrosarcoma, synovial sarcoma, angiosarcoma, epithelioid sarcoma and malignant peripheral nerve sheath tumor. STS considered high-risk as defined below:
    - Tumors greater than or equal to 5 cm, intermediate or high grade according to FNCLCC criteria, and a location deep or superficial to fascia.
    - Intermediate or high-grade tumors that are locally recurrent, metastatic or have had prior inadequate resections
    - Intermediate and High Grade Tumors shall be Grade 2 or 3 based on FNCLCC parameters (Trojani et al, 1984; Coindre 2006)
        - Tumor Differentiation
            - Score 1 (sarcomas closely resembling normal adult mesenchymal tissue)
            - Score 2 (sarcomas for which histological typing is certain)
            - Score 3 (embryonal and undifferentiated sarcomas)
        - Mitotic Count (HPF – high power field – 0.17 mm squared)
            - Score 1 (0-9 mitoses per 10 HPF)
            - Score 2 (10-19 mitoses per 10 HPF)
            - Score 3 (greater than or equal to 20 mitoses per 10 HPF)
        - Tumor Necrosis
            - Score 0 (no necrosis)
            - Score 1 (less than 50% tumor necrosis)
            - Score 2 (greater than or equal to 50% tumor necrosis)
        - Histological Grade
            - Grade 1 – total score 2 or 3
            - Grade 2 – total score 4 or 5
            - Grade 3 – total score 6, 7 or 8
3. Patients must have measurable disease as defined by RECIST v1.1.
4. Age $\geq$ 18 years at time of study entry
5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1

6. Life expectancy of $\geq$ 12 weeks based on investigator estimate
7. Adequate normal organ and marrow function as defined below:
   - Haemoglobin $\geq$ 9.0 g/dL
   - Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L ($\geq$ 1500 per mm^3)
   - Platelet count $\geq$ 100 x 10^9/L ($\geq$100,000 per mm^3)
   - Serum bilirubin $\leq$ 1.5 x institutional upper limit of normal (ULN). *[This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician.]*
   - AST (SGOT)/ALT (SGPT) $\leq$ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be $\leq$ 5x ULN
   - Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

     Males:

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

     Females:

     $$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg) x (140 – Age)}}{\text{72 × serum creatinine (mg/dL)}} \times 0.85$$
8. Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: $\geq$60 years old and no menses for $\geq$1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative urine pregnancy test upon study entry. If unsure postmenopausal status, hormone levels will be employed to verify.
9. Females of childbearing potential who are sexually active with a non-sterilized male partner and non-sterilized male subjects who are sexually active with a female partner of childbearing potential must be willing to use 2 methods of effective contraception (Table 1) from time of screening through 180 days after receipt of the final dose of Durvalumab + Tremelimumab combination therapy or 90 days after receipt of the final dose of Durvalumab Monotherapy, whichever is the longer time period.

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

Exclusion Criteria:

1. To limit the heterogeneity of the tumor population and reduce the risk of masking any clinical effect of the treatment regimen, multiple categories of STS subtypes will be excluded:
    - Patients with primarily bone-based sarcomas that can occur in the soft tissues, such as:
        - extraskeletal Ewing sarcoma
        - extraskeletal osteosarcoma
        - peripheral chordoma
        - mesenchymal chondrosarcoma
    - Patients with predominantly low-grade STS, such as:
        - solitary fibrous tumor / hemangiopericytoma
        - well-differentiated liposarcoma
        - dermatofibrosarcoma protuberans
        - Kaposi's sarcoma
    - Gastrointestinal stromal tumors (GIST)
2. Retroperitoneal soft tissue sarcoma
3. Patients with >2 liver metastases or >2 soft tissue non-lymph node (ex: intramuscular, subcutaneous) metastases, or liver or soft tissue non-lymph node metastases >1 cm
4. Patients with a surgically unresectable primary lesion
5. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
6. Any previous treatment with an anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapy, including Durvalumab and Tremelimumab
7. History of hypersensitivity to Durvalumab or any excipient
8. History of hypersensitivity to Tremelimumab or any excipient
9. History of hypersensitivity to the combination or comparator agent

10. History or clinically confirmed pneumonitis or interstitial lung disease
11. Receipt of the last dose of anti-cancer therapy (cytotoxic chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 4 weeks pers prior to the first dose of study drug (4 weeks pers prior to the first dose of study drug for subjects who have received prior TKIs [e.g., erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C *[If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period may be required]*)
12. Current or prior use of immunosuppressive medication within 4 weeks pers before the first dose of durvalumab or tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid
13. Any unresolved toxicity (> CTCAE grade 2) from previous anti-cancer therapy that may be expected to be exacerbated by study therapy. *NOTE: Subjects with irreversible/chronic toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy)*
14. Any prior immune-related adverse event (irAE) ≥ Grade 2 while receiving any previous immunotherapy agent, or any unresolved irAE > Grade 1
15. Active or prior documented autoimmune disease within the past 2 years. *NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.*
16. History of primary immunodeficiency
17. History of allogeneic organ transplant (e.g. solid organ/bone marrow transplant patients)
18. Uncontrolled intercurrent illness including, but not limited to:
    - Ongoing or active infections
    - Cardiac conditions, such as:
        - symptomatic congestive heart failure
        - uncontrolled hypertension
        - unstable angina pectoris
        - cardiac arrhythmia
    - Active peptic ulcer disease or gastritis
    - History of inflammatory bowel disease, ulcerative colitis or Crohn's Disease
    - Active bleeding diatheses

- Any subject known to have evidence of acute or chronic hepatitis B or hepatitis C. Patients with undetectable viral levels will be allowed.
- Any subject known to have evidence of human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)
- Uncontrolled seizures

19. Known history of current or recent clinical diagnosis of tuberculosis / TB (within six months prior to enrollment). A chest XR will be performed to screen for active TB for patients who have a history of treated TB.
20. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
21. Any signs or symptoms of bowel obstruction within 4 weeks pers prior to study entry
22. History of leptomeningeal carcinomatosis
23. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab, or active infection
24. History of psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
25. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
26. Previously enrolled in the present study
27. Participation in another clinical study with an investigational product during the last 6 months
28. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
29. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period

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ABBREVIATIONS AND DEFINITION OF TERMS

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

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

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

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

Abbreviation or special term	Explanation
PBMC	Peripheral blood mononuclear cell
PERCIST	Positron Emission Tomography (PET) Response Criteria in Solid Tumors
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT	Radiation Therapy
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SFGRT	Spatially fractionated GRID radiation therapy
SNP	Single nucleotide polymorphism

Abbreviation or special term	Explanation
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
SR	Surgical resection
STS	Soft tissue sarcoma
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

INTRODUCTION

Refer to the Investigator's Brochure (IB) for detailed background on Durvalumab (MEDI4736) and Tremimemulab

1.1 Disease Background

Immune responses directed against tumors are one of the body's natural defense against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers.with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung (Mu et al, 2011), renal (Thompson et al, 2005; Thompson et al, 2006; Krambeck et al, 2007), pancreatic (Nomi et al, 2007; Loos et al, 2008; Wang et al, 2010), ovarian cancer (Hamanishi et al, 2007), and hematologic malignancies (Andorsky et al, 2011; Brusa et al, 2013) tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir et al,

2008; Park et al, 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou and Chen, 2008).

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

In general, tumor response rates to anti-CTLA-4 therapy are low (~10%). However, in patients who respond, the responses are generally durable, lasting several months even in patients with aggressive tumors such as refractory metastatic melanoma. Because these agents work through activation of the immune system and not by directly targeting the tumor, responses can occur late and some patients may have perceived progression of their disease in advance of developing disease stabilization or a tumor response. In some cases, early growth of pre-existing lesions or the appearance of new lesions may have been due to immune-cell infiltration into the tumor and not due to proliferation and extension of neoplastic cells, per se (Wolchok et al, 2009). Overall, although the impact on conventionally-defined PFS can be small, durable response or stable disease seen in a proportion of patients can lead to significant prolongation of OS. The melanoma data with ipilimumab clearly demonstrate that a small proportion of patients with an objective response had significant prolongation of OS, supporting the development of this class of agents in other tumors. Although Phase 2 and Phase 3 studies of tremelimumab in metastatic melanoma did not meet the primary endpoints of response rate and OS, respectively, the data suggest activity of tremelimumab in melanoma (Kirkwood et al, 2010; Ribas et al, 2013). In a large Phase 3 randomized study comparing tremelimumab with dacarbazine (DTIC)/temozolomide in patients with advanced melanoma, the reported median OS in the final analysis was 12.58 months for tremelimumab versus 10.71 months for DTIC/temozolomide (HR = 1.1416, p = 0.1272; Ribas et al, 2013).

1.1.1 Soft Tissue Sarcoma

Soft tissue sarcomas (STS) are malignancies that arise from connective tissue and occur predominantly in the extremities and pelvis. They account for approximately 12,000 new cases and 5,000 deaths annually in the U.S. (Ng et al, 2013). This exceeds the total deaths from squamous cell skin cancer by over two-fold and is over half of the total melanoma deaths. Sixty-five percent of sarcomas are grade 2 (intermediate/IG) or 3 (high/HG) and have a 5-year overall survival (OS) of 75% and 45-55%, respectively (Coindre 2006; Coindre et al, 1996; Canter et al, 2008). Pelvis and extremity locations comprise 60% of all STS compared to 13% retroperitoneal, 9% head and neck, and 18% chest wall and torso (Steen and Stephenson, 2008). Although there are different subtypes of STS, numerous studies have shown that size and histological grade are the most important prognostic factor (Scurr et al, 2005). Less than 10% of STS are associated with clinically detectable metastases at presentation, but nearly 50% of all high-risk STS will develop distant metastasis. The vast majority (>80%) of metastases occur within 2 years of definitive treatment (Ferguson et al, 2011; Stojadinovic et al, 2002). Without treatment or after cessation of treatment, the median survival of patients with metastatic STS is approximately 6-months, and with treatment, median survival ranges from 9-15 months (Ng et al, 2013; Scurr et al, 2005; Billingsley et al, 1999b; Canter et al, 2007; Nakamura et al, 2011).

Limitations of Current System Treatment Options for STS

The current standard of care for high-risk STS (Grade 2/3, size greater than or equal to 5 cm, located deep or superficial to fascia) of the pelvis and extremities is neoadjuvant or adjuvant radiation therapy (RT) and wide surgical resection (Demetri et al, 2010: Casali and Blay, 2010). With appropriate management, local control rates are greater than 85 to 90% and isolated local recurrence rarely leads to mortality in the extremities (Biau et al, 2012; Engellau et al, 2005; Novais et al, 2010). Metastatic STS, however, is generally considered incurable, with only approximately 5-15% of patients alive at 5 years depending on the timing and extent of distant relapse (Scurr et al, 2005; Ferguson et al, 2011; Blay et al, 2003; Ramanathan et al, 1999). The role of cytotoxic chemotherapy is highly controversial and varies widely amongst centers (Maruzzo et al, 2013). Because the vast majority of high risk STS present with localized disease yet a high proportion develop incurable metastatic disease, there has been considerable effort over the past 30 years to develop an effective regimen to prevent development of distant disease. Unfortunately, there has been very limited success with chemotherapy in this regard, evidenced by the lack of strong recommendations for chemotherapy by either the European Society of Medical Oncology (ESMO) or the National Comprehensive Cancer Network (NCCN) (Demetri et al, 2010; Casali and Blay, 2010).

In 1997, a meta-analysis performed by the Sarcoma Meta-Analysis Collaboration (SMAC) on adjuvant chemotherapy consisting predominantly of doxorubicin found that there was a non-significant trend of improved OS in all STS patients and 7% absolute gain in OS for extremity STS (SMAC, 1997). This study, however, included low-grade and small STS, and lacked tumor-

specific information in some patients. Several updated meta-analyses including more recent studies with doxorubicin and ifosfamide have been published. A large European randomized phase III trial of 819 patients failed to show benefit in OS (Woll et al, 2012; Woll et al, 2007; La Cesne et al, 2008). Updates on the SMAC meta-analysis demonstrated improved disease-free survival (DFS) and OS at 5 years, but statistical significance was lost at 10 years (Pervaiz et al, 2008; O'Connor et al, 2008). Other studies have reported that some clinical benefits of adjuvant chemotherapy may not be sustained beyond 1 to 3 years (Cormier et al, 2004; Italiano et al, 2010).

The evidence for neoadjuvant chemotherapy is mixed. A European study found no significant difference in OS with neoadjuvant doxorubicin and ifosfamide, while a U.S. group reported improved OS with a preoperative regimen which included dacarbazine (DeLaney et al, 2003; Mullen et al, 2011; Gortzak et al, 2001). Doxorubicin and ifosfamide have steep dose-response curves and patients with low performance status are poor candidates for cytotoxic chemotherapy, particularly in the setting of localized disease and marginal clinical benefit (Spira and Ettinger, 2010).

Targeted therapy has demonstrated limited improvements in survival. Pazopanib (Votrient, GlaxoSmithKline, NC, USA) is a multiple tyrosine kinase inhibitor approved for use by the FDA for patients with unresectable or metastatic STS and who have failed prior chemotherapy. In a randomized phase III trial, pazopanib improved PFS by 3 months (median 4.6 vs 1.6 months) and OS by less than 2 months (12.6 vs 10.7 months) compared to placebo (van der Graaf et al, 2012). The latter was not statistically significant. The rate of long-term responders and survivors with pazopanib was similar to historical figures for metastatic STS (Scurr et al, 2005; Kasper et al, 2014; Billingsley et al, 1999a). The need for novel approaches to prevent distant relapse of STS is clear (Santoro 1999).

1.1.2 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors (. This amplification may be accomplished by blocking co-inhibitory molecules, such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), from binding with their ligands, B7 or B7-H1 (programmed cell death ligand 1 [PD-L1]).

1.1.3 Durvalumab

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

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for

use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1.

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of patients with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of patients with tumors lacking PD-L1 (Mu et al 2011). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of several non-clinical studies using mouse tumor models support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity.

Durvalumab has been given to humans as part of ongoing studies as a single drug or in combination with other drugs As of the DCO dates (15Apr2015 to 12Jul2015, durvalumab IB version 8.0), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

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

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

1.1.4 Tremelimumab

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

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

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures (Tarhini and Kirkwood 2008). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. (Refer to the tremelimumab IB, Edition 5.0, for more information.) Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules. As of the data cut-off date of 12 November 2014 (for all studies except D4190C00006, which has a cut-off date of 4 December 2014), 973 patients have received tremelimumab monotherapy (not including 497 patients who have been treated in the blinded Phase 2b study, D4880C00003) and 208 patients have received tremelimumab in combination with other agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.4.2.2. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.5 for guidance on management of tremelimumab-related toxicities.

Tremelimumab exhibited a biphasic PK profile with a long terminal phase half-life of 22 days. Overall, a low incidence of ADAs (<6%) was observed for treatment with tremelimumab.

1.1.5 Durvalumab in Combination with Tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012) because the mechanisms of action of CTLA-4 and PD-1 are non-redundant; therefore, AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish safety, PK/PDx, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 weeks (q2w) or every 4 weeks (q4w) up to Week 50 and 48 (12 months), combined with tremelimumab q4w up to Week 24 for 7 doses then every 12 weeks for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue.

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

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

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

1.2 Research Hypothesis

Hypothesis #1

The combination of Durvalumab, Tremelimumab and RT will demonstrate histopathologic response within the primary tumor upon surgical resection.

> Existing literature for neoadjuvant treatment for STS using conventional cytotoxic chemotherapy and RT demonstrate an association between histopathologic response rates and oncologic outcomes (Stacchiotti et al, 2009; Chen et al, 2013; Hermann et al, 2012; Canter et al, 2010; Donahue et al, 2010; Eilber et al, 2001; Evilevitch et al, 2008; Shah et al, 2012).

Hypothesis #2

The combination of Durvalumab, Tremelimumab and RT will demonstrate a beneficial effect by decreasing the size of the primary tumor.

Neoadjuvant chemoradiation therapy for localized high-risk STS provides approximately 50-60% stable disease, 20-30% partial response, and 10-20% progressive disease. Traditional chemotherapy for metastatic STS typically provides relatively short durations of objective response (Stacchiotti et al, 2009; Chen et al, 2013).

Hypothesis #3

This neoadjuvant regimen of combination immunotherapy plus radiation will be well tolerated by even those patients who would be deemed poor candidates for cytotoxic chemotherapy.

Traditional cytotoxic chemotherapy with doxorubicin and ifosfamide has a steep dose-response curve and is associated with significant cardiac toxicity and myelosuppression, limiting its use in the elderly or patients with decreased performance status (Spira and Ettinger, 2002; Edmonson et al, 1993). Immune checkpoint inhibitor therapy has been shown to have a relatively low rate of serious adverse drug reactions, even in geriatric patients, and only 6% discontinuation rate due to adverse reactions (Merck Sharp & Dohme Corp.). Because the bowels and lungs are not being irradiated, the combined toxicity of the neoadjuvant regimen will likely be lower than that seen for lung or other solid tumors (Tang et al, 2014). PD-L1 acts later in the process of T-cell activation than CTLA-4 and its inhibition expected to have reduced toxicity compared to inhibition of CTLA-4 (Fife and Bluestone, 2008). A prior study CD-ON-MEDI4736-1108 with Durvalumab monotherapy which included STS found the 10 mg/kg q2W dosing to be well-tolerated. CTLA-4 can result in modest rates of grade 1-2 side effects such as GI upset, but less than 5-7% of patients experience grade 3-4 adverse events (Ribas et al, 2012). Tremelimumab demonstrates efficacy at the lowest dose of 1 mg/kg and increasing doses do not improve antitumor activity at the expense of higher rates of adverse events (Antonia et al, 2016). Because of pelvic and extremity locations for STS, the effects of RT would likely be limited to temporary swelling and skin changes.

Hypothesis #4

Patients harboring tumors with T-cell inflamed phenotypes will have a greater response to immunotherapy, but radiation will facilitate tumor-specific immune responses even in patients with a non-T-cell inflamed phenotype.

Studies have demonstrated that tumors with a T-cell inflamed phenotype, characterized by the presence of activated tumor infiltrating lymphocytes (TIL), macrophages, and other markers, have a superior response to checkpoint inhibitors (Saloura et al, 2014; Kindler et

al, 2014; Llosa et al, 2014; Gajewski 2015). This vigorous immune microenvironment correlates closely with the mutagenic load of the tumor, microsatellite instability, silencing of DNA mismatch repair genes and the available tumor-specific neoantigens that can be recognized by TILs (Xiao and Freeman, 2015). Ionizing radiation reverses the immunosuppressive tumor microenvironment, facilitates tumor-antigen recognition by CTLs, increases tumor expression of PD-L1 and CTLA-4 and leads to increased immune activity against local and distant tumor cells (Deng et al, 2014).

