Investigational Drug	Durvalumab (MEDI4736) and tremelimumab
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A Pilot Pre-Surgical Study Evaluating Anti-PD-L1 Antibody (Durvalumab [MEDI4736]) Plus Anti-CTLA-4 Antibody (Tremelimumab) in Patients with Hormone Receptor Positive, HER2 Negative Breast Cancer

Sponsor: The University of Texas MD Anderson Cancer Center

PROTOCOL SYNOPSIS

Clinical Protocol 2016-0902 IND 134400

Study Title: A Pilot Pre-Surgical Study Evaluating Anti-PD-L1 Antibody (Durvalumab) Plus Anti-CTLA-4 Antibody (Tremelimumab) in Patients with Hormone Receptor Positive, HER2 Negative Breast Cancer
Clinical Phase: Pilot
Study Duration: 24 months
Investigational Product(s) and Reference Therapy: Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. Tremelimumab is supplied as a sterile solution for IV infusion, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL, accounting to 400 mg/vial) of tremelimumab, in an isotonic solution at pH 5.5.
Research Hypothesis Our hypotheses are: 1) that it will be feasible to enroll patients with hormone receptor (HR)-positive, HER2-negative breast cancer onto a trial evaluating anti-CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4) therapy (tremelimumab) plus anti-PD-L1 (programmed cell death ligand 1) therapy (durvalumab) prior to initiating standard neoadjuvant chemotherapy, 2) that the combination of tremelimumab plus durvalumab therapy will have an acceptable safety profile in HR+/HER2- breast cancer patients; and 3) that tremelimumab plus durvalumab therapy will lead to measurable immunologic changes, with identification of novel biomarkers that can be used for immune monitoring and clinical correlation in the setting of HR+/HER2- breast cancer.
Objectives: **Primary Objectives:** • To evaluate the feasibility of enrolling patients with HR+/HER2- breast cancer onto a trial evaluating investigational agents prior to initiating standard neoadjuvant chemotherapy. • To evaluate the safety and tolerability of tremelimumab plus durvalumab in patients with HR+/HER2- breast cancer.

Secondary Objective(s): To assess immunologic/molecular responses to tremelimumab and durvalumab in patients with HR+/HER2- breast cancer who receive the combination therapy. **Exploratory Objective(s):** To evaluate the pathologic response in patients with HR+/HER2- breast cancer receiving tremelimumab plus durvalumab prior to initiating standard neoadjuvant chemotherapy.
Study Design: Open-label, single-arm, presurgical pilot study in patients with HR+/HER2- breast cancer
Number of Centers: 1
Number of Subjects: 15
Study Population: Breast cancer patients with HR+/HER2- disease planned to receive neoadjuvant chemotherapy

Inclusion Criteria:

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

- 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

- Age ≥ 18 years at time of study entry

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

- Hormone receptor positive (defined as estrogen receptor [ER] and/or progesterone receptor [PR] positive), HER2 negative breast cancer that is clinically staged II-III with no known metastatic disease. ER and/or PR defined as positive if expression >10% by immunohistochemistry (IHC). HER2 negative or non-amplified as determined by the current ASCO-CAP criteria which are as follows: HER2 testing by IHC as 0 or 1+. If HER2 is 2+, ISH (in situ hybridization) must be performed. HER2 is positive if:

    - IHC 3+ based on circumferential membrane staining that is
        - complete, intense
    - ISH positive based on:
        - Single-probe average HER2 copy number ≥6.0 signals/cell.
        - Dual-probe HER2/CEP17 ratio ≥2.0;c,e with an average HER2 copy number ≥4.0 signals/cell
        - Dual-probe HER2/CEP17 ratio ≥2.0;c,e with an average HER2
        - copy number <4.0 signals/cell
        - Dual-probe HER2/CEP17 ratio < 2.0;c,e with an average HER2
        - copy number ≥6.0 signals/cell

- Chemotherapy is planned for the patient in the neoadjuvant setting

- Adequate normal organ and marrow function as defined below:

    - Hemoglobin ≥ 9.0 g/dL

    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 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 hemolysis or hepatic pathology), who will

be allowed only in consultation with their physician, Principal Investigators (PI) or co-PIs approval

- 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
- 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:

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

Females:

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

- Female subjects must either be of non-reproductive potential (ie, 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.
- 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:

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

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site)
- Participation in another clinical study with an investigational product during the last 1 month prior to initiation of therapy
- Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA4, including tremelimumab
- History of another primary malignancy except for:
  - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
  - Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer in situ
- Has received therapy for this current diagnosis of breast cancer including endocrine therapy or chemotherapy.
- A single QT interval corrected for heart rate (QTc) >/= 470 ms. If an ECG is interpreted to be a prolonged QT interval, 2 additional ECGs will be obtained. The PI will then evaluate all three ECGs and determine whether the patient should be excluded. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction
- Current or prior use of immunosuppressive medication within 28 days 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
- 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.

- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency
- History of allogeneic organ transplant
- History of hypersensitivity to durvalumab or tremelimumab or any excipient
- History of hypersensitivity to the combination or comparator agent (if applicable)
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
- Known history of previous clinical diagnosis of tuberculosis
- History of leptomeningeal carcinomatosis
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab
- Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
- Subjects with uncontrolled seizures.

Investigational Product(s), Dose, and Mode of Administration:

Durvalumab, 1500 mg Q4W (equivalent to 20 mg/kg Q4W) for 2 doses/cycles in patients ≥ 30 kg

Tremelimumab 75 mg Q4W (equivalent to 1 mg/kg Q4W) for 2 doses/cycles in patients ≥30 kg

Weight-based dosing should be utilized for patients <30 kg durvalumab 20 mg/kg Q4 and tremelimumab 1 mg/kg Q4

Study Assessments and Criteria for Evaluation:

The study's primary endpoints are to evaluate the feasibility of enrolling patients with HR+/HER2- breast cancer onto a trial evaluating investigational agents prior to initiating standard neoadjuvant chemotherapy and to evaluate the safety and tolerability of tremelimumab plus durvalumab in patients with HR+/HER2- breast cancer.

Feasibility Assessments:

Feasibility will be measured by 2 achievements. If both are met, then upfront treatment with tremelimumab plus durvalumab will be feasible for future trials in HR+/HER2- breast cancer patients. The 2 measures are:

- Patients are willing to enroll. This will be established if we can enroll all 15 patients within 12 months of starting the study.
- Patients can complete the protocol. If at least 10 patients complete the study and have available immune data, the trial meets this feasibility criterion.

Safety Assessments:

All patients who receive at least one dose of study drug will be included in the safety monitoring and safety analysis. For trial monitoring and decisions about future trials, a patient will be determined to have an extreme toxicity (ETOX) if either condition is met:

- The patient experiences any grade 3 or higher adverse event (AE) that is possibly, probably, or definitely related to therapy received on this protocol and occurs up to 90 days after the last dose of therapy (durvalumab + tremelimumab). As an exception, any such AE that is potentially treatable with steroids will only count as an ETOX if it does not improve to grade 1 or better within 2 weeks.

- The patient has a delay in surgery of 6 weeks or more due to AE, even if that AE does not meet the definition of ETOX

Statistical Methods and Data Analysis:

Feasibility will be assessed according to the endpoint definition provided above. Since it is not known whether durvalumab plus tremelimumab can be safely used in the presurgical setting in patients with HR+, HER2- breast cancer, our other primary endpoint is safety. Adverse events will be tabulated by CTCAE grade and ETOX status. Surgery delay will be reported with the numbers of patients with any delay, as well as the median, IQR, min and max for delay times. If 6 or more patients experience ETOX, then this combination will be determined to be too toxic for these patients.

For blood and tumor measures, descriptive statistics including plots, tabulations, mean, median and standard deviations will be used to summarize data. Differences and/or percent changes will be calculated between pre- and post-therapy samples from each patient and described as continuous measures.

Sample Size Determination:

The selection of 15 patients for this pilot trial is to provide preliminary information for feasibility and safety, as well as to have at least 10 patients with full immune measures pre and post treatment for hypothesis generation and testing in the next trial. An accrual rate of 2 patients per month is anticipated. A maximum sample size of 15 patients will be enrolled. No hypotheses will be formally tested, but with 15 patients we can determine whether an unreasonable proportion of patients have high grade toxicities and gather estimates of immune and molecular changes in tumor and peripheral blood. These measures will be used to design a larger, hypothesis-driven trial.

SCHEDULE OF STUDY ASSESSMENTS

Study Week		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Prior to Neoadjuvant Therapy**	**Surgery**
Study Cycle		**1**				**2**					
Cycle Day	**-28 to 0**	**1**	**8**	**15**	**28**	**1**	**8**	**15**	**28**	**Within 28 days**	**Within 56 days of completing neoadjuvant therapy**
Informed Consent	X										
Demographics	X										
Medical History	X										
General Physical[1]	X	X[2]				X				X	
Height, Weight[3]	X										
Vital signs	X	X[4]				X[4]				X	
Performance Status (ECOG)	X	X[2]				X				X	
Baseline Symptoms/Toxicity review	X	X[2]				X				X	
Review of concomitant medications	X	X[2]				X					
CBC	X	X[7]				X					
aPTT and INR[5]	X										
Chemistries[6]	X	X[7]				X				X	
TSH, free T4, free T3[8]	X	X[7]				X				X	
HBsAg, Anti HCV, HIV antibody, Hepatitis A antibody	X										
Creatinine clearance	X										
Pregnancy Test (urine)[9]	X										
Urinalysis[10]	X	X				X					
Mammogram	X										
Breast Ultrasound[11]	X									X	
12-lead ECG[12]	X	X									
Core Biopsy	X[13]									X	
Surgical Specimen											X

Blood for PBMCs	X									X	X
Serum	X									X	X
Durvalumab		X				X					
Tremelimumab		X				X					
Gamma glutamyltransferase	X	X[7]									

1. Full physical examination at baseline; targeted physical examination at other time points
2. If completed within 7 days of the date of treatment initiation, these do not need to be repeated.
3. Height only needs to be measured and recorded at the baseline assessment.
4. 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):
    a. At the beginning of the infusion (at 0 minutes)
    b. At 30 minutes during the infusion (±10 minutes)
    c. At the end of the infusion (60 minutes ±10 minutes)
    d. In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e. 90 and 120 minutes from the start of the infusion) (±10 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated
    e. If the infusion lasts longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.
5. Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.
6. Chemistries include: albumin, alkaline phosphatase, ALT, AST, amylase, lipase, calcium, bicarbonate, chloride, creatinine, glucose, LDH, magnesium, potassium, sodium, total bilirubin, total protein, BUN, uric acid. If total bilirubin is ≥ 2x ULN (and no evidence of Gilbert's syndrome), then bilirubin should be fractionated into direct and indirect bilirubin.
7. 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.
8. 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.
9. Pre-menopausal female subjects of childbearing potential only
10. Urinalysis performed at Screening, Day 1, then at Cycle 1, Day 1 and Cycle 2 Day 1, and as clinically indicated. Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.
11. Ultrasound evaluation of the breast tumor and nodal basins will use tumor volume to estimate changes in the tumor in the breast from baseline until after investigational therapy. Tumor volume = (length x width x height x π)/6
12. ECG during screening and on cycle 1 Day 1 within 1 hour prior to start of the first study treatment. Subsequent ECGs as clinically indicated. If an ECG is interpreted to be a prolonged QT interval, 2 additional ECGs will be obtained and the PI will then evaluate all 3 ECGs to determine whether the patient should be excluded.

13. Initial core biopsy will be completed after the patient is determined to be eligible for the study, prior to beginning therapy.

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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
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus

Abbreviation or special term	Explanation
HR	Hormone receptor
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1

Abbreviation or special term	Explanation
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 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
SAE	Serious adverse event
SD	Stable disease
SoC	Standard of Care
T_3	Triiodothyronine
T_4	Thyroxine
TIL	Tumor infiltrating lymphocytes
TNBC	Triple negative breast cancer
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal

1. INTRODUCTION

1.1 Immunotherapy and Breast Cancer

Historically breast cancer has been considered a nonimmunogenic tumor. More recent data demonstrates that there are tumor infiltrating lymphocytes (TIL) in breast tumors and that the extent of infiltrate varies with breast cancer subtype. In a study from Loi et al. across subtypes, the median percentage of infiltration of stromal lymphocytes was 10%; interquartile range 7.5% to 20% (Loi et al 2013). The percentage was lowest in HR+/HER2- tumors and highest in triple negative (TNBC). Based in part on this observation, the majority of studies conducted to date evaluating immunotherapy, specifically drugs targeting the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) pathway, have focused on TNBC.

In the KEYNOTE-012 trial, a multicenter, nonrandomized phase Ib trial of single-agent pembrolizumab (anti-PD-1), investigators reported that in 32 metastatic TNBC patients whose tumors expressed PD-L1, the drug was well tolerated with the majority of patients experiencing low grade toxicities to include arthralgia, fatigue, myalgia and nausea. Among the 27 patients evaluable for antitumor activity, the overall response rate (defined as the percentage of patients with a best overall response of complete response [CR] or partial response [PR]) was 18.5% with the median duration of response not reached; and with 3 responders remaining on study and receiving treatment for > 1 year (Nanda et al 2016). At the 2016 ASCO meeting, investigators reported on a phase Ib study evaluating the anti-PD-L1 antibody atezolizumab in combination with nab-paclitaxel in patients with metastatic TNBC. The combination was well tolerated and in 24 patients evaluable for efficacy, the overall response rate (defined as CR, PR or stable disease [SD]) was 42% (Adams et al 2016).