1.3 Rationale

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

The rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity. In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable. Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC, with further updated details presented in this clinical study protocol.

1.3.1 Pre-Clinical Rationale for Checkpoint Inhibitor Immunotherapy in STS

The first demonstration of effect with immunotherapy was Coley's toxins in 1891 on a patient with sarcoma (McCarthy 2006). While immunotherapy is not currently the standard of care for sarcomas, there is a strong preclinical rationale to predict efficacy. Checkpoint inhibitor immunotherapy in STS is a novel, but promising area of clinical investigation. Preclinical data has shown that approximately 60% of STS express PD-1/PD-L1 and its presence was associated with disease progression (Kim et al, 2013; D'Angelo et al, 2014). In a series of 29 cases of chondrosarcoma and liposarcoma, PD-L1 on tumor cells was found to be present in 100% of cases, but only 11% and 45% were found to have PD-1 positive infiltrating T-cells (Movva et al, 2014). Increased CTLA-4 T-cells were found in aggressive pediatric sarcoma patients (Hingorani et al, 2015). Radiation of sarcoma has been demonstrated to promote tumor-specific immune effectors and down-regulation of immune suppressors (Sharma et al, 2013). A pilot study of single agent anti-CLTA-4 for advanced synovial sarcoma did not lead to an objective RECIST response (Maki

et al, 2013). In a murine model, metastatic osteosarcoma was controlled with dual CTLA-4/PD-L1 blockade, but not controlled with PD-1 blockade alone (Lussier et al, 2015).

In a fibrosarcoma mouse model, PD-1/PD-L1 blockade was effective despite limited detectable up-regulation of PD-L1 prior to treatment (Wei et al, 2008). The mutagenic burden of tumors have been correlated with the strength of tumor-specific immune response with checkpoint inhibitor therapy (Saloura et al, 2014; Kindler et al, 2014; Llosa et al, 2014; Gajewski 2015; Xiao and Freeman, 2015). Microsatellite instability (MSI) correlates closely with silencing or mutations of DNA mismatch repair genes and up to 25-50% of sarcomas have been shown to harbor MSI (Campanella et al, 2015; Monument et al, 2012). The rationale of this study is to combine both CTLA-4 and PD-L1 blockade with RT to overcome limited systemic effect seen in prior studies with single-pathway blockade, with RT-alone, or with low mutagenic burden tumor phenotypes.

There are clinical trials undergoing accrual for checkpoint inhibitors as a second line agent for patients with advanced or unresectable sarcoma (ClinicalTrials.gov 2014). In contradistinction, the current trial proposes using Durvalumab and Tremelimumab as a front-line combination treatment in the neoadjuvant setting with RT for an enhanced abscopal effect to address micro- or oligo-metastatic disease when the immune system has not been yet depleted by chemotherapy or massive tumor burden (Spira and Ettinger, 2002; Pauken and Wherry, 2015).

The rationale for this study is to add an effective checkpoint inhibitor combination to the existing standard of care, RT plus surgery, in order to potentiate the immunomodulatory effects of both modalities. Harnessing these synergistic immunomodulatory effects represents a promising paradigm shift in the treatment of high risk STS.

1.3.2 Rationale for Immunotherapy + Radiation Therapy

The genesis of cancer is based on cell mutation and neoplastic growth within the host. In order for cancer to thrive, its constituent cells must avoid elimination by the immune system. The host anticancer immune response is based on a series of steps including

1. presentation of tumor antigens by specialized dendritic and antigen-presenting cells (APCs)
2. priming and activation of the adaptive immune response
3. infiltration of the tumor by cytotoxic T-cells
4. recognition and destruction of tumor cells, and
5. further release of tumor antigens.

There are, however, several hurdles to this cancer immunity cycle (Chen and Mellman, 2013; Marraco et al, 2015). First, the adaptive immune system typically has a poor naïve repertoire of

self antigen-specific CD8 T-cells. Second, APCs for tumor antigens are relatively inefficient and have poor priming capacity. Third, cytotoxic T-cells experience "T-cell exhaustion", a dysfunctional state in the setting of chronic exposure to tumor antigens.

Acute infection and exposure to foreign antigens lead to T-cell expansion, elimination of the offending entity, and differentiation of effector T-cells into memory T-cells for future similar exposures. In the case of cancer, however, tumor antigens are typically weakly immunogenic and the tumor microenvironment is highly immunosuppressive towards infiltrating T-cells. Checkpoint receptors such as programmed cell death protein 1 (PD-1) and cytotoxic T lymphocyte antigen 4 (CTLA-4) are endogenous mechanisms to prevent excessive inflammatory responses normally, but in the setting of cancer, are activated by the tumor to cause T-cell exhaustion (Jiang et al, 2015).

Blockade or inhibition of these immune checkpoint receptor pathways with antibodies such as anti-PD-L1, anti-PD-1, and anti-CTLA-4 may partially restore the intrinsic antitumor activity by overcoming T-cell exhaustion. Durvalumab is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody (MAb) directed against human PD-L1. Tremelimumab is an IgG1 human monoclonal antibody that binds to CTLA-4 on activated T-cells and inhibits B7-CTLA-4-mediated downregulation of T-cell activity. Immunotherapeutic antibodies have been shown to be produce objective responses in numerous solid malignancies including melanoma, lymphoma, renal cell carcinoma and even those considered resistant to immunotherapy such as non-small cell lung cancer (Tang et al, 2014; Pauken and Wherry, 2015). Small animal models have demonstrated the ability of immunotherapy to prevent distant inoculation of tumor or metastasis and even rechallenge with a homologous tumor (Pauken and Wherry, 2015). Baseline high levels of PD-L1 expression by tumor cells and the presence of PD-1 positive T-cells at the invasive margin of the tumor were predictive of poorer prognosis, but also predictive of a therapeutic response to immunotherapy (Pauken and Wherry, 2015; Woo et al, 2015; Lyford-Pike et al, 2012). Malignancies with high levels of somatic mutations such as melanoma and colorectal cancer tend to be more readily recognized by the immune system, leading to T-cell infiltration (Woo et al, 2015; Lawrence et al, 2013; Teixido et al, 2015). Unlike targeted gene therapy however, checkpoint blockade is not dependent on specific genetic alterations and may be more widely applicable to cancer patients. Preclinical evidence suggests that combination therapy with blockade of both CTLA-4 and the PD-1/PD-L1 pathway will have an additive effect (Mahoney et al, 2015).

Checkpoint blockade has also been reported to be effective in some patients without markers of T-cell exhaustion such as PD-1, suggesting that their simple presence or absence is not completely indicative of the dysfunctional state (Teixido et al, 2015). Combination therapy using anti-CTLA-4 with anti-PD-L1 in a non-small cell lung cancer human trial demonstrated antitumor activity and an acceptable safety profile (Antonia et al, 2016).

Immunotherapy plus Radiation in Cancer

Multiple clinical studies and small animal models have demonstrated superior rates of response for checkpoint blockade when combined with RT or with another checkpoint receptor compared to immunotherapy alone (Jiang et al, 2015). Ionizing radiation reverses the immunosuppressive tumor microenvironment, facilitates tumor-antigen recognition by CTLs, increases tumor expression of PD-L1 and leads to increased immune activity against local and distant tumor cells (Deng et al, 2014). In addition to the immunogenic effects of RT on the primary tumor, the well-described abscopal effect of localized RT on distant metastases is widely felt to be immune-mediated. Numerous small animal tumor models and multiple clinical case examples have been reported where localized RT had a beneficial effect on other sites of disease (Barker and Postow, 2013). Clinical studies that have used anti-PD-1 *alone* report only 13-24% objective response rates and RT used *alone* rarely induces a clinically significant abscopal effect (Pauken and Wherry, 2015; Brahmer et al, 2012). When combined with RT, however, anti-PD-1 has been shown to strongly potentiate both the local and the abscopal effect of RT, leading to primary tumor regression and resistance to implantation of secondary or metastatic tumors (Tang et al, 2014; Postow et al, 2012; Victor et al, 2015; Ferrara et al, 2009; Park et al, 2015). In this manner, RT may facilitate utilization of the primary tumor essentially as an in-situ vaccine to train the immune system and eliminate or prevent metastases, even in weakly immunogenic tumors (Tang et al, 2014).

1.3.3 Durvalumab + Tremelimumab Combination Therapy Dose Rationale

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

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

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

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

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

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

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

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR),

1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD). (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Additionally, of all cohorts, the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. All together, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development. We have chosen an equivalent fixed dosing regimen of 1500 mg durvalumab and 75 mg tremelimumab q4 weeks.

1.3.4 Rationale for Combination Therapy Followed by Monotherapy

Long-term follow up on melanoma patients treated with ipilimumab, an anti-CTLA-4 targeting antibody (dosed every 3 weeks [q3w] for 4 doses and then discontinued), shows that patients responding to ipilimumab derive long-term benefit, with a 3-year OS rate of approximately 22%. Furthermore, the survival curve in this population reached a plateau at 3 years and was maintained through 10 years of follow up (Schadendorf et al 2013).

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

Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg), and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis (Hodi et al 2014, Brahmer et al 2014, Drake et al 2013). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis (Topalian et al 2014).

MPDL3280a (anti-PD-L1) and the combination of nivolumab with ipilimumab, in which patients were dosed for a finite time period and responses maintained beyond treatment discontinuation have been reported (Herbst et al 2013, Wolchok et al 2013).

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

1.4 Benefit/Risk and Ethical Assessment

1.4.1 Potential Benefits

1.4.1.1 Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first time in-human, single-agent study (Study 1108) in patients with advanced solid tumors. Data from Study 1108 were presented at the European Society for Medical Oncology 2014 Congress. Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%). (Antonia et al 2014b).

1.4.1.2 Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an RR of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis; Korn et al 2008) were observed. In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed an RR of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant. Additionally, a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who had responded or remained stable failed to achieve statistical significance. The primary endpoint of PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

1.4.1.3 Durvalumab + Tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.1.4 also supports the synergy of this combination. Available data, such as those presented by Wolchok et al, suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound

and durable benefits in patients with melanoma. Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab in Study D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

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

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

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

1.4.2 Potential risks

The risks associated with this study primarily concern adverse reactions to the study drugs. Durvalumab and Tremelimumab are not yet FDA approved. The proposed protocol is of an investigational use of the medications Durvalumab (MEDI4736) and Tremelimumab in new clinical methodology.

Additionally, any time information is collected for a study, there is a small risk of breach of confidentiality. However, this risk is not greater than the risk that already exists in clinical settings when handling medical data. To minimize this risk all study staff are trained in human subjects confidentiality. The investigator will work to ensure that all PHI will be protected to the greatest extent possible; all research data will be stored and managed in a secure manner following all

applicable federal regulations and guidelines and according to institutional policies and practices. Hard copy documents containing subject data and patient identifiers (and contact information) will be stored in secure document containers (file cabinets, lockers, drawers, etc.) in accordance with standard document management practices. All electronic records of study data will be password protected, and stored on HIPAA compliant computers maintained in private, locked offices within secure areas of the University of Maryland Medical Center institution.

1.4.2.1 Durvalumab

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

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

discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were ≥ Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

1.4.2.2 Tremelimumab

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated gastrointestinal (GI) events including enterocolitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin;

endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; hepatitis including autoimmune hepatitis and increased serum ALT and AST; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratory tract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the data cutoff date of 12 November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014 and not including 497 patients who have been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 4 weeks pers and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product (IP), and deaths.

1.4.2.3 Durvalumab + tremelimumab

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

Study D4190C00006: The safety profile of durvalumab and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjects treated with durvalumaband tremelimumab combination therapy (not including subjects treated with blinded investigational product). As of 15Apr2015, 95 of 102 subjects (93.1%) reported at least 1 AE. All subjects in the tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; subjects in the durvalumab 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest AE rate (77.8%). Treatment-related AEs were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjects being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each), rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related ≥ Grade 3 AEs reported in ≥ 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment-related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase

in 2 subjects; myasthenia gravis in 1 subject; and pericardial effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the MEDI4736 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported SAEs, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty-six subjects (35.3%) experienced treatment-related SAEs. Twenty-seven subjects (26.5%) permanently discontinued treatment due to AEs. Treatment-related AEs resulting in discontinuation in ≥ 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3 subjects), and increased AST (2 subjects).Additional safety results from this study are presented in Section 0 and the durvalumab IB.

In the literature, using the combination of the same class of drugs (eg, anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of AEs assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with Grade 3 or 4 events assessed by the Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment-related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment-related in the combination therapy included hepatic events (in 15% of patients), GI events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

1.4.2.4 Fixed Dosing for durvalumab and tremelimumab

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

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) [Wang et al. 2014]. Population PK model indicated minor impact of body WT on PK of tremelimumab

(coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

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

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 750 mg Q2W MEDI4736 (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

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

There are two large international Phase III registrational studies previously approved by the FDA that are being conducted using the fixed dose combination of Durvalumab and Tremelimumab.

- KESTREL in 1L squamous cell carcinoma head and neck: NCT02551159 (https://clinicaltrials.gov/ct2/show/NCT02551159?term=Kestrel&rank=1)
- DANUBE in 1L urothelial bladder cancer: NCT02516241 (https://clinicaltrials.gov/ct2/show/NCT02516241?term=Durvalumab+uc&rank=1)

Tremelimumab population PK model was developed using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) [Wang et al. 2014]. The final population PK model parameters are presented in Table 1X below.

Table 1X: Final Parameter Estimates and Confidence Interval from the Final Model

	Final Model				Bootstrap Final Model		
Parameter	Estimate	Relative Standard Error (%)	95% CI		Estimate	95% CI	
CL (L/day)	0.26	2.35	0.2596	0.2604	0.26	0.25	0.27
IgG effect on CL	0.26	23.37	0.1432	0.3768	0.26	0.13	0.379
CL_{cr} effect on CL	0.24	18.45	0.15	0.33	0.244	0.156	0.323
LDH effect on CL	0.0851	38.78	0.02	0.15	0.085	0.022	0.149
CRP effect on CL	0.104	10.48	0.08	0.13	0.104	0.084	0.123
ECOG effect on CL	0.15	28.66	0.07	0.23	0.15	0.066	0.236
CL in females	−0.174	16.55	−0.23	−0.12	−0.173	−0.223	−0.12
V1 (L)	3.97	2.16	3.8	4.14	3.97	3.81	4.14
Body weight effect on V1	0.51	17	0.34	0.68	0.51	0.343	0.675
V1 in females	−0.154	22.27	−0.22	−0.09	−0.15	−0.219	−0.088
Q (L/h)	0.0192	9.32	0.0151	0.0227	0.0195	0.0176	0.0231
V2 (L)	3.71	4.15	3.41	4.01	3.72	3.434	3.978
CL IIV	31.80%	—	—	—	—	—	–
V1 IIV	20.40%	—	—	—	—	—	–

Q = intercompartmental clearance; V2 = peripheral volume of distribution.

Although population PK analysis identified few statistically significant covariates, they were not considered clinically relevant since the change in CL (or exposure) was <30%, supporting no need for dose adjustments based these factors. In particular, population analysis indicated minor impact of body WT on PK of tremelimumab (weight coefficient on volume of distribution ~0.5; weight was not identified as covariate on clearance). Indicators of disease severity and tumor burden (ECOG and LDH) and biomarkers of cancer inflammation (CRP) contribute more variability in PK compared to body weight. The magnitude of covariate effects are presented in Figure 1X below. We have made similar observations for the pharmacokinetics of durvalumab. The fixed dosing regimen of durvalumab and tremelimumab are currently being evaluated in multiple clinical studies.

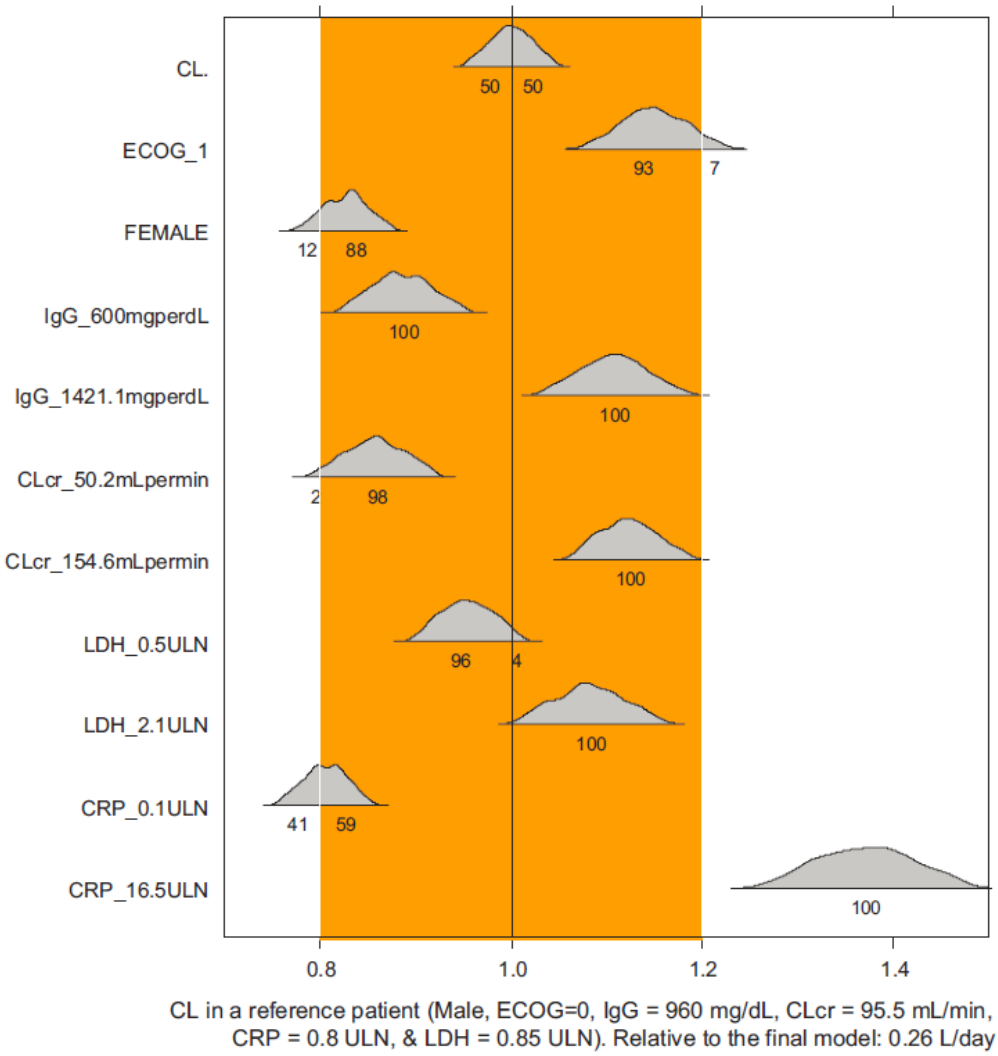


Figure 1X: Covariate effects in Tremelimumab Clearance. Typical relative clearance is presented at the top of the plot for the reference individual. The covariate effects for CL are provided on a relative scale by dividing the median of the typical CL, thus providing the proportional size and precision for CL. The distributions (from 2.5th quantile to 97.5th quantile) of the 1000 nonparametric bootstrap estimates are provided as a probability density plot. The numbers of the density plot represent the percent of observations falling within the vertical shaded region denoting a range of 80–120% of the reference CL value.