Other studies have evaluated single agent therapy targeting PD-1/PD-L1 in HR+/HER2- disease. At the 2015 San Antonio Breast Cancer Symposium, data from the Javelin trial, a phase IB study of avelumab (anti-PD-L1) was presented. The trial enrolled patients with locally advanced or metastatic breast cancer unselected for ER/PR and HER2. Among the 72 patients with HR+/HER2- disease, the response rate was only 2.8% (Dirix et al 2015). At that same meeting, results of the KEYNOTE-028 study evaluating pembrolizumab in patients with HR+ tumors was presented. In that study, there were 25 patients with HR+ MBC with an overall response rate of 12% (Rugo et al 2015).

It is possible that the low response rate to anti-PD-1 or anti-PD-L1 in HR+/HER2- breast cancer is due to the low rate of TIL in these tumors which could be described as nonimmunogenic (“cold”). In order to enhance response to anti-PD-1/anti-PD-L1 therapy, it is likely that an immune response will need to be stimulated thereby converting these “cold” tumors to immunogenic, “hot” lesions (Sharma and Allison 2015). One strategy to enhance the immune infiltrate is to treat with the anti-CTLA-4 antibody tremelimumab. Unpublished data from our collaborator, Dr. James Allison has shown that, in prostate cancer, also an immunologically “cold” tumor, tremelimumab induces an intratumoral T cell infiltrate. That T cell infiltrate is notable for increased PD-1 expression thereby justifying the combination with the anti-PD-L1 antibody durvalumab.

1.1.1 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 (Peggs et al 2009). 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]).

1.1.2 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.

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

As of 09Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (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.

Durvalumab is currently being evaluated in a number of breast cancer specific studies including: 1) an open label single arm trial evaluating durvalumab in combination with paclitaxel (NCT02628132), 2) an open label pilot study evaluating the safety, tolerability and efficacy of the combination of durvalumab with Vigil™ autologous tumor cell immunotherapy (NCT02725489), 3) a phase Ib pharmacodynamics study in patients with HER2+ metastatic breast cancer receiving trastuzumab (NCT02649686), 4) a single arm neoadjuvant phase I/II study of durvalumab in combination with weekly Nab-paclitaxel and dose-dense doxorubicin/cyclophosphamide for clinical stage I-III TNBC (NCT02489448), and 5) a randomized phase II study investigating the addition of durvalumab to a taxane-anthracycline containing chemotherapy regimen in TNBC (NCT02685059).

1.1.3 Tremelimumab

The non-clinical and clinical experience is fully described in the current version of the tremelimumab Investigator's Brochure (IB Version 7.0).

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. Refer to the current tremelimumab IB for a complete summary of non-clinical and clinical information; see Section 6.6 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.

1.1.4 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 28 days [AUC_{0-28}]) of both durvalumab and tremelimumab was observed over the dose range of 3 to 15 mg/kg durvalumab Q4W and 1 to 10 mg/kg tremelimumab Q4W. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. It is to be noted that steady state PK parameters are based on limited numbers of subjects. The observed PK exposures of durvalumab and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

As of 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.

The combination of tremelimumab and durvalumab is currently being investigated in several trials enrolling patients with metastatic breast cancer including: 1) a phase I study evaluating the safety and tolerability of the combination in patients with advanced ovarian cancer, colorectal cancer, non-triple negative breast cancer, renal cell carcinoma or cervical cancer (NCT01975831), 2) a phase I trial of hypofractionated radiotherapy in combination with tremelimumab and durvalumab for patients with metastatic melanoma, non-small cell lung cancer, breast cancer or pancreatic adenocarcinoma (NCT02639026), and 3) a single arm phase II study evaluating the efficacy and safety of the combination in patients with metastatic HER2- breast cancer (NCT02536794).

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.

A population PK model was developed for MEDI4736 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 MEDI4736 (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of MEDI4736 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 2009). 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 MEDI4736, 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 S et al 2012; Narwal R 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 (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W MEDI4736 (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 recommend 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.

1.2 Research hypotheses

This study will address the following hypotheses:

1. That it will be feasible to enroll patients with hormone receptor (HR)-positive, HER2-negative breast cancer onto a trial evaluating anti-CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4) therapy (tremelimumab) plus anti-PD-L1 (programmed cell death ligand 1) therapy (durvalumab) prior to initiating standard neoadjuvant chemotherapy.

2. That the combination of tremelimumab plus durvalumab therapy will have an acceptable safety profile in HR+/HER2- breast cancer patients.

3. That tremelimumab plus durvalumab therapy will lead to measurable immunologic changes, with identification of novel biomarkers that can be used for immune monitoring and clinical correlation in the setting of HR+/HER2- breast cancer.

1.3 Rationale for conducting this study

At The University of Texas MD Anderson Cancer Center, we are initiating a trial platform to evaluate immunotherapeutic and targeted agents to turn nonimmunogenic ("cold") hormone receptor positive, HER2 negative breast cancers into immunogenic ("hot") lesions (Sharma and Allison 2015). The trials will each enroll 15 patients with newly-diagnosed hormone receptor positive, HER2 negative breast cancer that are planned for neoadjuvant chemotherapy. The investigational agent or combination of agents will be administered prior to initiation of chemotherapy. All patients will undergo pre- and post-treatment biopsies which will be analyzed for immunologic responses to the investigational agents. These immune studies will be performed by the immunotherapy platform under the direction of Drs. Jim Allison and Padmanee Sharma. The strength of this trial platform is that each study will require only 15 patients and because of the robust immunologic analysis performed on pre- and post-treatment specimens, promising agents that can be moved forward into more definitive clinical trials will be identified quickly.

This trial platform is similar to that employed by our collaborator Dr. Sharma. A previous study performed at MD Anderson by Dr. Sharma evaluated the use of an anti-CTLA-4 antibody (ipilimumab) as pre-surgical therapy in patients with localized urothelial carcinoma of the bladder (Carthon et al 2010). Immunological analyses of pre- and post-treatment tumor tissues indicate that ipilimumab therapy resulted in significant activation of immune cells and infiltration of immune cells into tumor tissues (Chen et al 2009; Liakou et al 2008). 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 (Pardoll 2012). This has been demonstrated in preclinical models (Curran et al 2011; Duraiswamy et al 2013) as well as in clinical trials where 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 (Wolchok et al 2013). Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC (Antonia et al 2014), with further updated details presented in this clinical study protocol.

This study will allow us to evaluate the feasibility of enrolling patients with HR+/HER2- breast cancer onto a trial evaluating investigational immunotherapeutic agents prior to initiating standard neoadjuvant chemotherapy, and to evaluate the safety and tolerability of the combination of tremelimumab plus durvalumab in patients with HR+/HER2- breast cancer. Importantly, we will also be able to assess the immunologic/molecular responses to the combination of tremelimumab plus durvalumab in patients with

HR+/HER2- breast cancer as well as to evaluate the pathologic response in HR+/HER2- breast cancer patients receiving the combination prior to initiation of standard neoadjuvant chemotherapy. The study will therefore allow us to test the clinical activities of these immune checkpoint therapies against HR+/HER2- breast cancer as well to identify biomarkers to guide potential use of these agents in the setting of HR+/HER2- breast cancer. The study will therefore inform the design of subsequent studies evaluating these agents in both the neoadjuvant setting for patients with disease as well as in the setting of metastatic HR+/HER2- breast cancer.

2. STUDY OBJECTIVE

2.1.1 Primary objective(s)

- To evaluate the feasibility of enrolling patients with HR+/HER2- breast cancer onto a trial evaluating investigational agents prior to initiating standard neoadjuvant chemotherapy.

- To evaluate the safety and tolerability of tremelimumab plus durvalumab in patients with HR+/HER2- breast cancer.

2.1.2 Secondary objective

To assess immunologic/molecular responses to tremelimumab and durvalumab in patients with HR+/HER2- breast cancer who receive the combination therapy.

2.1.3 Exploratory objective

To evaluate the pathologic response in patients with HR+/HER2- breast cancer receiving tremelimumab plus durvalumab prior to initiating standard neoadjuvant chemotherapy.

3. STUDY DESIGN

3.1 Overview of study design

This is an open-label, single-arm, presurgical pilot study in patients with HR+/HER2- breast cancer.