The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen (Figure 2X).

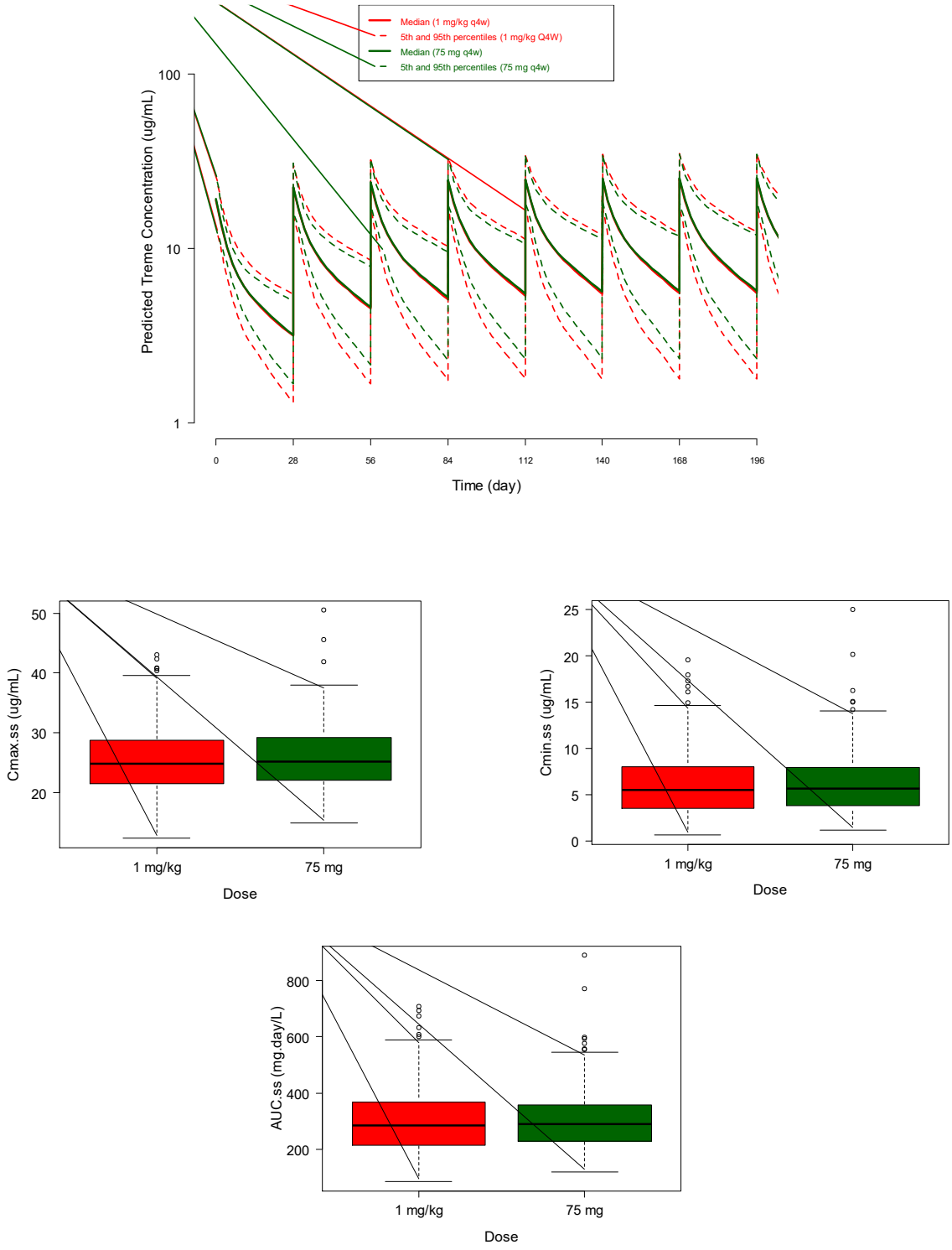


Figure 2X: Predicted PK Exposure Following WT-based and Fixed Dosing Regimens of Tremelimumab

2. STUDY OBJECTIVE

2.1.1 Primary Objectives

- **Objective:** Phase I component: To evaluate the safety and tolerability of neoadjuvant Durvalumab/Tremelimumab and radiation therapy in patients with high-risk STS.

- **Objective:** Phase II component: To evaluate the proportion of patients achieving an excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor regression) on histopathologic examination of the surgical specimen.

2.1.2 Secondary Objectives

- **Objective:** To evaluate the clinical outcomes of distant relapse, progression of disease, and disease-specific survival with neoadjuvant Durvalumab/Tremelimumab and RT followed by surgical resection.

- **Objective:** To evaluate the histopathologic effect of neoadjuvant Durvalumab/Tremelimumab and radiation therapy on the primary tumor.

- **Objective:** To evaluate the effect of neoadjuvant Durvalumab/Tremelimumab and radiation therapy on the primary tumor using RECIST v1.1 criteria and the immune-related response criteria (irRC).

- **Objective:** To evaluate whether neoadjuvant Durvalumab/Tremelimumab and radiation therapy produces tumor-specific immune responses within the tumor, the infiltrative margins and surrounding reactive zone, and in the peripheral blood, and whether the strength of these responses correlate with the extent of tumor microsatellite instability and mutagenic burden.

2.1.3 Exploratory Objective(s)

- **Objective:** To evaluate the effect of neoadjuvant Durvalumab/Tremelimumab and radiation therapy on the primary tumor using PERCIST criteria.

3. STUDY DESIGN

3.1 Overview of Study Design

This is an integrated phase I/II clinical trial investigating the combination of IgG2 mAb anti-CTLA-4 Tremelimumab and IgG1κ mAb anti-PD-L1 Durvalumab/MEDI4736 as a neoadjuvant to radiation therapy, followed by surgical resection, in patients with high risk Soft Tissue Sarcoma's. The accrual goal is 35 patients. The primary objective for the phase I portion of the study is evaluation of safety and tolerability of Tremelimumab and Durvalumab. For the phase II portion of the study, the objectives are evaluation of treatment response on histologic examination. Additional phase II objectives include evaluation of radiographic response rate, clinical outcomes, overall and patient reported quality of life, as measured by the PROMIS-CA Bank v1.1 Physical Function, PROMIS Pain Interference SF8a v1.0 and PROMIS Pain Interference SF6b v1.0 questionnaires.

Patients that meet the eligibility criteria will undergo a complete history and physical exam (Schedule of Assessments Table 1). Imaging will include magnetic resonance imaging (MRI) of the primary site of disease, and a whole-body positron-emission tomography (PET-CT) scan including diagnostic computed tomography chest / abdomen / pelvis (CT C/A/P), and plain radiographs (XR) if warranted from orthopedic stand point. If the patient's medical insurance does not cover PET-CT, then a CT C/A/P and whole body bone scan (WBBS) will be performed. All patients will be discussed at a multi-disciplinary tumor board. As highlighted in the study schema, patients will be treated concurrently with Tremelimumab at 75 mg intravenous and Durvalumab at 1500 mg intravenous for 3 cycles of 4 weeks per cycles. Patient will receive radiation therapy starting week 2 or 3 (at least 1 week after first dose of immunotherapy) of cycle 1 of neoadjuvant immunotherapy treatment. The radiation course will take place over 5 weeks. For bulky sarcomas, defined as > 10 cm in greatest dimension, a single 15 Gy fraction of spatially fractionated GRID radiation therapy (SFGRT) will be delivered to the tumor within 1-3 days prior to start of standard external beam radiotherapy if deemed safe and appropriate by the treating radiation oncologist. SFGRT is akin to virtual brachytherapy, by which high dose beamlets of external beam radiotherapy are delivered to the tumor in a checkerboard pattern resembling interstitial catheters. SFGRT has both direct and indirect effects on cancer cells and has resulted in enhanced local control and tumor regression for radioresistant tumors such as sarcomas compared to standard external beam radiotherapy alone (Sathishkumar et al, 2002; Mohiuddin et al, 1999; Kaiser et al, 2012; Snider et al, 2014). One report suggests that SFGRT and immune checkpoint inhibition can be used together with limited toxicity and result in significant tumor regression (Mohiuddin et al, 2015). Following SFGRT (if delivered), external beam radiation therapy (EBRT) will then be delivered to the primary tumor with a minimum dose of 50 Gy in 1.8 - 2 Gy per fraction at the discretion of the treating radiation oncologist for non-metastatic patients. The treatment area for EBRT will encompass the primary tumor and a margin of normal tissue at the discretion of the treating radiation oncologist. SFGRT will be delivered to the primary tumor without a margin of

normal tissue. Regional metastases will be treated with RT using shrinking field/sequential boost technique and 1.8 - 2 Gy per fraction. Radiation will be withheld for patients with contraindications including genetic conditions that predispose to skin cancer (e.g. xeroderma pigmentosum) and connective tissue diseases (e.g., lupus). In the setting of patients with metastatic disease, a hypofractionated course of EBRT may be used at the discretion of the treating radiation oncologist. SFGRT may still be used for bulky tumors, again, at the discretion of the treating radiation oncologist. Either photon, electron, or proton radiotherapy may be utilized for delivery of EBRT at the treating radiation oncologists' discretion.

After neoadjuvant immunoradiotherapy (IRT), an MRI of the primary lesion will be performed. If covered by insurance, a PET-CT of the primary lesion will be performed as well to assess response to neoadjuvant IRT. PET-CT has been shown to correlate with histopathologic response and prognosticate clinical outcomes (Schuetze et al, 2005; Eary et al, 1998; Eary et al, 2008; Folpe et al, 2000). Surgical resection will be performed 5-8 weeks after cessation of radiation therapy, depending on the condition of the surrounding soft tissues. En-bloc removal of the primary lesion with negative margins of 1-2 cm distance (muscle/fat/cancellous bone) or of anatomic boundaries (fascia / periosteum) will be endeavoured depending on proximity of vital structures. Preoperative embolization by interventional radiology may be performed to decrease blood loss. Mode of anaesthesia (e.g., spinal, general, etc) will be at the discretion of the attending anaesthesiologist in discussion with the surgeon and will be recorded. If there are inadvertent positive margins after primary resection, a re-resection of margins will be performed as soon as possible postoperatively. Pulmonary metastatectomy will be considered for patients with the following criteria: no contraindications to thoracotomy; adequate lung function; completely resectable pulmonary and extrapulmonary disease; no extensive involvement of the chest wall or mediastinum; and slow pace of disease (Abdall and Pisters, 2002; Casson et al, 1991; Dear and Tattersall, 2010; Predine et al, 2011; Sardenberg et al, 2010; Smith et al, 2009; Stephens et al, 2011; Treasure et al, 2012). It is expected that less than 10% of patients with metastatic disease will be candidates for pulmonary metastatectomy (Canter et al, 2007, Blackmon et al, 2009). Radiofrequency or other ablative techniques will be considered in patients with a small number of large lung nodules who are not surgical candidates. After surgery, patient will receive 4 cycles of Adjuvant monotherapy Durvalumab of 4 weeks per cycle. Adjuvant monotherapy will be restarted at least 4 weeks post surgery or after the wound has healed per clinical judgment.

Upon the end of the 4 cycles of adjuvant monotherapy Durvalumab treatment, patient will be evaluated radiographically for response per section 9.0. If the patient has NED after surgical resection and 4 cycles of adjuvant montherapy, the patient will enter the surveillance phase of serial imaging per section 9.0. If the patient has metastases or if there is unresectable local residual disease after surgery and the 4 cycles of adjuvant monotherapy, a maintenance phase will be started for an additional 5 cycles of monotherapy Durvalumab.

Peripheral blood samples will be collected prior to neoadjuvant treatment, the day of surgery, at cycle 2 day 15 of the adjuvant monotherapy, cycle 4 day 15 of adjuvant monotherapy treatment, at cycle 7 day 15 of the maintenance phase, and at the end of the maintenance phase. Tumor samples from the initial biopsy and at the time of definitive resection will be collected. Any tumor samples from lymph node, pulmonary or extra-pulmonary metastases during the course of treatment or surveillance will be collected as well. All lesions will be carefully measured on MRI or CT before and after neoadjuvant RT. The Response Evaluation Criteria in Solid Tumors RECIST and the immune-related response criteria (irRC) will be used to classify treatment response of the primary lesion and any metastatic involvement and the duration of response. If covered by insurance, a PET-CT of the primary lesion will be performed before and after neoadjuvant IRT to assess response according to PERCIST. Pathologic specimens will be processed and evaluated as per standard protocol. Margin status, closest margin, grading, percent necrosis, and neoadjuvant treatment effect will be recorded. Margins will be recorded as R2 (macroscopically positive), R1 (microscopically positive only), R0 (microscopically negative). If the primary lesion is resected with positive margins and additional margins were separately resected, the margin will be deemed contaminated (ex: contaminated R0 resection). Any interruptions in neoadjuvant IRT will be recorded. After completion of treatment, patients will be clinically followed up for progression with physical exam, MRI of the primary location, and CT scan of the lungs every 3 months for 2 years, then every 6 months for 3 years, then every year up to 10 years (per standard of care). After 10 years, they will be followed every 3-5 years. Oncologic outcomes will be recorded including local recurrence (LR), distant relapse (DR), overall survival (OS) and disease-specific survival (DSS) for all patients, disease-free survival (DFS) for patients presenting with localized disease, and progression-free survival (PFS) for patients presenting with metastases. Patient pain, fatigue and function will be assessed using the Patient Reported Outcomes Measurement Information System – Physical Function, Pain Interference and Cancer (PROMIS-PF, PI, Ca), validated functional measures created by the National Institutes of Health (NIH) (Cella et al, 2008; Amtmann et al, 2010). Evaluation time points will be prior to infusion on cycle 1 day 1 of neoadjuvant treatment, prior to surgery, prior to the start of adjuvant phase, at the end of adjuvant phase, and 5 months after the end of adjuvant phase.

Radiation toxicity will be recorded according to the RTOG (Radiation Therapy Oncology Group) criteria for acute (1 to 90 days from commencement of RT) and late (>90 days) morbidity. If any unexpected or severe toxicity develops, RT will be stopped and treatment plans will be reviewed for potential causes and needed adjustments. All surgical complications will be classified including infection, hematoma, delayed wound healing, and flap complications. Each complication will be graded according to a previously validated classification scheme for surgical complications (Dindo et al, 2004). The Common Terminology Criteria for Adverse Events version 4.0 will be used to classify the adverse events. Adverse events of special interest to Durvalumab/Tremelimumab include colitis, pneumonitis, liver toxicity, nephritis and endocrinopathy. Appropriate efforts will be made to rule out other non-immunotherapy-related etiologies. Immune-related adverse events will be managed with corticosteroids given orally or intravenously, immunosuppressive agents

(for colitis or hepatic IrAE's), and hormone replacement therapy for endocrine IrAEs at the treating oncologists' discretion. Serious adverse events include those that result in death, is immediately life-threatening, requires inpatient hospitalization, or results in persistent or significant disability or incapacity.

The study will be designed as described as an integrated phase I/II study. See sections 11.1.1 and 11.1.2 for detailed design with statistical considerations.

3.2 Study Schema and Procedures Charts

Table 1. Schedule of Assessments: Treatment

Table 1 Treatment Calendar: All assessments to be performed pre-infusion unless stated otherwise	Screening		Neoadjuvant Treatment	Pre-Surgery[28]	Surgery	Post-Surgery	Adjuvant Treatment	End of Adjuvant Treatment[23]
	Within 4 weeks pers of C1D1	Within 14 days of C1D1	Durvalumab + Tremelimumab combination 3 cycles [22]	Within 1 week of surgery	5-8 weeks post end of radiotherapy	4 weeks post surgery or wound heal	Durvalumab monotherapy 4 cycles [22]	
ADMINISTRATIVE								
Written informed consent/assignment of subject identification number [1]	X							
Preliminary eligibility fulfillment (PI/AI opinion)	X							
Previous treatments for STS and disease details	X							
Formal verification of eligibility criteria	X							
Medical and surgical history	X							
Demography and social history [2]	X							
Prior and concomitant medication review [3]	X	X	X	X	X		X	X
Adverse event/serious adverse event assessment	X [4]	X	X	X	X		X	X
DISEASE TREATMENT [5]								
Durvalumab Infusion			X				X	
Tremelimumab infusion			X					
Radiation therapy (RT) [8-9]			Per Radiation Plan					
Surgical Resection of primary lesion [10]					X			
LABORATORY ASSESSMENTS								
Hepatitis B and C; HIV				ACI				
Urine hCG or serum βhCG [11]		X	X	X	ACI		X	X

Table 1 Treatment Calendar: All assessments to be performed pre-infusion unless stated otherwise	**Screening**	**Neoadjuvant Treatment**	**Pre-Surgery[28]**	**Surgery**	**Post-Surgery**	**Adjuvant Treatment**		**End of Adjuvant Treatment[23]**
	Within 4 weeks pers of C1D1	**Within 14 days of C1D1**	**Durvalumab + Tremelimumab combination**	**Within 1 week of surgery**	**5-8 weeks post end of radiotherapy**	**4 weeks post surgery or wound heal**	**Durvalumab monotherapy**	
			3 cycles [22]				**4 cycles [22]**	
Comprehensive serum chemistry (complete clin chem panel, **including** liver enzymes) [12]		X	X	X	ACI		X	X
Thyroid function tests (TSH and fT3 and fT4) [13]			X	As clinically indicated (ACI)			X	X
Hematology/CBC with differential [12]		X	X	X	ACI		X	X
Coagulation parameters [14]				X				
CLINICAL ASSESSMENTS								
Full Physical examination [15]	X							
Targeted physical examination [16]			X	X			X	X
Vital signs[6]	X		X	X			X	X
Weight	X		X	X			X	X
Electrocardiogram [17]			C1D1. All other visits as clinically indicated					
ECOG performance status	X		X	X			X	X
EFFICACY AND OUTCOME ASSESSMENTS								
Tumor Assessment [18, 24]	X			X		X	X[24]	
PERCIST + PET Scan	X			X				
Histopathological evaluation of tumor	X				X			
Patient questionnaires (PROMIS-PF, PROMIS-PI, PROMIS-Ca)			C1D1 Only	X			C1D1	X
SPECIMEN COLLECTION								
Archival tumor sample or fresh tumor biopsy collected ***standard of care*** [19]	X							
Correlative studies tumor biopsy [20]	X				X			
Correlative studies blood collection [21]			C1D1 Only		X		C2D15, C4D15	

Table 2. Schedule of Assessments: Post Treatment

Tabe 2 Post Treatment Calendar	Maintenance Therapy		Clinical Follow-Up for Pre-Progression[25]		Survival F/U
	5 Cycles [22]	30 Day Safety F/U from last dose [26]	Month 2 and 3	Schedule per Section 8.1.4.1	Schedule per Section 8.1.4.2
Prior and concomitant medication review [3]	X	X			
Adverse event/serious adverse event assessment	X	X	X		
Durvalumab Infusion	X				
Urine hCG or serum βhCG [11]	X	X			
Comprehensive serum chemistry (complete clin chem panel, **including** liver enzymes) [12]	X	X	X		
Thyroid function tests (TSH and fT3 and fT4) [13]	X	X	X		
Hematology/CBC with differential [12]	X	X	X		
Targeted physical examination [16]	X	X	X	Month 5	
Vital signs [6]	X	X	X		
Weight	X	X	X		
Electrocardiogram [17]	ACI	ACI	ACI		
ECOG performance status	X	X	X		
Tumor Assessment [18, 24]	X[24]		X[24]	X	
Patient questionnaires (PROMIS-PF, PROMIS-PI, PROMIS-Ca)	Performed 5 Months After End of Adjuvant Therapy				
Correlative studies blood collection [21]	C7D15 & C9D15		Month 2	Month 5	
New anti-cancer therapies		X	X	X	X
Survival				X	X

ALL REFERENCES FOR TABLES 1 & 2

[1] Written consent must be obtained prior to performing any protocol specific procedure. All consented subjects will be given a unique number. The performance site should contact the coordinating center to obtain each subject's unique, sequential number. That number will be used to identify subject throughout the study. The number will not contain any direct subject identifiers.

[2] Including alcohol and tobacco use

[3] All medications the patient is taking will be recorded

[4] For AEs/SAEs reported during prescreening additional information such as medical history and concomitant medications may be needed.

[5] Response, based on tumor imaging and clinician evaluations after surgical resection, will determine subsequent study treatment plan. Patients presenting with metastases or unresectable local residual disease after surgery will enter the maintenance phase (see section 8.1.2)

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

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)

Vital sign measurement timepoints must be observed for both drugs during the neoadjuvant phase.

[7] If the patient presents with metastases or if there is unresectable local residual disease after surgery, a maintenance phase will be started after 16 weeks of adjuvant Durvalumab monotherapy treatment, in which one dose of Durvalumab is given every four weeks for a total of up to one year from beginning of study treatment/regimen

[8] Standard external beam radiation therapy (EBRT) will be delivered to the primary tumor with a minimum dose of 50 Gy and 1.8 - 2 Gy per fraction at the discretion of the treating radiation oncologist. For bulky sarcomas, defined as > 10cms in greatest dimension, a single 15 Gy fraction of spatially fractionated GRID radiation therapy (SFGRT) will be delivered to the tumor within 1-3 days prior to start of standard external beam radiotherapy (EBRT)

[9] During radiation treatment the patient's will be seen by a radiation oncology at least every week with directed physical exam and toxicity evaluation. The patient can be seen more frequently if clinically indicated. Radiation will be withheld for patients with contraindications including genetic conditions that predispose to skin cancer (e.g.. xeroderma pigmentosum) and connective tissue diseases (e.g., lupus))

[10] Surgical resection will be performed 5 – 8 weeks after cessation of radiation therapy, depending on the condition of the surrounding soft tissues

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

[12] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.

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

[14] Coagulation tests: prothrombin time, APTT, PT and INR – only performed at pre-op.

[15] Full physical exam at baseline; targeted physical exam at other time points

[16] Targeted physical examinations will include assessments of the head, eyes, ears, nose and throat, and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurologic, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only

[17] ECG on Day1 – baseline. Baseline and abnormal ECG performed in triplicate (2-5 minutes apart), others performed in single. Triplicate ECGs should be taken within an hour prior to the start of the infusion and a single ECG at least one time point 0 to 3 hours after the infusion on Cycle 1 day 1. Thereafter as clinically indicated.

[18] Imaging during initial staging(screening) and work-up will include plain radiographs (if warranted from an orthopaedic standpoint), magnetic resonance imaging (MRI) of the primary site of disease, and a whole-body 18F-FDG positron-emission tomography (PET) scan including diagnostic computed tomography chest / abdomen / pelvis (CT C/A/P). If the patient's medical insurance does not cover PET-CT, then a CT C/A/P and whole body bone scan (WBBS) will be performed. All patients will be discussed at a multi-disciplinary tumor board. PET scans will be obtained prior to and after neoadjuvant treatment to assess disease response, provided insurance coverage. Following initial work up tumor assessments will consist of a chest CT and MRI with and without contrast of the primary tumor site. If clinically indicated an abdomen/pelvis scan can be performed as well. If clinically indicated scans may be done halfway through Durvalumab Monotherapy Phase.

[19] An initial clinic visit to evaluate a new soft tissue mass typically leads to the ordering of a biopsy of the mass, unless the patient presents with a prior biopsy or resection and a known diagnosis. Patients will be screened for participation in this study based on their tumor biopsy, which is considered standard of care. The tumor specimen used for screening should be from within 24 weeks prior to enrollment in the study.

[20] See section 8.2.7

[21] C1D1 of Neoadjuvant Treatment, Day of surgery, C2D15 of Adjuvant Treatment, End of Adjuvant Treatment, C7D15 and C9D15 of Maintenance Therapy OR Month 2 and Month 5 of Pre-Progression Follow-Up

[22] Cycles are 4 weeks long. Maintenance Phase cycles start at cycle 5 continuing from adjuvant monotherapy.

[23] Only performed if patient is NED and doubles as the 30 day safety follow-up. Patient will proceed to Pre-Progression Safety Follow-Up.

[24] Tumor Assesments performed per section 8.1.4.1

[25] For patients that have completed protocol therapy and achieved disease control or who were taken off of treatment for any other reason. Patients remain on clinical follow-up for pre-progression until disease progression.

[26] For patients that are removed from study after surgery and prior to starting adjuvant therapy the 30 day safety follow-up will be the pre-op visit.

[27] Only performed for maintenance 30 day F/U.

[28] Considered 30 Day Safety Follow-Up for patients that do not start Durvalumab adjuvant therapy after surgery.

3.3 Study Oversight for Safety Evaluation

Radiation toxicity will be recorded according to the RTOG (Radiation Therapy Oncology Group) criteria for acute (1 to 90 days from commencement of RT) and late (>90 days) morbidity. If any unexpected or severe toxicity develops, RT will be stopped and treatment plans will be reviewed for potential causes and needed adjustments.

All surgical complications will be classified including infection, hematoma, delayed wound healing, and flap complications. Each complication will be graded according to a previously validated classification scheme for surgical complications (Dindo et al, 2004).

The Common Terminology Criteria for Adverse Events version 4.0 will be used to classify the adverse events. Adverse events of special interest to Durvalumab/Tremelimumab include colitis, pneumonitis, liver toxicity, neuropathy, dermatitis, pancreatitis, nephritis and endocrinopathy. Appropriate efforts will be made to rule out other non-immunotherapy-related etiologies. Immune-related given orally or intravenously, immunosuppressive agents, and hormone replacement therapy for endocrine IrAEs at the treating oncologists' discretion. Serious adverse events include those that result in death, is immediately life-threatening, requires inpatient hospitalization, prolongs a current hospitalization, or results in persistent or significant disability or incapacity.

4. STUDY POPULATION

4.1 Diagnosis/Condition for Entry into the Trial

Each patient must meet all of the inclusion criteria (Section 4.2) and none of the exclusion criteria (Section 4.3) for this study. Under no circumstances will there be exceptions to this rule.

Patients with a biopsy-proven adult-type high-risk STS in the pelvis or extremities will be included. High-risk STS will be defined as tumors greater than or equal to 5 cm, intermediate or high grade according to FNCLCC criteria, and a location deep or superficial to fascia. Intermediate or high-grade tumors that are locally recurrent, metastatic or have had prior inadequate resections will also be included as high risk. Histologies will include the most common adult-type STS such as undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, fibrosarcoma, synovial sarcoma, angiosarcoma, epithelioid sarcoma and malignant peripheral nerve sheath tumor. Patients must have measurable disease as defined by RECIST v1.1. Their ECOG performance status must be <2and have adequate organ and marrow function. Patients must be ≥18 years old. Patients who have had prior cytotoxic chemotherapy or targeted systemic therapy (ex: Pazopanib, Trabectidin) will be included as long as it is cessated greater than 4 weeks prior to the start of study intervention. Patients with surgically unresectable primary lesions will not be included.

All patients will undergo a complete history and physical exam. Imaging will include magnetic resonance imaging (MRI) of the primary site of disease, a whole-body positron-emission tomography (PET-CT) scan including diagnostic computed tomography chest / abdomen / pelvis (CT C/A/P). If the patient's medical insurance does not cover PET-CT, then a CT C/A/P and whole body bone scan (WBBS) will be performed, and plain radiographs (XR) if warranted from orthopedic stand point. All patients will be discussed at a multi-disciplinary tumor board.

4.2 Inclusion Criteria

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

1. Written informed consent and any locally-required authorization (e.g., HIPAA) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations

2. Patients with a biopsy-proven adult-type high-risk soft tissue sarcoma (STS) in the trunk (non-retroperitoneal) or extremities. Histologies will include the most common adult-type STS such as undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, fibrosarcoma, synovial sarcoma, angiosarcoma, epithelioid sarcoma and malignant peripheral nerve sheath tumor. STS considered high-risk as defined below:

- Tumors greater than or equal to 5 cm, intermediate or high grade according to FNCLCC criteria, and a location deep or superficial to fascia.

- Intermediate or high-grade tumors that are locally recurrent, metastatic or have had prior inadequate resections

- Intermediate and High Grade Tumors shall be Grade 2 or 3 based on FNCLCC parameters (Trojani et al, 1984; Coindre 2006)
  - Tumor Differentiation
    - Score 1 (sarcomas closely resembling normal adult mesenchymal tissue)
    - Score 2 (sarcomas for which histological typing is certain)
    - Score 3 (embryonal and undifferentiated sarcomas)
  - Mitotic Count (HPF – high power field – 0.17 mm squared)
    - Score 1 (0-9 mitoses per 10 HPF)
    - Score 2 (10-19 mitoses per 10 HPF)
    - Score 3 (greater than or equal to 20 mitoses per 10 HPF)
  - Tumor Necrosis
    - Score 0 (no necrosis)
    - Score 1 (less than 50% tumor necrosis)
    - Score 2 (greater than or equal to 50% tumor necrosis)
  - Histological Grade
    - Grade 1 – total score 2 or 3
    - Grade 2 – total score 4 or 5
    - Grade 3 – total score 6, 7 or 8

3. Patients must have measurable disease as defined by RECIST v1.1.

4. Age $\geq$ 18 years at time of study entry

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

6. Life expectancy of $\geq$ 12 weeks based on investigator estimate

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

   - Haemoglobin $\geq$ 9.0 g/dL

   - Absolute neutrophil count (ANC) $\geq$ 1.5 x 10^9/L ($\geq$ 1500 per mm^3)

- Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)

- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). *[This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician.]*

- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN

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

  Males:

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

  Females:

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

8. Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative urine pregnancy test upon study entry. If unsure postmenopausal status, hormone levels will be employed to verify.

9. Females of childbearing potential who are sexually active with a non-sterilized male partner and non-sterilized male subjects who are sexually active with a female partner of childbearing potential must be willing to use 2 methods of effective contraception (Table 1) from time of screening through 180 days after receipt of the final dose of Durvalumab + Tremelimumab combination therapy or 90 days after receipt of the final dose of Durvalumab Monotherapy, whichever is the longer time period.

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

4.3 Exclusion Criteria

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

1. To limit the heterogeneity of the tumor population and reduce the risk of masking any clinical effect of the treatment regimen, multiple categories of STS subtypes will be excluded:
    - Patients with primarily bone-based sarcomas that can occur in the soft tissues, such as:
        - extraskeletal Ewing sarcoma
        - extraskeletal osteosarcoma
        - peripheral chordoma
        - mesenchymal chondrosarcoma
    - Patients with predominantly low-grade STS, such as:
        - solitary fibrous tumor / hemangiopericytoma
        - well-differentiated liposarcoma
        - dermatofibrosarcoma protuberans
        - Kaposi's sarcoma
    - Gastrointestinal stromal tumors (GIST)
2. Retroperitoneal soft tissue sarcomas
3. Patients with >2 liver metastases or >2 soft tissue non-lymph node metastases (ex: intramuscular, subcutaneous), or liver or soft tissue non-lymph node metastases >1 cm
4. Patients with a surgically unresectable primary lesion
5. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
6. Any previous treatment with an anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapy, including Durvalumab and Tremelimumab
7. History of hypersensitivity to Durvalumab or any excipient
8. History of hypersensitivity to Tremelimumab or any excipient
9. History of hypersensitivity to the combination or comparator agent
10. History or clinically confirmed pneumonitis or interstitial lung disease
11. Receipt of the last dose of anti-cancer therapy (cytotoxic chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 4 weeks pers prior to the first dose of study drug (4 weeks pers prior to the first dose of study drug for subjects who have received prior TKIs

[e.g., erlotinib, gefitinib and crizotinib] and within 6 weeks for nitrosourea or mitomycin C *[If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period may be required]*)

12. Current or prior use of immunosuppressive medication within 4 weeks pers before the first dose of durvalumab or tremelimumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid

13. Any unresolved toxicity (> CTCAE grade 2) from previous anti-cancer therapy. *NOTE: Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy)*

14. Any prior immune-related adverse event (irAE) ≥ Grade 2 while receiving any previous immunotherapy agent, or any unresolved irAE > Grade 1

15. Active or prior documented autoimmune disease within the past 2 years. *NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.*

16. History of primary immunodeficiency

17. History of allogeneic organ transplant (e.g. solid organ/bone marrow transplant patients)

18. Uncontrolled intercurrent illness including, but not limited to:
    - Ongoing or active infections
    - Cardiac conditions, such as:
        - symptomatic congestive heart failure
        - uncontrolled hypertension
        - unstable angina pectoris
        - cardiac arrhythmia
    - Active peptic ulcer disease or gastritis
    - History of inflammatory bowel disease, ulcerative colitis or Crohn's Disease
    - Active bleeding diatheses
    - Any subject known to have evidence of acute or chronic hepatitis B or hepatitis C. Patients will undetectable levels of virus will be allowed to participate.
    - Any subject known to have evidence of human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS)
    - Uncontrolled seizures

19. Known history of current or recent clinical diagnosis of tuberculosis (within 6 months prior to enrollment). A chest XR will be performed to screen for active TB for patients who have a history of treated TB.
20. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
21. Any signs or symptoms of bowel obstruction within 4 weeks pers prior to study entry
22. History of leptomeningeal carcinomatosis
23. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab, or active infection
24. History of psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
25. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
26. Previously enrolled in the present study
27. Participation in another clinical study with an investigational product during the last 6 months
28. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
29. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period

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

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

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.4

4.4 Discontinuation of Subjects from Study Treatment

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

1. Withdrawal of consent or lost to follow-up
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
4. Pregnancy or intent to become pregnant
5. Any AE that meets criteria for discontinuation as defined in Section 10.3.
6. Dose-limiting toxicity (See Section 5.5 for definition of DLT)
7. Grade ≥ 3 infusion reaction
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 progressive disease and investigator determination that the subject is no longer benefiting from treatment.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.3 including the collection of any protocol-specified blood specimens, unless consent is withdrawn, the subject is lost to follow-up, or enrolled in another clinical study. Subjects who decline to return to the site for evaluations will be followed-up by phone per the schedule in section 8.1.4.2 as an alternative. All subjects will be followed for survival.

Patients who discontinue neoadjuvant study treatment (e.g., because of treatment intolerability or lack of response) will be assessed by the treating medical oncologist and attending surgeon for surgical resection or non-surgical standard-of-care treatment measures (if not amenable for surgery).

Withdrawal of consent

Patients have the right to voluntarily withdraw from the study at any time for any reason.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation. If subjects withdraw from the correlative studies, all data collected up to that point will be kept confidential and secure.

4.5 Removal of Participants from Study

The investigator has the right to remove a patient from the study without consent at any time.

Reasons for removal from the study may include, but are not limited to, the following:

- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator
- Intent to become pregnant
- Inappropriate behavior towards study personnel

Subjects withdrawn before initiation of study treatment regimen has begun will be replaced.

4.6 Criteria for Early Trial or Performance Site Termination

Performance site termination will be the result of meeting one of the criteria specified below:

- Quality or quantity of data recording is inaccurate or incomplete.
- Poor adherence to protocol and regulatory requirements.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab and Tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply Durvalumab and Tremelimumab to the investigator as solutions for infusion after dilution.

5.1.1 Formulation, Packaging and Storage

Durvalumab

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiration date on the label.

See section 5.3 for additional information regarding management of study drugs on site.

Tremelimumab

Tremelimumab will be supplied by AstraZeneca as a 400-mg vial solution for infusion after dilution. The solution contains 20 mg/mL of tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA); it has a pH of 5.5. The nominal fill volume is 20.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Tremelimumab must be used within the individually assigned expiration date on the label.

Any defects noted in the investigational products will be reported to the company upon discovery.

5.2 Dose and Treatment Regimens

5.2.1 Treatment Regimens

Neo-adjuvant Therapy: Durvalumab + Tremelimumab Combination Therapy

Patients (>30 kg) will receive concurrently Tremelimumab at 75 mg intravenous and Durvalumab at 1500 mg intravenous every 4 weeks for 3 cycles of 4 weeks per cycles. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion). Dosing outside the window should be discussed with the Study Physician.