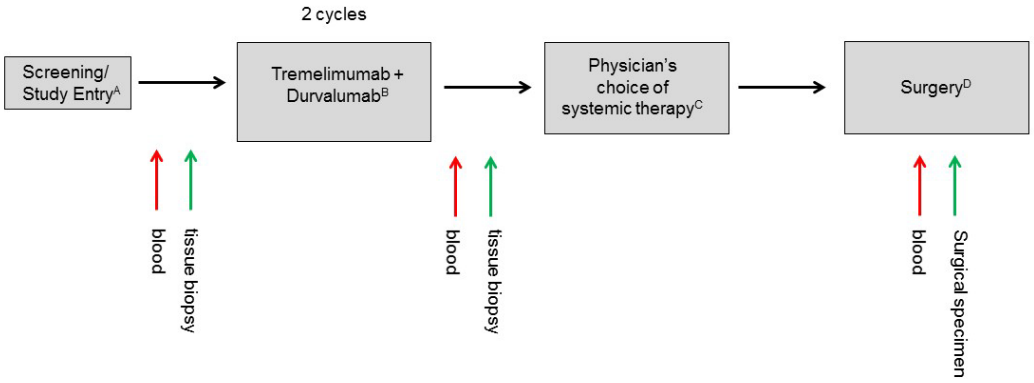
There will be 15 patients enrolled.

Patients will receive durvalumab at 1500 mg plus tremelimumab at 75 mg every 4 weeks for a total of 2 doses. A standard regimen of neoadjuvant chemotherapy will be initiated within 4 weeks after the last infusion of durvalumab and tremelimumab. A biopsy will be obtained after the last infusion of durvalumab and tremelimumab before neoadjuvant chemotherapy is started.

Patients will undergo surgery after the completion of standard neoadjuvant chemotherapy.

3.2 Study schema

Figure 1. Study Schema



Notes:

A. Eligible patients include those with HR+/HER2- breast cancer, clinical stage II-III, planned for neoadjuvant chemotherapy.

B. The first day of dosing is considered Day 1. Tremelimumab will be administered first. The duration of tremelimumab infusion will be 1 hour. Durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion. The duration of durvalumab infusion will be 1 hour.

C. Neoadjuvant systemic therapy will begin within 28 days of the last infusion of tremelimumab and durvalumab.

D. Surgery will be performed within 8 weeks of completing neoadjuvant systemic therapy.

3.3 Study Oversight for Safety Evaluation

The study would be stopped if an unacceptable number of patients experience an extreme toxicity (ETOX). For trial monitoring, a patient will be determined to have an ETOX if either condition is met:

- The patient experiences any grade 3 or higher adverse event (AE) that is possibly, probably, or definitely related to therapy (durvalumab + tremelimumab) received on this protocol and occurs up to 90 days after the last dose of therapy. As an exception, any such AE that is potentially treatable with steroids will only count as an ETOX if it does not improve to grade 1 or better within 2 weeks.

- The patient has a delay in initiation of neoadjuvant systemic therapy of 6 weeks or more due to AE, even if that AE does not meet the definition of ETOX.

Based on the method of Thall (Thall et al 1995), we will monitor ETOX continually after the 5th patient receives treatment. We assume Θ_T ~ beta (0.20, 0.8) for the current study, where Θ_T is the probability of a patient experiencing an ETOX. Our stopping rule is given by the following probability statement: $P_T(\Theta_T>0.20 \mid \text{data}) > 0.90$. That is, we will stop the trial if, at any time during the study, we determine that there is more than an 90% chance that the ETOX rate is more than 20%.

The stopping boundaries for this toxicity rule are to terminate the trial if the number of patients with ETOX compared to the number of patients on trial exceed the limits in table 1, with operating characteristics for this rule in table 2. After 5 patients, this table will be consulted prior to enrolling each patient. Enrollment will not require waiting for complete information for the previous patient, unless an ETOX in that patient would result in hitting the stopping rule.

Table 1. Stopping Criteria for Excessive Toxicities Based on ETOX

If there are this many patients with ETOX	3	4	5	6 or more
Stop if this many patients (or fewer) have been evaluated at least once for toxicity	6	10	13	15*

* The trial will stop at 15 patients, but if 6 or more patients experience ETOX, this regimen will be too toxic for further study in this population.

Table 2. Operating Characteristics for Toxicity Monitoring

True ETOX rate	Probability of Stopping Early	Median (25th %ile, 75th %ile)	Average Number of Patients	Average Number Patients with ETOX
0.05	0.003	15 (15, 15)	15.0	0.75
0.10	0.02	15 (15, 15)	14.8	1.5
0.20	**0.17**	**15 (15, 15)**	**13.7**	**2.7**
0.30	0.45	15 (6, 15)	11.6	3.5
0.40	0.72	8 (5, 15)	9.3	3.7

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study.