Adjuvant Durvalumab Monotherapy

Patients who have completed the neoadjuvant Durvalumab + Tremelimumab combination therapy will begin the Durvalumab monotherapy for 4 cycles of 4 weeks following surgical resection or after the wound has healed. Patients (>30 kg) will receive 1500 mg durvalumab via IV infusion over 1 hr at day 1 of each cycle for 4 cycles. A 1-hour observation period is required after the first infusion of durvalumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion). Dosing outside the window should be discussed with the Study Physician.

5.2.2 Duration of Treatment and Criteria for Continuation of treatment

If the patient presented with metastases or if there is unresectable local residual disease after surgery and the 4 cycles of adjuvant Durvalumab monotherapy, a maintenance phase will be started for an additional 5 cycles of Durvalumab monotherapy.

The same treatment guidelines followed during the initial adjuvant monotherapy treatment period will be followed during the maintenance phase period, including the same dose and frequency of treatments and the same schedule of assessments.

Patients receiving durvalumab may undergo the maintenance phase in the following clinical scenarios described below:

1. Patients who complete the adjuvant treatment (4 cycles of the monotherapy durvalumab) with clinical benefit per Investigator judgment, but have evidence of persistent disease or present with metastases or unresectable local residual disease after surgery, with or without confirmation according to RECIST 1.1 or irRECIST.

2. For the durvalumab maintenance phase treatment group, before restarting their assigned treatment, the Investigator should ensure that the patient:
    a. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient
    b. Still fulfills the eligibility criteria for this study
    c. Has not have received an intervening systemic anticancer therapy after their assigned treatment discontinuation.
    d. Has had a baseline tumor assessment within 4 weeks pers of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial months of treatment until study treatment is stopped (maximum of up to 12 months total of treatment).

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. A patient with confirmed progression while receiving neoadjuvant durvalumab + tremelimumab cannot continue therapy or obtain maintenance treatment.

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

5.2.3 Study Drug Preparation of Durvalumab and Tremelimumab

Based on average body WT of 75 kg, fixed doses of 1500 mg q4 wks durvalumab (equivalent to 20 mg/kg q4w) and 75 mg q4w tremelimumab (equivalent to 1 mg/kg q4w) are included in the current study. Fixed dosing will be performed for patients >30 kg and weight based dosing will be performed for patients <30 kg.

Preparation of Durvalumab Doses for Administration with an IV Bag

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

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

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

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

For patients < 30 kg weight based dosing should be used. Calculate the dose volume for durvalumab and number of vials needed for the subject to achieve the accurate dose. Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For examples of fixed and weight based dose calculations, see appendix.

Durvalumab will be administered at room temperature by controlled infusion into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be

administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-μm in-line filter. Less than 55 minutes is considered a deviation.

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

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Preparation of Tremelimumab Doses for Administration with an IV Bag

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

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

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

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Tremelimumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 μm or 0.22 μm in-line filter. However, administration sets containing cellulose-based filters should not be used with tremelimumab.

For patients <30 kg use weight-based dosing. Calculate the dose volume for tremelimumab and number of vials needed for the subject to achieve the accurate dose. Patient weight at baseline should be used for dosing calculations unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For examples of fixed and weight-based dose calculations, see the Appendix.

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

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

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours. Patients will remain on the unit for observation after the infusion.

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

5.2.4 Monitoring of Dose Administration

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

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥ Grade 3 or higher in severity, study drug will be discontinued.

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

5.2.5 Product distribution to participating sites

The investigational product will be provided to the Coordinating Center by AstraZeneca. Initial supplies of Tremelimumab and Durvalumab will be sent to participating sites by the University of Maryland Investigational Drug Services (IDS) Pharmacy. Additional re-supply may be obtained by completing an investigational product re-supply request form and faxing it to:

ATTN: Myounghee Lee, PharmD, RPh, PhD
University of Maryland Medical Center Investigational Drug Service Pharmacy
Fax: 410-328-7326 Phone: 410-328-5468.

6. TREATMENT PLAN

6.1 Subject Enrollment

Patients will be screened for participation in this study based on a standard of care tumor biopsy. The tumor specimen should be from within 24 weeks prior to enrollment in the study. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and eligibility is confirmed by the Site Investigator, patients will be approached for their consent to participate in the trial. Informed consent will be obtained prior to initiation of study regimens, but will not impede standard of care disease management.

The attending physician will initiate and conduct the consent conversation. The consent process will involve a dialogue. Specifically, patients and their families will be provided with information describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate.

All consent must be obtained from the patient in this study; no legally authorized representatives or surrogates may consent on behalf of the patient.

Once consented into the study, baseline data regarding patient characteristics, disease characteristics, medical history, co-morbidities (including current use medications) and other information described in section 8.1, will be collected and entered in to the chosen data collection system. Some of this information will be obtained via a brief interview with the patient.

6.1.1 Procedures for Handling Subjects Incorrectly Enrolled

Potentially eligible participants will be carefully screened for full eligibility by the PI or AI prior to enrollment, and will monitored for continued eligibility throughout study participation. Subjects that are incorrectly enrolled but not yet initiated on the study treatment will be withdrawn from the study, and replaced with an eligible participant.

6.2 Dosage and Administration

Refer to sections 1.1.3, 1.1.4, 5.1.1 and 5.2 for the administration, monitoring of administration, dosage and handling of durvalumab and tremelimumab.

6.3 Dose Escalation Decision Rules – N/A

6.4 Definition of DLT

Dose-limiting toxicities (DLTs) will be evaluated during the duration of the trial. The period for evaluating DLTs will be 4 weeks from the time of first administration of durvalumab or tremelimumab. Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. Grading of DLTs will follow

the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- 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 toxicity that prevents the patient to proceed to or experience substantial delays of more than 2 weeks in the start of definitive radiotherapy or surgery based on toxicity
- 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 × ULN or total bilirubin > 5 × ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below
- Based on combination of agents, determination of DLT not described here will be at discretion of treating clinician.

The definition excludes the following conditions:

- 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 Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- 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
- Grade 3 acute skin toxicity attributable to radiation will not be considered a DLT. It will be managed appropriately to avoid progression to grade 4. Grade 4 skin toxicity attributable to radiation will be a DLT

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 prior to designation as a DLT.

Regarding skin related toxicities:

Radiation therapy should be continued without interruption; grade 3 acute toxicity should not lead to interruption of radiation therapy. However, interruptions in RT may be necessitated by ≥ grade 4 skin toxicity. Should severe radiation associated toxicity such as moist desquamation unresponsive to topical dressings occur, treatment may be interrupted in order to relieve morbidity at the sole discretion of the treating radiation oncologist.

Acute local toxicity attributable to radiation effects (≤ grade 3) and not the study drug should be managed accordingly with optimal supportive care measures. Grade 3 toxicity should not progress to grade 4 if managed appropriately. if toxicity ≥ grade 4 persists, then a radiation break is allowable as defined above. Every effort should be made to avoid breaks in radiation treatment. If drug is held due to other toxicity attributed solely to the drug, radiation therapy should be continued.

Grade 3 acute skin toxicity attributable to radiation will not be considered a DLT. It will be managed appropriately to avoid progression to Grade 4. Grade 4 skin toxicity attributable to radiation will be a DLT.

6.5 Dose Modification and Toxicity Management

6.5.1 Durvalumab and Tremelimumab

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab or tremelimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab and tremelimumab (see Appendix 1).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab or tremelimumab should be permanently discontinued.

Following the first dose of durvalumab or tremelimumab, subsequent administration of durvalumab or tremelimumab can be modified based on toxicities observed (see Appendix 1).

Based on the mechanism of action of durvalumab or tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

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

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 10.1.3. All toxicities will be graded according to NCI CTCAE v4.0.

7. RESTRICTIONS AND CONCOMITANT TREATMENT(S)

7.1 Restrictions During Study Participation

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

Females of childbearing potential who are sexually active with a non-sterilized male partner must use 2 methods of effective contraception (Table 1) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

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

Non-sterilized males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 1) from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy, whichever is the longer time period.

Restrictions relating to concomitant medications are described in Section 7.2.

Table 3. Effective methods of contraception (2 methods must be used)

Barrier methods	Intrauterine device methods	Hormonal methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormonal shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (eg, Mirena®)[a]	Combined pill
		Minipill
		Patch

[a] This is also considered to be a hormonal method.

Blood Donation:

Subjects should not donate blood while participating in this study for at least 90 days following the last infusion of durvalumab or tremelimumab, or until after 4-5X the half-life of all study agents (as described in the drug prescribing information), whichever occurs longest.

7.2 Concomitant Treatment(s)

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

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 6.5 for guidance on management of IP-related toxicities.

7.2.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 7.2.2.

7.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

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

2. Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated comparator or combination regimens. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted.

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

Table 4. Prohibited and Rescue Medications

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

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

8. STUDY PROCEDURES

8.1 Schedule of Study Procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided in Section 3.0.

8.1.1 Screening Phase

Screening procedures will be performed up to 4 weeks pers before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

An initial clinic visit to evaluate a new soft tissue mass typically leads to the ordering of a biopsy of the mass, unless the patient presents with a prior biopsy or resection and a known diagnosis. Patients will be screened for participation in this study based on their tumor biopsy, which is considered standard of care. The tumor specimen should be from within 24 weeks prior to enrollment in the study. Biopsy of the tumor will be performed by radiology utilizing core needle biopsy. Multiple passes through the substance of the tumor will be carried out under image guidance and with needles at least 18 gauge in diameter. If CNB is not possible or based on clinical circumstance, open incisional biopsy may be performed. Pathology will be present to perform preliminary frozen sections to confirm adequate diagnostic tissue prior to processing the entirety of the sample for final diagnosis.

Patients with a biopsy-proven adult-type high-risk STS in the pelvis or extremities will be included. High-risk STS will be defined as tumors greater than or equal to 5 cm, intermediate or high grade according to FNCLCC criteria, and a location deep or superficial to fascia. Intermediate or high-grade tumors that are locally recurrent, metastatic or have had prior inadequate resections will also be included as high risk. Histologies will include the most common adult-type STS such as undifferentiated pleomorphic sarcoma, liposarcoma, leiomyosarcoma, fibrosarcoma, synovial sarcoma, angiosarcoma, epithelioid sarcoma and malignant peripheral nerve sheath tumor. Patients must have measurable disease as defined by RECIST v1.1. Their ECOG performance status must be ≤2 and have adequate organ and marrow function. Patients must be ≥18 years old. Patients who have had prior cytotoxic chemotherapy or targeted systemic therapy (ex: Pazopanib, Trabectidin) will be included as long as it is greater than 4 weeks prior to the start of the neoadjuvant therapy.

All patients will undergo a complete history and physical exam. Imaging will include magnetic resonance imaging (MRI) of the primary site of disease, and a whole-body positron-emission tomography (PET-CT) scan including diagnostic computed tomography chest / abdomen / pelvis (CT C/A/P), and plain radiographs (XR) if warranted from orthopedic stand point. If the patient's medical insurance does not cover PET-CT, then a CT C/A/P and whole body bone scan (WBBS) will be performed. A chest XR will be performed in all patients to screen for active TB unless there has been a prior chest XR or CT scan of chest within 1 month of entry. All patients will be discussed at a multi-disciplinary tumor board. MRI with and without contrast of the primary tumor site will be performed prior to commencement of neoadjuvant radiation and chemotherapy, between neoadjuvant therapy and surgical resection, and following surgical resection.

Peripheral blood samples will be collected prior to neoadjuvant treatment, the day of surgery, at cycle 2 day 15 of the adjuvant monotherapy, at the end of adjuvant monotherapy treatment, at cycle 7 day 15 of the maintenance phase, and at the end of the maintenance phase. Tumor samples from the initial biopsy and at the time of definitive resection will be collected. Any tumor samples from lymph node, pulmonary or extra-pulmonary metastases during the course of treatment or surveillance will be collected as well.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Histological confirmed adult type high risk soft tissue sarcoma (STS)
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- Review of prior/concomitant medications
- Review of tumor biopsy collected SOC
- Imaging by SOC whole body PET/CT/WBBS/XR
- Clinical laboratory tests for:
    - Hematology (see Table 5)
    - Clinical chemistry (see Table 6)
    - Creatinine Clearance
    - Urine pregnancy test (for women of childbearing potential only)

8.1.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessment Tables 1 and 2. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

8.1.2.1 Neoadjuvant Immunotherapy

Durvalumab (1500 mg) and Tremelimumab (75 mg) will be administered every 4 weeks starting on cycle 1, day 1. Radiation will start no sooner than 1 week after the first dose of immunotherapy and will occur in week 2 or 3 of cycle 1. This delay allows for pre-radiation imaging and treatment planning. The patient will receive 3 cycles of the neoadjuvant therapy prior to surgery. There will be at least 5-8 weeks between the last day of neoadjuvant radiotherapy and the surgery.

8.1.2.2 Neoadjuvant Radiation Therapy

For bulky sarcomas, defined as > 10 cms in greatest dimension, a single 15 Gy fraction of spatially fractionated GRID radiation therapy (SFGRT) will be delivered to the tumor within 1-3 days prior to start of external beam radiotherapy if deemed safe/appropriate by the treating radiation oncologist. SFGRT is akin to virtual brachytherapy, by which high dose beamlets of external beam radiotherapy are delivered to the tumor in a checkerboard pattern resembling interstitial catheters. SFGRT has both direct and indirect effects on cancer cells and has resulted in enhanced local control and tumor regression for radioresistant tumors such as sarcomas compared to standard external beam radiotherapy alone (Mohiuddin et al, 1999; Kaiser et al, 2012; Snider et al, 2014). One report suggests that SFGRT and immune checkpoint inhibition can be used together with limited toxicity and result in significant tumor regression (Mohiuddin et al, 2015). Following SFGRT, external beam radiation therapy (EBRT) will then be delivered to the primary tumor with a minimum dose of 50 Gy and 1.8 - 2 Gy per fraction at the discretion of the treating radiation oncologist for patient without metastatic disease. The treatment area for EBRT will encompass the primary tumor and a margin of normal tissue at the discretion of the treating radiation oncologist. Only the gross tumor volume will be targeted for SFGRT. In the setting of patients with metastatic disease, a hypofractionated course may be used at the discretion of the treating radiation oncologist. Radiation will be withheld for patients with contraindications including genetic conditions that predispose to skin cancer (e.g. xeroderma pigmentosum) and connective tissue diseases (e.g., lupus). Either photon, electron, or proton radiotherapy may be utilized for delivery of EBRT at the treating radiation oncologists' discretion.

8.1.2.3 Surgical Resection

Surgical resection will be performed between 5 to 8 weeks after cessation of neodjuvant radiotherapy depending on the condition of the surrounding soft tissues. Any delays in surgery beyond 8 weeks will be discussed with the principle Investigator. En-bloc removal of the primary lesion with negative margins of 1-2 cm distance (muscle/fat/cancellous bone) or of anatomic boundaries (fascia / periosteum) will be endeavored depending on proximity of vital structures. Preoperative embolization by interventional radiology may be performed to decrease blood loss. Mode of anaesthesia (e.g., spinal, general, etc.) will be at the discretion of the attending anaesthesiologist in discussion with the surgeon and will be recorded. If there are inadvertent positive margins after primary resection, a re-resection of margins will be performed as soon as possible postoperatively.

Pulmonary metastatectomy will be considered for patients with the following criteria: no contraindications to thoracotomy; adequate lung function; completely resectable pulmonary and extrapulmonary disease; no extensive involvement of the chest wall or mediastinum; and slow pace of disease. It is expected that less than 10% of patients with metastatic disease will be candidates for pulmonary metastatectomy. Radiofrequency or other ablative techniques will be considered in patients with a small number of large lung nodules who are not surgical candidates.

All lesions will be carefully measured on MRI or CT before and after neoadjuvant immunoradiotherapy (IRT) treatment. Post neoadjuvant scans should be as close as possible to the surgery date. The Response Evaluation Criteria in Solid Tumors (RECIST v1.1) and the immune-related response criteria (irRC) will be used to classify treatment response of the primary lesion and any metastatic involvement and the duration of response (Tirkes et al, 2013). If covered by insurance, a PET-CT of the primary lesion will be performed before and after neoadjuvant therapy to assess response according to PERCIST.

Pathologic specimens will be processed and evaluated as per standard protocol. Margin status, closest margin, grading, percent necrosis, and neoadjuvant treatment effect will be recorded. Margins will be recorded as R2 (macroscopically positive), R1 (microscopically positive only), R0 (microscopically negative). If the primary lesion is resected with positive margins and additional margins were separately resected, the margin will be deemed contaminated (ex: contaminated R0 resection).

8.1.2.4 Adjuvant Treatment

Adjuvant Durvalumab therapy of 1500 mg infusion, will be started 4 weeks following surgery or after the wound has healed and continued for 4 cycles of 4 weeks pers per cycle.

Adjuvant treatment will be ceased if there is clinical deterioration or if there is intolerable toxicity. Imaging may be done if clinically indicated during monotherapy adjuvant treatment and if there is progressive disease according to RECIST v1.1 and confirmed no less than 4 weeks later with a repeat scan monotherapy adjuvant treatment will be ceased. However, patients may continue to receive treatment with Durvalumab while awaiting confirmatory scans, or if investigators consider that patients are continuing to benefit from treatment despite progressive disease. These immunotherapy treatment modifications of RECIST v1.1 are based on the findings that response to immunotherapy may be delayed or occur after progressive disease based on conventional criteria that new lesions may not necessarily represent progressive disease while on immunotherapy, and stable disease while on immunotherapy may be durable and represent clinical benefit (Wolchok et al, 2009).

If the patient has no evidence of disease (NED) after 4 cycles of adjuvant monotherapy treatment, the patient will enter the surveillance follow up. If the patient presented with metastases or if there

is unresectable local residual disease after 4 cycles of adjuvant monotherapy, a maintenance phase will be started.

8.1.3 Maintenance Treatment

If the patient presented with metastases or if there is unresectable local residual disease after surgery and the 4 cycles of adjuvant monotherapy, a maintenance phase will be started for additional 5 cycles of Durvalumab of 4 weeks per cycle. The first cycle of maintenance therapy will be cycle 5 continuing from adjuvant monotherapy.

8.1.4 Follow Up

8.1.4.1 Clinical Follow Up

After completion of neoadjuvant, surgical resection, and adjuvant treatment patients will be monitored with MRI of the primary location, CT scan of the lungs and if clinically indicated abdomen pelvis every 3 months for 2 years starting at the end of adjuvant treatment visit, then every 6 months for 3 years, then every year up to 10 years. After 10 years, they will be followed every 3-5 years. Oncologic outcomes will be recorded including local recurrence (LR), distant relapse (DR), overall survival (OS) and disease-specific survival (DSS) for all patients, disease-free survival (DFS) for patients presenting with localized disease, and progression-free survival (PFS) for patients presenting with metastases.

Patient pain, fatigue and function will be assessed using the Patient Reported Outcomes Measurement Information System – Physical Function, Pain Interference and Cancer (PROMIS-PF, PI, Ca), validated functional measures created by the National Institutes of Health (NIH) (NIH PROMIS, 2016; Cella et al, 2008; Amtmann et al, 2010.

8.1.4.2 Survival Follow Up

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study. Every 3 months for 2 years, then every 6 months for 3 years, then every year up to 10 years. After 10 years, they will be followed every 3-5 years.

8.1.5 End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab or tremelimumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit.

Assessments for subjects who have completed durvalumab and tremelimumab treatment and achieved disease control, or have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progressive disease are provided in Table 2.

Assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in Table 2.

Treatment Summary:

- Week 1 Cycle 1 Day 1: Durvalumab + Tremelimumab
- Week 2-3 of Cycle 1: Begin neoadjuvant radiation therapy for 5-8 weeks
- Cycle 2 Day 1: Durvalumab + Tremelimumab
- Cycle 3 Day 1: Durvalumab + Tremelimumab
- Surgical resection of primary lesion (if soft tissue conditions are adequate, between 5-8 weeks after completion of radiation neoadjuvant therapy)
- Four weeks post surgery or wound heal: Adjuvant Durvalumab monotherapy starts for 4 cycles of 4 weeks pers per cycle.
- Post-adjuvant monotherapy treatment:
    - If no evidence of disease, enter surveillance phase
    - If persistent gross metastatic or locally unresectable disease, enter maintenance phase (continued Durvalumab monotherapy for extra 5 cycles of 4 weeks per cycle)

8.2 Description of Study Procedures

8.2.1 Medical History

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, and smoking history, will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to CTACE v. 4.0. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

8.2.2 Physical Examination

A complete physical examination will be performed according to the assessment schedule. Full physical examinations should include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Limited symptom-directed physical examinations

should be performed at specified postbaseline visits and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.3 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure, and temperature. Vital signs should be measured according to the assessment schedules.

On infusion days, patients receiving durvalumab + tremelimumab treatment will be monitored during and after infusion of IP as presented in the bulleted list below.

Supine BP will be measured using a semi-automatic BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving durvalumab + tremelimumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]).
- Approximately 30 minutes during the infusion (**halfway** through infusion).
- At the end of the infusion (approximately 60 minutes ±5 minutes).

A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab.

If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Body weight is recorded along with pre-vist vital signs. Height will be measured at screening only.

Situations in which vital signs results should be reported as AEs are described in Section 10.3.

8.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded on cycle 1 day 1 and as clinically indicated throughout the study. ECGs for each patient should be obtained from the same machine wherever possible. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while

the patient remains in that position. At cycle 1 day 1, 12-lead ECG will be obtained in triplicate (2-5 minutes apart) within 1 hour before first infusion and then a single ECG within 3 hours after the last infusion. For subsequent visits, where clinicially indicated, a single ECG will be obtained on which QTcF must be <470 ms.

In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

8.2.5 Laboratory and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis. Please refer to the Schedule of Assessments for specific tests required at screening and subsequent visits

- Hematology

Table 5. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
Mean corpuscular hemoglobin concentration	

- Coagulation parameters: Activated partial thromboplastin time (aPTT) and International normalized ratio (INR) to be assessed at baseline and as clinically indicated
- Comprehensive clinical chemistry (serum or plasma)

Table 6. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

[b] At baseline and as clinically indicated

- Pregnancy test (female subjects of childbearing potential only)
    - A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (at least 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
    - Urine human chorionic gonadotropin
- Thyroid
    - Thyroid stimulating hormone. free T3 and free T4 only if TSH is abnormal
- Other laboratory tests (as clinically indicated pre-surgery)
    - Hepatitis A antibody,
    - HBV serology: HBsAg, total HBcAb. If a patient has a negative HBsAg test and a positive total HBcAb test, an HBV DNA test must be performed to determine whether the patient has an HBV infection.
    - HCV serology: HCV antibody and HCV RNA (only if HCV antibody test is positive) If a patient has a positive HCV antibody test, an HCV RNA test must also be performed to determine if the patient has an active HCV infection.
    - HIV antibody

8.2.6 Patient Reported Outcomes Measure Information System (PROMIS)

Patients will complete paper questionnaire forms to capture PROMIS data. Evaluation time points will be prior to infusion on cycle 1 day 1 of neoadjuvant treatment, prior to surgery, prior to the start of adjuvant phase, at the end of adjuvant phase, and 5 months after the end of adjuvant phase. Scheduled assessments are outlined in assessment schedule

Patient pain, fatigue and function will be assessed using the Patient Reported Outcomes Measurement Information System – Physical Function, Pain Interference and Cancer (PROMIS-PF, PI, Ca), validated functional measures created by the National Institutes of Health (NIH).

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient before the patient receives any information on disease status and prior to the performance of non-PRO assessments and the administration of study treatment. Study personnel should review all questionnaires for completeness before the patient leaves the investigational site.

8.2.7 Corollary Research

Handling of blood and tissue specimens at non-University of Maryland Participating Sites

All tumor specimens in the form of formalin fixed paraffin embedded (FFPE) will be shipped to the Coordinating Center for study-related testing. Blood samples will be processed at the participating site using standard Ficoll technique to obtain a mononuclear cell layer of all WBCs except granulocytes. The cells will then be counted and frozen for later analysis. If blood is collected in Ficoll Hypaque Heparin tubes (Red & Green top tubes), they can be processed into mononuclear cell layers and re-suspended into freezing media (FBS/10% DMSO) and frozen using gradient freezing (-20 deg C for 2 hours, -80 deg C overnight, then liquid nitrogen cryo storage). The blood specimens will be stored at the participating site until shipped to Coordinating Center for testing.

Peripheral blood populations

Evaluating the absolute number and distribution of immune cells subsets and their activation status (based on phenotype) will offer novel insights and potential associations as they relate to treatment outcome. We will assess the levels of various immune cells in circulation including:

- Cytotoxic CD8 T cells, as PD-L1, as preliminary data indicate that activated T cells can also express PD-L1 (CD3, CD8, PD-1, Tim3, Lag-3, TIGIT, CTLA4)
- NK (CD94/NKG2A, KIR, CD56, CD57, PD-1)
- B cells (CD20, CD19, PD-L1)
- Tregs (CD4, CD25, FoxP3),which are known to play a critical role in immune activity against cancers

We will analyze the absolute count per ul and percentages of these cells types in the peripheral blood over time. Blood (20ml) and blood serum (1ml) will be drawn at the following timepoints:

- C1D1 of Neoadjuvant Treatment
- Day of surgery
- C2D15 of Adjuvant Treatment
- End of Adjuvant Treatment
- C7D15 and C9D15 of Maintinance Therapy
  OR
- Month 2 and Month 5 of Pre-Progression Follow-Up

Changes in the frequency of or the phenotype of these cells will be retrospectively analysed using flow cytometry to determine any potential correlations with efficacy endpoints.

Blood samples will be 20 ml blood and 1 ml serum for the corollary studies. This is in addition to the blood required as standard testing for medical oncology purposes. The blood samples will be processed immediately, and serum samples will be cryopreserved.

Immunohistochemistry (IHC) analysis

Immunohistochemistry analysis of tumor specimens with multiphoton or confocal microscopy of the initial biopsy, the final tumor resection specimen and the infiltrating margin of the tumor for markers of T-cell exhaustion (PD-L1, LAG3, TIM3, TIGIT) will be performed.

Immunohistochemistry will be performed in standard fashion. Specimens are fixed within 30 mins of excision in 10% neutral buffered formalin for 24-48 hrs at room temperature and then embedded in paraffin. Formalin fixed paraffin embedded (FFPE) blocks will be stored at ambient temperature and protected from light. The FFPE blocks will be sectioned with a microtome and mounted on slides which are then deparaffinized and rehydrated with xylene and ethanol. Antigen retrieval will be performed according to the method recommended by the specific antibody manufacturer's instructions (enzymatic vs heat-induced). The antibody concentration will then be optimized by several series of dilutions.

Antibodies for the following markers of T-cell exhaustion will be tested: PD-L1, CTLA-4, TIM-3, LAG-3, and TIGIT. The PD-L1 (ABCAM PD-L1 ab2015921)**,** CTLA-4, TIM-3, LAG-3 and TIGIT assays will need to be optimized. Immunohistochemistry will be performed using the Dako EnVision FLEX + detection system (DAKO, Carpinteria, CA). The Dako PT link is used for deparaffinization and heat-induced epitope retrieval using Dako EnVision FLEX + Target Retrieval Solution, Low or High pH (dependent upon optimization), for twenty minutes and rinsed in Dako wash buffer according to the manufacturer's instructions. Endogenous peroxidase activity is blocked with EnVision FLEX Peroxidase-Blocking Reagent ten minutes before incubation with the designated antibody, followed by incubation with EnVision FLEX/HRP Detection Reagent for thirty minutes. The sections are then incubated with diaminobenzene before they are

counterstained with Dako FLEX hematoxylin, rinsed and mounted in Cytoseal XYL (Thermo Scientific, Waltham, MA).

Multiphoton imaging will be performed at the University of Maryland Core Facilities for the Center for Innovative Biomedical Resources (CIBR) where there are 2-photon microscope. Capabilities to visualize and localize three antibodies at the same time in one sample are available. Scoring will be performed separately by two researchers blinded to other clinicopathologic information. To minimize interobserver variability, the same field of view will be used to score. The consensus for scoring will be reached after discussion with all the authors. To quantify TIL's bearing immune checkpoint receptors, the number of marker-positive TILs will be counted in the highest five numbered high power fields (HPF). The totals from each of the HPF's will be counted and progressively added to the final tally. To quantify tumor cells expressing ligands for immune checkpoint receptors, the intensity and area of staining will be scored. The range for intensity will be 0 (no staining), 1 (weak staining), 2 (intermediate staining), and 3 (strong staining) and the range for area will be 0 (0-10% total), 1 (11-33%), 2 (34-66%), 3 (67-100%) (Kim JR et al, 2013). The sum of the intensity and area will be used for statistical further analysis.

Microsatellite Instability Testing (MSI)

Mutational load as a predictive biomarker of response to immune checkpoint inhibition is surfacing as strong correlate in several cancer types. Studying MSI in sarcoma may uncover associations between treatment outcome and which might further extended to associations with immune cell analyses (number, distribution and phenotype). The rationale of this study is to combine both CTLA-4 and PD-L1 blockade with RT to overcome limited systemic effect seen in prior studies with single-pathway blockade, with RT-alone, or with low mutagenic burden tumor phenotypes.

We will measure MSI using the Bethesda panel of microsatellite loci including D2S123, D5S346, D17S250, BAT25 and BAT26 in tumor samples prior to initiation of neoadjuvant immunoradiation treatment and compare these to MSI from peripheral blood mononuclear cells (5ml blood draw). Genetic material will be collected from tumor using needle biopsies while immune cells will be collected by blood draw. Associations between MSIs and treatment efficacy as well as T cell phenotype (collected from blood samples and tumor infiltrating cells) will be analyzed.

Molecular, genetic, and in vitro analysis of blood and serum samples may be performed

8.3 Biological Sampling Procedures

8.3.1 *Pharmacokinetic Sampling and Evaluation Methods – N/A*

8.3.2 *Immunogenicity Sampling and Evaluation Methods – N/A*

8.3.3 *Pharmacodynamic Sampling and Evaluation Methods – N/A*

8.3.4 Estimate of Volume of Blood to be Collected

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

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

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Comprehensive blood/serum clinical chemistry	9 mL	6	36 mL
Hematology/CBC w. differential	3 mL	6	12 mL
Thyroid function	2.7 ml	4	10.8 mL
Correlative studies blood	20 mL	6	120 mL
Total		22	178.8

8.3.5 Archival Tumor Samples and Fresh Tumor Biopsies

An initial clinic visit to evaluate a new soft tissue mass typically leads to the ordering of a biopsy of the mass, unless the patient presents with a prior biopsy or resection and a known diagnosis. Patients will be screened for participation in this study based on their tumor biopsy, which is considered standard of care. The tumor specimen used for screening should be from within 24 weeks prior to enrollment in the study.

Biopsy of the tumor will be performed by radiology utilizing core needle biopsy. Multiple passes through the substance of the tumor will be carried out under image guidance and with needles at least 18 gauge in diameter. If CNB is not possible or based on clinical circumstance, open incisional biopsy may be performed. Pathology will be present to perform preliminary frozen sections to confirm adequate diagnostic tissue prior to processing the entirety of the sample for final diagnosis.

At the University of Maryland, School of Medicine, the Pathology Biorepository Shared Services (PBSS) collects tumor and normal tissue in excess of what is needed for standard of care diagnosis. Collections require coordination with OR staff, pathology residents and pathologists to ensure samples are collected as close to resection time as possible for preservation of downstream DNA/RNA analysis. PBSS procures tissue for internal and external customers with appropriate

IRB approval and/or materials transfer agreement (MTA) if applicable. All samples are de-identified at the time of collection and stored within the PBSS laboratory. All associated clinicopathologic data is maintained within a secure database.

A. Types of Tissue Collections
    a. Frozen Tissue Procurement
        i. Matched tumor and normal (if available) tissue aliquots are weighed and placed in labeled DNAse/RNase corning vials.
        ii. Tissue is snap frozen in liquid nitrogen.
        iii. Tissue is placed in -140° C freezer for long term storage.
        iv. All chain of custody time points are captured on collection form (i.e. Time of resection, time placed in liquid nitrogen, etc.)
    b. Fresh Tissue Procurement
        i. Matched tumor and normal (if available or requested) tissue is placed in a labeled conical vial containing RPMI media.
        ii. All chain of custody time points are captured on collection form (i.e. Time of resection, time placed in RPMI, etc.)
    c. Formalin Fixed Paraffin Embedded (FFPE) Procurement
        i. Matched tumor and normal (if available) tissue aliquots are placed in labeled tissue cassettes and submitted to histology for routine formalin fixation, processing, and paraffin embedding.
        ii. All chain of custody time points are captured on collection form (i.e. Time of resection, time placed in formalin, etc.)
    d. Researcher-specific Collections
        i. PBSS will collaborate with researchers if specific guidelines are required for a tissue collection protocol pending standard of care diagnosis is not affected.
B. Tissue Storage
    a. Frozen tissue is retained in daily monitored freezers within the PBSS laboratory.
    b. FFPE tissue is retained at room temperature within the PBSS laboratory.
    c. All PBSS collection samples are retained indefinitely or released upon applicable researcher request.

8.3.5.1 Corollary Research Sampling

Immunohistochemistry (IHC) and Multiphoton Microscopy

Immunohistochemistry will be performed in standard fashion. Specimens are fixed within 30 mins of excision in 10% neutral buffered formalin for 24-48 hrs at room temperature and then embedded in paraffin. Formalin fixed paraffin embedded (FFPE) blocks will be stored at ambient temperature and protected from light. The FFPE blocks will be sectioned with a microtome and mounted on slides which are then deparaffinized and rehydrated with xylene and ethanol. Antigen

retrieval will be performed according to the method recommended by the specific antibody manufacturer's instructions (enzymatic vs heat-induced). The antibody concentration will then be optimized by several series of dilutions.

Antibodies for the following markers of T-cell exhaustion will be tested: PD-L1, CTLA-4, TIM-3, LAG-3, and TIGIT. The ABCAM, CTLA-4, TIM-3, LAG-3 and TIGIT assays will need to be optimized. Immunohistochemistry will be performed using the Dako EnVision FLEX + detection system (DAKO, Carpinteria, CA). The Dako PT link is used for deparaffinization and heat-induced epitope retrieval using Dako EnVision FLEX + Target Retrieval Solution, Low or High pH (dependent upon optimization), for twenty minutes and rinsed in Dako wash buffer according to the manufacturer's instructions. Endogenous peroxidase activity is blocked with EnVision FLEX Peroxidase-Blocking Reagent ten minutes before incubation with the designated antibody, followed by incubation with EnVision FLEX/HRP Detection Reagent for thirty minutes. The sections are then incubated with diaminobenzene before they are counterstained with Dako FLEX hematoxylin, rinsed and mounted in Cytoseal XYL (Thermo Scientific, Waltham, MA).

Multiphoton imaging will be performed at the University of Maryland Core Facilities for the Center for Innovative Biomedical Resources (CIBR) where there are 2-photon microscope. Capabilities to visualize and localize three antibodies at the same time in one sample are available. Scoring will be performed separately by two researchers blinded to other clinicopathologic information. To minimize interobserver variability, the same field of view will be used to score. The consensus for scoring will be reached after discussion with all the authors. To quantify TIL's bearing immune checkpoint receptors, the number of marker-positive TILs will be counted in the highest five numbered high power fields (HPF). The totals from each of the HPF's will be counted and progressively added to the final tally. To quantify tumor cells expressing ligands for immune checkpoint receptors, the intensity and area of staining will be scored. The range for intensity will be 0 (no staining), 1 (weak staining), 2 (intermediate staining), and 3 (strong staining) and the range for area will be 0 (0-10% total), 1 (11-33%), 2 (34-66%), 3 (67-100%) (Kim JR et al, 2013). The sum of the intensity and area will be used for statistical further analysis.

8.3.6 Withdrawal of Informed Consent for Donated Biological Samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator will:

- Ensure that biological samples from that subject, if stored at the local study site, are immediately identified, disposed of /destroyed, and the action documented

- Ensure the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensure that the subject is informed about the sample disposal

9. EVALUATION OF DISEASE RESPONSE

Hematoxylin and eosin-stained slides will be reviewed in a blinded fashion by a single musculoskeletal pathologist. The extent of necrosis will be assessed relative to the percentage of residual viable tumor. The percentage of histologically intact and percentage of necrotic tumor will be scored per slide, and the mean percentage of tumor necrosis will be calculated for the entire specimen, excluding non-neoplastic tissue. (Donahue et al, 2010).