4.1 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. Age ≥ 18 years at time of study entry

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

4. Hormone receptor positive (defined as estrogen receptor [ER] and/or progesterone receptor [PR] positive), HER2 negative breast cancer that is clinically staged II-III with no known metastatic disease. ER and/or PR defined as positive if expression >10% by immunohistochemistry (IHC). HER2 negative or non-amplified as determined by the current ASCO-CAP criteria which are as follows: HER2 testing by IHC as 0 or 1+. If HER2 is 2+, ISH (in situ hybridization) must be performed. HER2 is positive if:

    - IHC 3+ based on circumferential membrane staining that is
        - complete, intense
    - ISH positive based on:
        - Single-probe average HER2 copy number ≥6.0 signals/cell.
        - Dual-probe HER2/CEP17 ratio ≥2.0;c,e with an average HER2 copy number ≥4.0 signals/cell
        - Dual-probe HER2/CEP17 ratio ≥2.0;c,e with an average HER2
        - copy number <4.0 signals/cell
        - Dual-probe HER2/CEP17 ratio < 2.0;c,e with an average HER2
        - copy number ≥6.0 signals/cell

5. Chemotherapy is planned for the patient in the neoadjuvant setting

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

    - Haemoglobin ≥ 9.0 g/dL

    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 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 hemolysis or hepatic pathology), who will be allowed only upon treating physician, Principle Principal Investigators (PI) or co-PI approval.

- 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

- 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:

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

Females:

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

7. Female subjects must either be of non-reproductive potential (ie, 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

8. 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

4.2 Exclusion criteria

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

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

2. Participation in another clinical study with an investigational product during the last 1 month prior to initiation of therapy

3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA4, including tremelimumab

4. History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma in situ without evidence of disease eg, cervical cancer in situ

5. Has received therapy for this current diagnosis of breast cancer including endocrine therapy or chemotherapy
6. A single QT interval corrected for heart rate (QTc) ≥470. If an ECG is interpreted to be a prolonged QT interval, 2 additional ECGs will be obtained and the PI will then evaluate all 3 ECGs to determine whether the patient should be excluded. Mean QT interval corrected for heart rate (QTc) >/= 470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction
7. Current or prior use of immunosuppressive medication within 28 days 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
8. 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.
9. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
10. History of primary immunodeficiency
11. History of allogeneic organ transplant
12. History of hypersensitivity to durvalumab or tremelimumab or any excipient
13. History of hypersensitivity to the combination or comparator agent (if applicable)
14. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
15. Known history of previous clinical diagnosis of tuberculosis
16. History of leptomeningeal carcinomatosis

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

18. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control

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

20. Subjects with uncontrolled seizures

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of study treatment with durvalumab and tremelimumab

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

1. Withdrawal of consent or lost to follow-up

2. Adverse event that, in the opinion of the investigator or AstraZeneca/MedImmune, 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. Grade ≥ 3 infusion reaction

7. Subject noncompliance that, in the opinion of the investigator or AstraZeneca/MedImmune, warrants withdrawal; eg, refusal to adhere to scheduled visits

8. Initiation of alternative anticancer therapy including another investigational agent

9. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab + tremelimumab

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from receiving investigational product will be

followed for safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

4.4 Replacement of subjects

Should a patient withdraw or not be able to complete therapy with durvalumab and tremelimumab and study biopsy, additional subjects can be enrolled at the discretion of Dr. Litton and/or Dr. Mittendorf to complete the 15 patient accrual with scheduled biopsies.

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 a solution for infusion after dilution.

5.1.1 Formulation/packaging/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 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 expiry date on the label.

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 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 expiry date on the label.

5.2 Dose and treatment regimens

5.2.1 Treatment regimens

Durvalumab + tremelimumab combination therapy

Patients will receive 1500 mg durvalumab via IV infusion q4w ± 3 days for 2 doses/cycles and 75 mg tremelimumab via IV infusion q4w ± 3 days for 2 doses/cycles. Dosing outside the window should be discussed with Dr. Litton and/or Dr. Mittendorf. 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 will be 30 minutes +/- 5 minutes unless otherwise specified by the investigator.