Imaging during initial staging and work-up will include plain radiographs (if warranted from an orthopaedic standpoint), magnetic resonance imaging (MRI) of the primary site of disease, and a whole-body 18F-FDG positron-emission tomography (PET) scan including diagnostic computed tomography chest / abdomen / pelvis (CT C/A/P). If the patient's medical insurance does not cover PET-CT, then a CT C/A/P and whole body bone scan (WBBS) will be performed. All patients will be discussed at a multi-disciplinary tumor board. PET scans will be obtained prior to and after neoadjuvant treatment to assess disease response. MRI with and without contrast of the primary tumor site will be performed prior to commencement of neoadjuvant radiation and immunotherapy, between neoadjuvant therapy and surgical resection. Chest CT and MRI with and without contrast of primary tumor site will be performed after surgical resection and before commencement of adjuvant treatment and after adjuvant treatment to determine if the pateient will go onto maintenance therapy or clinical follow-up. If patient goes on to maintenance therapy, a Chest CT and MRI with and without contrast of the primary tumor site will be performed halfway through maintenance therapy in cycle 7 and at the end of maintenance therapy. During clinical follow-up Chest CT and MRI with and without contrast of the primary tumor site will be performed q12 wks ±2 wk for 2 years, every 6 months ±3 wks for 3 years, and every year ±4 wk up to 10 years.

Measurements will be performed by an independent radiologist blinded to the histopathologic results using RECIST v1.1.

Definition

Measurable lesions: Lesions that can be accurately measured in at least one dimension with longest diameter at least ≥10 mm on CT scan (or >20 mm by Xray). Cystic lesions thought to represent cystic metastasis can be considered as measurable lesions.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan with slice thickness ≤ 5 mm or MRI. At baseline and follow-up, only the short axis will be measured and followed.

Non-measureable lesions: All other lesions < 10 mm or lymph nodes <15 mm by CT scan with slice thickness ≤ 5 mm or MRI.

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

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

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

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

irRECIST (irRC)

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anti-cancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with immunotherapy would continue between the initial assessment of progression and confirmation for progression. If there is suspicion of PD during neoadjuvant therapy, it will be confirmed on the primary tumor MRI and either PET/CT or CTs performed after neoadjuvant therapy and prior to surgery. If there is suspicion of PD during adjuvant therapy, it will be confirmed on the routine q12 week surveillance imaging or sooner (but no earlier than 4 weeks) if indicated clinically.
- In addition, subjects may continue to receive durvalumab + tremelimumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects continue to receive benefit from treatment.

Modification of RECIST and use of irRC as described may discourage the early discontinuation of durvalumab + tremelimumab and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria.

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

9.1.1 Response Evaluation Criteria RECIST and irRC in Solid Tumors

Response determination will be defined based on RECIST v1.1 and irRC:

Table 8a. Definition of Response in Target Lesions

Response	Definition
Complete Response (CR)	Disappearance at target lesion
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions compared to baseline sum of target lesions, or any new lesions
Stable Disease (SD)	Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD

Table 10b. Response using irRC

Response	Definition
irCR	Complete disappearance of all lesions and no new lesions, confirmed by repeat consecutive assessment no less than 4 wks later
irPR	At least 50% decrease in tumor burden relative to baseline, confirmed by repeat consecutive assessment no less than 4 wks later
irPD	At least 25% increase in tumor burden relative to minimum recorded tumor burden, confirmed by repeat consecutive assessment no less than 4 wks later
irSD	Neither sufficient decrease to qualify as a irPR nor sufficient increase to qualify as irPD

After treatment of STS patients with radiation, it may be difficult to distinguish residual disease from treatment effect/normal tissue. This will be a critical consideration after treatment with radiation, immunotherapy, and surgical resection. As detailed above, PET/CT/MRI can play a significant role in determination of residual disease. If a target lesion remains, however SUVpeak is ≤ 1.5 this area (when previously was PET avid) then the patient is considered to have a complete response. At the discretion of the treating physician, biopsy of the residual area can be done and if biopsy is negative then the patient will be considered to have a complete response. If a residual lesion has an unequivocal SUVpeak of 1.5 then a biopsy can be done and if negative the patient will be considered to have a complete response. If a biopsy is not possible in this later situation, then the patient will be considered to have a PR or SD. In addition to the specific parameters discussed, biopsy can be done to evaluate possible residual disease at the discretion of the investigator based on PET/CT/MRI results.

For RECIST 1.1 and irRC, response should be confirmed by a repeat CT scan or MRI with slice thickness ≤ 5 mm. The scan for confirmation of response may be performed, at the earliest, 4 weeks after imaging that showed response if clinically indicated or at the next scheduled scan.

Lesions that can be measured clinically on physical exam (skin lesions or palpable LN) will be measured by the investigator with the longest axis recorded. These measurements can be used to guide clinical decision making, for example prompting an earlier CT scan to evaluate disease, however only measurements based on radiology will be used to determine response.

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

Table 9. Assessment of Non-Target Lesions

Response	Definition
Complete Response (CR)	Disappearance of all non-target lesions
Incomplete response/ Stable Disease (SD)	Persistence of one or more non-target lesions
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Stable Disease (SD)	Neither sufficient decrease to qualify as a PR or sufficient increase to qualify as PD

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail

Table 10. Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	PR/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence.

Given the observed pattern of response with immunotherapy medications (anti-PD-L1, mAb, anti-PD-L1 mAb, and anti-CTLA4 mAb) where some patients develop evidence of progressive disease by RECIST 1.1, with significant increase in size of target lesions and/or new lesions, followed by regression of disease to SD or PD/CR, all imaging showing progressive disease by RECIST 1.1, in the absence of significant clinic deterioration of the patient will be confirmed by a repeat CT scan or MRI with slice thickness $\leq$ 5 mm at least 4 weeks from the initial imaging showing progression. Clinically stable patients will continue treatment in the interim before this scan. If progressive disease by RECIST 1.1 with clinical deterioration by the patient will be counted as progressive disease and the study treatment will be discontinued.

Determination of clinical deterioration is at the discretion of the treating physician as defined by progression of disease at critical sites requiring urgent interventions (for example, cord compression), or development of signs and symptoms of disease progression and/or significant decline in ECOG performance status.

Whole-body ^{18}F-FDG PET / diagnostic quality CT images with and without contrast will be performed prior to commencement of neoadjuvant therapy and between neoadjuvant therapy and surgical resection as part of exploratory endpoint.

PET response will be determined by changes in peak SUV (SUV_{peak}) from baseline to follow-up in accordance with modified PET Response Criteria in Solid Tumors (PERCIST 1.0) (Wahl et al, 2009). The following modifications will be used: body weight–adjusted SUV rather than lean body mass–adjusted SUL, and SUV_{peak} of a measurable target lesion at least 2 SDs above the mean liver SUV rather than 1.5-fold of the mean liver SUV plus 2 SDs. This less stringent cutoff will be used because several studies reported low ^{18}F-FDG uptake in certain STS lesions, especially in the grade 1 and 2 categories (Benz et al, 2010; Rakheja et al, 2012). Mean healthy liver SUV will be defined as mean SUV computed in a 15 cm^3 cubic volume of interest placed in the center of the right hepatic lobe, assuming normal liver. For binary hazard analysis, any response will be defined as the presence of partial response or complete response. No response will be defined as the presence of stable disease or progressive disease. All measurements will be performed by a radiologist specialized in nuclear medicine.

PERCIST (Positron Emission Tomography Response Criteria in Solid Tumors)

Response Category	**Criteria**
Complete Metabolic Response	Normalization of all lesions to SUVpeak less than mean liver SUV and equal to normal surrounding tissue SUV
Partial Metabolic Response	>30% decrease in SUVpeak (minimum 0.8 unit decrease) on single most active lesion on each scan
Progressive Metabolic Disease	>30% increase in SUVpeak (minimum 0.8 unit increase) on single most active lesion on each scan, or >75% increase in total lesion glycolysis in 5 most active lesions, or visible increase in extent of FDG uptake, or new lesions
Stable Metabolic Disease	Does not meet other criteria

Oncologic outcomes will be recorded and updated at each surveillance imaging timepoint including local recurrence (LR), distant relapse (DR), overall survival (OS) and disease-specific

survival (DSS) for all patients, disease-free survival (DFS) for patients presenting with localized disease, and progression-free survival (PFS) for patients presenting with metastases.

The finding of a new lesion on surveillance imaging should be unequivocal: i.e., not attributable to differences in scanning technique or representative of something other than tumor. If a new lesion is equivocal, for instance due to its small size, continued therapy and follow-up imaging will clarify if it is truly new disease. If repeat imaging or biopsy confirm new disease, then local or distant relapse will be declared using date of scan on which it initially appeared.

Subjects who have disease control following completion of 12 months of treatment or subjects who are withdrawn from durvalumab + tremelimumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Tables 3 and 4).

10. ASSESSMENT OF SAFETY

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

10.1.1 Safety Parameters

10.1.1.1 Definition of Adverse Event (AE)

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

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

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

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

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

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

10.1.2 Definition of Serious Adverse Events (SAE)

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

- Results in death

- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above:
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca. AstraZeneca web-based education resources will be utilized to improve awareness amongst pertinent study peronnel regarding common types of adverse events for study drugs.

10.1.3 Durvalumab + Tremelimumab Adverse Events of Special Interest

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

AESIs for durvalumab and tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

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

AESIs observed with durvalumab and tremelimumab include:

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

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

Pneumonitis

AEs of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Table 7.

Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time. For all infusion reactions, SAEs should be reported to AstraZeneca Patient safety as described in Section 10.3.

Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in Table 7.

Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the IP. Guidelines for management of patients with hepatic function abnormality are provided in Table 7.

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving tremelimumab are provided in Table 7.

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Table 7.

Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Table 7.

Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Table 7.

Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc). Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Table 7.

10.1.4 Immune-Related Adverse Events

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (Hodi et al 2010; Brahmer et al 2012; Topalian et al, 2012). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients 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, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Table 1, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Table 7). These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab or mycophenolate).
- If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the Study Physician.

10.2 Assessment of Safety Parameters

10.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.0.The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (death)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.2.1. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of Relationship

An investigator who is a qualified physician will evaluate all adverse events, as described in The Evaluating Adverse Events Table, as follows:

Table 11. Evaluating Adverse Events (NCI CTCTA v4.0)

NCI CTCAE v4.0	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of study product that: ◦ **†Results in death**; or ◦ **†Is life threatening**; or places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or ◦ **†Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or ◦ **†Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or ◦ **†Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or ◦ **Is a new cancer;** (that is not a condition of the study) or ◦ **Is an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours. ◦ **Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action Taken	Did the adverse event cause the MedImmune product to be discontinued?	
Relationship to study drugs	Did the MedImmune product(s) cause the adverse event? The determination of the likelihood that the MedImmune product(s) caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialled document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information **The following components are to be used to assess the relationship between the MedImmune product(s) and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the MedImmune product(s) caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the MedImmune product(s) such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

Relationship to study drugs (cont)	**Time Course**	Did the AE follow in a reasonable temporal sequence from administration of the MedImmune product(s)? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors
	Dechallenge	Was the MedImmune product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the MedImmune product(s); or (3) the trial is a single-dose drug trial); or (4) MedImmune product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the MedImmune product(s) in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) MedImmune product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MEDIMMUNE PRODUCT(S), OR IF REEXPOSURE TO THE MEDIMMUNE PRODUCT(S) POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency w. Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the MedImmune product(s) or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following:		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a MedImmune product(s) relationship).**
Yes, there is a reasonable possibility of MedImmune product(s) relationship.		There is evidence of exposure to the MedImmune product(s). The temporal sequence of the AE onset relative to the administration of the MedImmune product(s) is reasonable. The AE is more likely explained by the MedImmune product(s) than by another cause.
No, there is not a reasonable possibility of MedImmune product(s) relationship.		Subject did not receive the MedImmune product(s) OR temporal sequence of the AE onset relative to administration of the MedImmune product(s) is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)

10.3 Recording of Adverse Events and Serious Adverse Events

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

The following variables will be collected for each AE:

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

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to CTCAE G3 G4 or CTCAE G4 skin toxicity
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to durvalumab or tremelimumab (yes or no)

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

10.3.1 Study Recording Period and Follow-Up for AE and SAE

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (from time of screening through 180 days after receipt of the final dose of Durvalumab + Tremelimumab combination therapy or 90 days after receipt of the final dose of Durvalumab Monotherapy, whichever is the longer time period).

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

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

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

Follow-up of unresolved adverse events

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

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

Post study events

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

10.3.2 Reporting of serious adverse events for Coordinating Center

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

The investigator and/or sponsor must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21

CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-16-11953)

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

**** Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.

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

10.3.2.1 Reporting of Serious Adverse Events for Participating Sites

Any serious adverse event, or follow up to a serious adverse event (including death due to any cause other than progression of the cancer under study) that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier (whether or not related to protocol therapy) must be reported by fax and email within 24 hours to the Sponsor (Attn: Vincent Y. Ng, MD; FAX: 410-328-0534; vng@som.umaryland.edu) using FDA Form 3500A (MedWatch form). The sponsor will then report the event to AstraZeneca within 2 working days of becoming aware of the event. The event should also be reported locally to the site Institutional Review Board (IRB) per local policy.

Additionally, any serious adverse event considered by an investigator (who is a qualified physician) to be related to protocol therapy that is brought to the attention of the study team at any

time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor using FDA Form 3500A (MedWatch Form). The sponsor will then report the event to AstraZeneca using FDA Form 3500A (MedWatch Form).

Non-serious Events of Clinical Interest and any other relevant safety information that does not meet SAE criteria are to be forwarded by the performance site to AstraZeneca using the applicable study case report form. If the protocol CRF does not contain enough information, Merck may contact the performance site to request additional information.

If the event meets the criteria for FDA mandatory IND safety reporting (serious AND unexpected), the Coordinating Center will report the event to the FDA using FDA Form 3500A (MedWatch form). Events which are assessed as "unexpected fatal or life-threatening" should be reported to FDA by the Coordinating Center as soon as possible, but no later than 7 calendar days following the Sponsor's initial receipt of the information. All other unexpected serious suspected adverse reactions suggesting significant risk to human subjects should be reported to FDA no later than 15 calendar days following the Sponsor's initial receipt of the information.

A copy of all 15 Day Reports and Annual Progress Reports are to be submitted by the Sponsor as required by FDA, Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. The Sponsor will cross reference this submission according to local regulations to the AstraZeneca Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally the Sponsor will submit a copy of these reports to AstraZeneca at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome/resolution for at least 90 days after stopping protocol therapy.

10.3.2.2 Reporting of Deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab + tremelimumab safety follow-up period must be reported as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

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

Deaths that occur following the protocol-defined 90-day post-last-dose of MEDI4736 safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

10.3.3 Other Events Requiring Reporting

10.3.3.1 Overdose

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

Any overdose of a study subject with durvalumab + tremelimumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 10.3 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

The investigator will use clinical judgment to treat any overdose.

10.3.3.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

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

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

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

10.3.3.3 Pregnancy

10.3.3.4 Maternal Exposure

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

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

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

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

The same timelines apply when outcome information is available.

10.3.4 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

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

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Trial Design & Description of Analysis Sets

This trial is a seamless phase I/II single-arm trial of a fixed dose of Durvalumab (D)/Tremelimumab (T) combined with a fixed schedule of radiation therapy (RT).

The phase I component establishes the safety and provides a provisional characterization of the toxicity profile of D/T/RT by continual assessment of high-grade toxicity as defined in section 6.4 in the first 12 cases enrolled on the trial. The phase I component uses a Pocock boundary to make a decision to stop or continue the trial after each patient evaluated with respect to early toxicity.

The phase II component uses a Simon two-stage design with excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor regression) on histopathologic examination as its endpoint. A total of 33 patients will have been enrolled at the end of the second stage. All patients enrolled during the phase I component will be evaluable with respect to efficacy as well. A full analysis of toxicity and efficacy, including clinical efficacy endpoints, will be conducted in the full trial population using the intention to treat principle.

11.1.1 Phase I Component Design and Sample Size

The endpoint is high-grade toxicity: severe (G3-5), early non-hematologic toxicity and severe (G4) skin toxicity attributable to the drug-radiation combination. Based on the literature review, G3-5 non-hematologic acute toxicity occurs in <10% of patients with the mAb alone and G4 skin toxicity occurs in < 10% of patients with neoadjuvant radiation-alone or chemoradiation for soft tissue sarcoma (Jacob et al, 1999; Kraybill et al, 2006). Early stopping for unexpected, high-grade early toxicity is based on continuous monitoring of toxicity with the aim of keeping the probability of early stopping at around 5% if the true underlying rate of this toxicity is 20%.

Table 12. Pocock Boundary[1]

Number of Patients, *n*	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Boundary, b_n	-	-	3	3	4	4	5	5	5	6	6	6

Following Ivanova et al. (Ivanova et al, 2005) we use the boundary proposed by Pocock (Pocock SJ, 1977). If $\geq b_k$ patients with toxicity have been observed after enrolling the first k patients, the combination will be declared too toxic. Values of b_k for the current design are given in Table 16.

[1] Pocock boundary for early stopping due to high-grade toxicity with a probability of stopping of about $\phi = 0.05$ and assuming the true toxicity rate is $\theta_0 = 0.2$

It is important for the validity and practical implementation of this strategy that the sequence of patients entered into the study is strictly recorded and preserved. Ideally, the design assumes that the outcome, i.e. the incidence of excessive toxicity among the first *i* patients is known when entering patient *i*+1. However, the accrual rate is expected to be around 1-2 patients per month and the time window for observing early toxicity in a patient is pragmatically defined as the time during and within two weeks after the completion of RT; therefore, insisting on complete observations before entering the next patient will slow down accrual considerably. Instead, we will allow staggered entry of cases. For patient safety reasons, no more than 4 patients will be allowed to be on active neoadjuvant treatment at any point during the phase I portion of the trial.

If the boundary is crossed, the treatment with D/T will be discontinued in all patients on treatment at that point in time. If 12 patients are enrolled and have completed neoadjuvant therapy without crossing the toxicity boundary, the phase I component will be concluded and the outcome will be reported. Accrual will be continued with respect to the phase II efficacy question, although toxicity will still be recorded and reported for the whole phase II cohort.

The design parameters for the phase I portion of the trial are chosen to give a high probability of stopping the study in case of unexpectedly high incidence of high-grade toxicity. The probability of early stopping is 4.9% if the true incidence of high-grade toxicity is 20%; the probability of early stopping is 97% if the true incidence of high-grade toxicity is 70% or more.

If the toxicity boundary is crossed, the outcome of the phase I component will be analyzed and reported. After review of all toxicities by the independent DSMB, a decision will be made by the investigators and the sponsor as to whether an independent phase I/II trial should be initiated with D/RT or T/RT. If this is the case, the same design as above will be employed.

11.1.2 Phase II Component Design and Sample Size

All patients entered during the phase I component are evaluable with respect to the efficacy endpoints. The endpoint for phase II is an excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor regression) on histopathologic examination. Based on the literature review (Stacchiotti S et al, 2009; Chen et al, 2013; Hermann et al, 2012; Canter et al, 2010; Donahue et al, 2010; Eilber et al, 2001; Evilevitvh et al, 2008; Shah et al, 2012) for cytotoxic chemo/radiotherapy, we propose that if the excellent response rate is lower than 20% the combination is not superior to existing modalities in this regard, whereas a response rate of 40% will be seen as promising for further development. There is no consensus on how to assess treatment response for STS [College of American Pathologists 2020]. The semi-quantitative assessment for tumor response is based upon the Modified Ryan Scheme for Tumor Regression [Ryan et al, 2005] that takes into account measures of residual viable tumor, coagulative necrosis, hyalinization/fibrosis and infarction.

Modified Ryan Scheme for Tumor Regression Score

Description	Tumor Regression Score
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Simon's two-stage design will be used (Simon R, *Controlled Clinical Trials*). The null hypothesis that the true response rate is 20% will be tested against a one-sided alternative. In the first stage, 18 patients will be accrued. If there are 4 or fewer responses in these patients, the study will be stopped. Otherwise, 15 additional patients will be accrued for a total of 33. The null hypothesis will be rejected if 11 or more responses are observed in 33 patients. This design yields a type I error rate of 4.5% and power of 80% when the true response rate is 40%.

11.2 Description of Analysis Sets

11.2.1 Safety Analysis Set

The Safety Analysis Set (SAS) comprises the patients who receive 1 or more doses of the study medication. The DLT evaluation set are the patients who receive 1 dose and are followed for the three neoadjuvant duravlumab and tremelimumab cycles plus 90 days, or who have a DLT. This definition is conservative in terms of reporting the safety profile of the experimental therapy.

Patients who do not complete the full planned course of therapy and who are *withdrawn for any other reason than toxicity* will be replaced in the SAS for the phase I component. The cause of withdrawal will be verified by independent review by the DSMB.

11.2.2 Efficacy Analysis Set

The Efficacy Analysis Set (EAS) is defined using a strict intention to treat principles: any patient enrolled on the trial will be included in the EAS. Patients who do not undergo surgery will be scored as non-responders with respect to the primary trial endpoint. In addition to the primary analysis, the excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor

regression) on histopathologic examination rate will be reported in all patients undergoing surgical resection. All clinical efficacy endpoints will only be analyzed in the full EAS.

11.3 Methods of Statistical Analyses

11.3.1 Safety Analyses

The distribution of all early toxicities, graded according to the CTCAE v. 4.0 as well as their attribution to therapy will be tabulated as absolute and relative frequencies where relevant with the upper bound of the 1-sided 95% confidence limit on the incidence of a specific toxicity. In addition, we will summarize the actual dose of D/T/RT received by each patient. The SAS is defined in 11.2.1.

Late toxicities, defined as toxicities occurring more than 90 days after the completion of the RT, will be analyzed using the Kaplan-Meier method with the upper bound of the 1-sided 95% confidence limit estimated using Greenwood's formula.

An exploratory analysis of early or late toxicity as a function of patient or treatment characteristics (including dose-volume metrics) will be conducted if the number of events allow this using ordinal logistic regression or Cox proportional hazards model, respectively.

11.3.2 Efficacy Analyses

The prevalence of the primary endpoint, excellent response (grade 0 or 1 score on a semi-quantitative assessment for tumor regression) on histopathologic examination, will be estimated as a proportion with the 2-sided, exact 95% confidence limit. The distribution of pathological response grades will be presented as a frequency table with 95% confidence limits where appropriate.

All clinical efficacy endpoints, including progression-free survival (PFS) and overall survival (OS), will be estimated using the Kaplan-Meier method and summarized by the median and 2-year estimates with 95% confidence intervals. Primary tumor control is the absence of local progression. Marginal failures will be considered events for local progression. Distant metastases are not considered local progression. Death or loss to follow-up will be treated as censoring events.

For PFS progression in local, regional or distant position will be treated as a failure. Death irrespective of the cause of death is treated as an event. Only patients who are alive without clinical or radiological signs of progression at the time of their last follow-up will be censored on that date.

All efficacy and survival endpoints will be analyzed and reported in the EAS defined in section 9.1.1.

11.3.3 Exploratory Analyses of Immunogenicity Markers

To quantify tumor cells expressing ligands for immune checkpoint receptors, the intensity and area of staining will be scored as explained in section 8.3.5.1. The range for intensity and area will be

scored using an arbitrary 4-point scale for each. Marker distributions will be summarized as relative frequency distributions with exact 95% confidence intervals where appropriate.

The results from the analyses of tertiary (correlative) endpoints will not provide definitive answers to any a priori research questions as the study is not statistically powered for these analyses. Rather, these results will be considered exploratory to generate future hypotheses for exploration in larger cohorts. However, to illustrate our ability to detect associations between pairs of markers or between a marker and the grade of pathological response, we have performed a power calculation for testing the hypothesis that Spearman's rank correlation, R_S, between the two variables is different from zero. With a sample size of 32 and a 2-tailed α=0.05, our exploratory analyses will have a power of 80% under the alternative hypothesis that R_S=0.53. Associations that are weaker than this are unlikely to be biologically or clinically relevant. This power calculation does not adjust for multiple comparisons.

The ordinal logistic and the proportional hazard regression models could be utilized to adjust for possible confounding covariates in exploring the possible associations between markers and outcome.

11.3.4 Interim Analyses

The phase I component uses a Pocock boundary to allow early stopping of the trial after continual evaluation of unexpectedly high incidence of toxicity in the first 12 patients receiving the study therapy.

The phase II component uses a Simon two-stage design with a stopping rule for transitioning into the second stage.

Any grade 4 or 5 toxicity will be reviewed by the independent DSMB who has a mandate to terminate enrollment on the trial if indicated.

Interim analysis is performed and early stoppage rule is applied as described above in section 11.1.2. All outcome data will be blinded to the investigators as long as the trial is open but reports will be produced for the DSMB at regular intervals to be decided by this committee. The trialists will receive regular reports on accrual numbers and completeness of recorded data but without any toxicity or efficacy outcome data.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection. It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, ICH Guidelines, Good Clinical Practice, and rules of the local IRB.

12.2 Ethics and regulatory review

It is the investigator's responsibility to conduct the protocol under the current version of Declaration of Helsinki, ICH Guidelines, Good Clinical Practice, and rules of the local IRB. The investigator must ensure that the patient's anonymity be maintained. All study forms, reports, and other records that are part of the study data collection materials will be identified in such a way as to maintain patient confidentiality.

Clinical information will not be released without written permission of the patient, except as necessary for monitoring by the IRB, study sponsor, or other regulatory agencies. Consent procedures and forms, and the communication, transmission and storage of patient data will comply local site IRB requirements for compliance with The Health Insurance Portability and Accountability Act (HIPAA).

12.3 Informed consent

Eligible patients will be approached for their consent to participate. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed.

The subject's clinician will be involved in the consent conversation. Patients will be informed of the study goals and data to be collected. Additionally, Patients and their families will be provided with a written information describing the study, the risks and benefits of participation and what will be expected of them if they choose to participate.

The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. Copies of the signed consent forms will be given to the patient, and this fact will be documented in the patient's record.

Due to the high-risk nature of this study, no proxy (LAR) consent will be obtained. Prior to initiating the consent process, the participant's treating physician will confirm that the participant has the ability to understand the relevant study information and communicate and maintain a choice. If the physician determines that the patient lacks the capacity to consent, the patient will be declared ineligible.

Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study. The research staff will endeavour to answer all questions posed by the patient and his/her family to ensure their understanding of the protocol at all times. A limited number of questions will be asked of all patients after they are introduced to the study and have reviewed the consent form. These questions assess the person's understanding of the study and what it means to participate, their appreciation of the consequences of participation, and their ability to consider alternatives to participation. A formal comprehension test may be utilized, or comprehension will be assessed by the person(s) obtaining the consent. The patient's physician will ask the questions and determine the appropriateness of the responses.

The study will not include children or prisoners.

12.4 Changes to the protocol and informed consent form

Any changes to the study protocol will first be submitted to the study sponsor for approval, and then submitted to the local IRB and Human Research Protections Office. Any changes to the protocol requiring updated consent documents will also be submitted to the local IRB. Once approved by the IRB, all officially approved consent documents will be made available to the study sponsor, where requested or required.

12.5 Audits and inspections

The PI will be responsible for site monitoring consistent with ICH, FDA, IRB and study sponsor guidelines. Site monitoring will occur in a manner consistent with University of Maryland Medical System standard operating procedures and will include a combination of onsite monitoring activities to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The site PI will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the Office for Human Research Protections (OHRP), study sponsor, or other regulatory authorities for confirmation of the study data.

12.6 Institutional Review Board (IRB) for Participating Sites

The Coordinating Center (University of Maryland, Baltimore) Institutional Review Board will serve as the IRB of record for participating sites. No changes to the protocol or related study documents will be made without review and approval by the Coordinating Center and its IRB. All instances of reportable new information (i.e., unanticipated problems, data breaches, etc) as well as study data will be submitted to the Coordinating Center. The Greenebaum Cancer Center Data Safety and Monitoring Board (DSMB) will also provide trial oversight per its standard operating procedures. The Coordinating Center will submit major amendments to the FDA and the University of Maryland, Baltimore IRB for review and approval before Participating Site distribution.

12.7 Records Retention

Essential documents should be retained by performance sites until notification is received from the Coordinating Center that the documents may be destroyed. In general, documents should be maintained at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records may be maintained in secure offsite storage after completion of study follow-up and data analysis. Performance sites should notify the Coordinating Center in writing of the new document location when documents are transferred off site.

12.8 Data Management

Clinical data will be entered into the OnCore® database by the designated performance site personnel. Information can be entered into Oncore® in a way that is 21CRF11.10 (electronic medical records) compliant. OnCore® is equipped for HIPAA-compliant internet-based entry of protocol tracking and review information.

All study data will be collected by the research team at each and every study visit and recorded in the research record. This data will then be entered in to the OnCore® study database.

All source documents will be obtained and retained along with any study forms, and placed into the patient's research record.

12.9 Study governance and oversight

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

The PI will be responsible for site monitoring consistent with ICH, IRB, study sponsor and OHRP guidelines. Site monitoring will occur in a manner consistent with University of Maryland Medical System standard operating procedures and will include a combination of onsite monitoring activities to ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records. The site PI will make study documents (e.g., consent forms, case report forms) and pertinent hospital or clinic records readily available for inspection by the local IRB, the Office for Human Research Protections (OHRP), study sponsor, or other regulatory authorities for confirmation of the study data.

At all times only listed key personnel specifically designated and authorized by the Principal Investigator shall have access to any research related documents, including electronic data. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct.

Research related documents (including electronic data), and medical records will be accessible only by key personnel specifically designated and authorized by the Principal Investigator. All such personnel will be properly trained and supervised regarding the management and handling of confidential materials. The Principal Investigator assumes full responsibility for such training, supervision, and conduct. This information will also be available for audit by study monitors and representatives of the local IRB, the study sponsor (and other study sponsors if applicable), and the OHRP.

There is a possibility that genetic analyses performed on these samples in the future will meet the criteria for genetic testing. The Guidance on the Genetic Information Nondiscrimination Act states that “among the risks typically associated with genetic research, investigators, IRBs, and research subject advocates, among others, have identified the potential adverse impact on insurability or employability if genetic information about the subject obtained as part of the research was disclosed to, or sought by, insurers or employers.” These risks will be minimized by de-identifying samples prior to storage. There will be no mechanism to connect genetic tests results to study participants. Furthermore, results from these tests will only be published in aggregate form. It is possible that this donated tissue will help to develop new products in the future. There are no plans to share any potential financial gain with the participants.

13.2 Monitoring of the study

13.2.1 Source data

Data will include medical and surgical histories, laboratory reports, radiologic studies, clinian examinations, adverse event and serious adverse event recording, efficacy variable outcomes and patient interviews. Source documents including CRFs, laboratory results, patient surveys, medical records, etc. will be maintained at the site and will be made available to study monitors, and representatives of regulatory agencies including the study sponsor, IRB, FDA and local OHRP.

13.3 Study timetable and end of study

The following is an estimated study timeline:

- Contract execution to IRB approval: 3 months
- IRB/IEC approval to first subject in: 1 month
- First subject in to 50% enrollment: 18 months
- 50% enrollment to last subject in: 18 months
- Last subject in to last subject last visit: 24 months
- Last subject last visit to completion of final study report: 2 months
- Date anticipated publication: 01 July 2018 (for preliminary results)

After completion of radiation therapy and surgical resection, patients will be monitored with physical exam, MRI of the primary location, and CT scan of the lungs every 3 months for 2 years, then every 6 months for 3 years, then every year up to 10 years. After 10 years, they will be followed every 3-5 years. Oncologic outcomes will be recorded including local recurrence (LR), distant relapse (DR), overall survival (OS) and disease-specific survival (DSS) for all patients, disease-free survival (DFS) for patients presenting with localized disease, and progression-free survival (PFS) for patients presenting with metastases.

14. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

14.1 Identity of investigational product(s)

Table 13. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	500 mg (nominal) per vial solution for infusion after dilution	MedImmune
Tremelimumab	400 mg (nominal) per vial solution for infusion after dilution	MedImmune

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16. APPENDICES

Appendix 1. Dosing Modifications for Toxicity

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) 19 August 2016 Version

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

Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) 19 August 2016 Version

Dose Modifications	Toxicity Management
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	

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

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			(abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (stool frequency of <4 over baseline per day)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (stool frequency of 4 to 6 over baseline per day)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeksa. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consult study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥4 weeks pers and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥4 weeks pers and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × ULN)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥4 weeks pers and consider prophylactic antibiotics,

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b]	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥4 weeks pers and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		For Grade 4: Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated.

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines].

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥4 weeks pers and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Radiotherapy Skin Reactions	Grade 0 (RTOG) no visible changes to skin	– Monitor extent of skin reaction – Apply aqueous cream initially twice daily	– Promote hydrated skin – Maintain skin integrity
	Grade 1 (RTOG) Faint or dull erythema. Mild tightness of skin and itching may occur	– Monitor extent of skin reaction – Increase aqueous cream as needed – 1% Hydrocortisone cream may be also be prescribed for symptomatic relief. Commence analgesia as guided by WHO analgesic ladder	– Monitor extent of skin reaction – Increase aqueous cream as needed – 1% Hydrocortisone cream may be also be prescribed for symptomatic relief. Commence analgesia as guided by WHO analgesic ladder
	Grade 2 bright erythema/dry desquamation. Sore, tichy and tighty skin Grade 2.5 (RTOG) Patchy moist desquamation. Yellow/pale green exudate. Soreness with oedema	Grade 2: – Increase application of aqueous cream as needed – Continue RTOG 1 interventions Grade 2.5: – Continue aqueous cream on unbroken skin – Stop hydrocortisone on broken skin. Apply an appropriate amount of dressing to exuding areas (e.g. PolyMem, Mepilex,	Grade 2: – As RTOG 1 Grade 2.5: – To promote comfort. – Reduce risk of complications of further trauma and infection – To reduce pain, soreness and discomfort

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		Allevyn N.A. / Gentle are all suitable options). – Analgesia as guided by WHO analgesic ladder. Loose fitting clothing.	
	Grade 3 (RTOG) Confluent moist desquamation. Yellow/pale green exudate. Soreness with oedema	– Stop using aqueous cream on moist/broken skin – Continue with RTOG 2.5 interventions	– To promote comfort – Reduce risk of complications of further trauma and infection
	Grade 4 (RTOG) Ulceration, bleeding and necrosis	Permanently discontinue study drug	– Seek specialisk Clinical Oncologist/Radiotherapy Clinical Nurse/Radiographer Specialist)
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Consult endocrinologist. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Initiate hormone replacement as needed for management. – Evaluate endocrine function, and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥4 weeks pers and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than	**For Grade 3 or 4:** – Consult endocrinologist.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.	– Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥4 weeks pers and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See “Any Grade” recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study	**For Grade 2:** – Discuss with the study physician. – Obtain neurology consult.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Discuss with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥4 weeks pers.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** − Discuss with study physician. − Recommend hospitalization. − Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

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

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

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

Infusion-related Reactions

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

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

Non-immune-mediated Reactions

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

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Appendix 2. Durvalumab DOSE CALCULATIONS

For durvalumab dosing done depending on subject weight (for patients <30 kg):

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

Dose (mL) = XY mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

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

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

Example:

1. Cohort dose: 10 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 300 mg = 10 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 300 mg / 50 (mg/mL) = 6.0 mL

5. The number of vials required for dose preparation:

Number of vials = 6.0 (mL) / 10.0 (mL/vial) = 1 vial

Appendix 3. Durvalumab DOSE VOLUME CALCULATIONS

For durvalumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

Dose (mL) = X mg / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

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

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

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

Example:

1. Cohort dose: 1500 mg

2. Dose to be added into infusion bag:

Dose (mL) = 1500 mg/ 50 (mg/mL) = 30.0 mL

3. The number of vials required for dose preparation:

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

Appendix 4. Tremelimumab DOSE CALCULATIONS

For tremelimumab dosing done depending on subject weight (for patients <30 kg):

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) × Y (kg)

4. Dose to be added into infusion bag:

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

where 20 mg/mL is tremelimumab nominal concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.

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

Number of vials = Dose (mL) / 20.0 (mL/vial)

Example:

1. Cohort dose: 1 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 30 mg = 1 (mg/kg) × 30 (kg)

4. Dose to be added into infusion bag:

Dose (mL) = 30 mg / 20 (mg/mL) = 1.5 mL

5. The number of vials required for dose preparation:

Number of vials = 1.5 (mL) / 20.0 (mL/vial) = 1 vial

Appendix 5. Tremelimumab DOSE VOLUME CALCULATIONS

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

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

where 20 mg/mL is tremelimumab nominal concentration

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

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

Number of vials = Dose (mL) / 20.0 (mL/vial)

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

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

3. The number of vials required for dose preparation:

Number of vials = 3.8 (mL) / 20.0 (mL/vial) = 1 vial