5.2.2 Duration of treatment

Patients will receive 1500 mg durvalumab via IV infusion q4w +/- 3 days for 2 doses/cycles and 75 mg tremelimumab via IV infusion q4w +/- 3 days for up to 2 doses/cycles. A standard regimen of neoadjuvant chemotherapy will be initiated within 28 days after the last infusion of durvalumab and tremelimumab. A biopsy will be obtained after the last infusion of durvalumab and tremelimumab before chemotherapy is started.

5.2.3 Study drug preparation of durvalumab and tremelimumab

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

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

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

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

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

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

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

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

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

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

Durvalumab hold and infusion times

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

In the event that either preparation time or infusion time exceeds the time limits outlined in the table, a new dose must be prepared from new vials. 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 using aseptic technique. Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

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

It is recommended that the prepared final IV bag be stored in the dark at 2ºC-8°C (36°F-46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The

refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Doses of 75 mg tremelimumab for patients ≥30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter. Remove 3.8 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8 mL of tremelimumab (ie, 75 mg of tremelimumab) is added to the IV bag such that final concentration is within 0.1 mg/mL to 10 mg/mL (IV bag volumes 50 to 500 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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

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

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

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

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

Tremelimuab hold and infusion times

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

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

5.2.4 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs as per Schedule of Study Assessments.

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

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 Accountability and dispensation

Drug accountability and dispensation will occur through the Department of Pharmacy Investigational Drugs and all standard operating procedures of the University of Texas MD Anderson Cancer Center.

5.2.6 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be maintained as part of Institutional current standard operating procedures.

6. TREATMENT PLAN

6.1 Subject enrollment

Patients who have signed informed consent and have undergone screening will be enrolled onto this study and can begin therapy. There is no randomization. This is a single arm, open-label presurgical pilot study prior to the initiation of standard neoadjuvant chemotherapy of the physician's choice for patients with clinical stage II-III HR+/HER2- breast cancer. Patients who are unable to complete all

scheduled study requirements including the pre and post treatment breast biopsies can be replaced at the request of Dr. Litton and/or Dr. Mittendorf and/or the study team.

6.1.1 Procedures for handling subjects incorrectly enrolled

Subjects who are incorrectly enrolled, but not yet initiated on treatment will be withdrawn from the study and replaced.

6.2 Dosage and Administration

Patients will receive 1500 mg durvalumab via IV infusion q4w +/- 3 days for 2 doses/cycles and 75 mg tremelimumab via IV infusion q4w +/- 3 days for 2 doses/cycles. Dosing outside the window should be discussed with Dr. Litton and/or Dr. Mittendorf. 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).

6.3 Dose Modification and Toxicity Management

6.3.1 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 appendix 1. All toxicities will be graded according to NCI CTCAE v4.03.

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

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

– Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 **highly** effective method of contraception (Table 3) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

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

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

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

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had

chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 3. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 3 Highly Effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method

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 electronic medical record.

Restricted, prohibited, and permitted concomitant medications are described in the following tables.

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 (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment.

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

4. Live attenuated vaccines within 30 days of durvalumab 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.

Prohibited medication/class of drug:	Usage:
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.

8.1.1 Screening Phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB -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. Refer to the Study Calendar for complete list of all the procedures that will be performed during the Screening Visit.

8.1.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 7 days of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

8.1.3 End of Treatment

End of treatment is defined as the last planned dose of tremelimumab and durvalumab. This will be followed by physician's choice of systemic therapy, followed by standard of care surgical intervention. Any further adjuvant therapy is at the discretion of the treating physician. Also, should the treating physician deem it is in the patient's best interest to proceed with surgery after the completion of the 2 doses each of tremelimumab and durvalumab, the physician may proceed with surgery with adjuvant therapies as per physician discretion.

All subjects will be followed until the time of breast surgery.

8.2 Description of study procedures

8.2.1 Medical history and physical examination, electrocardiogram, weight and vital signs

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

Physical examinations will be performed on study days noted in the Schedule of Assessments.

8.2.2 Physical examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at Screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10.

8.2.3 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. 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 Screening, a single ECG will be obtained on which QTcF must be <470 ms. If an ECG is interpreted to be a prolonged QT interval, 2 additional ECGs will be obtained and the PI will then evaluate all 3 ECGs to determine whether the patient should be excluded.

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.

Situations in which ECG results should be reported as AEs are described in Section 10.0.

8.2.4 Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules.

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

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]).

Halfway through the infusion (approximately 30 minutes ± 10 minutes).

At the end of the infusion (approximately 60 minutes ± 10 minutes), 30 minutes, and 60 minutes after the infusion (i.e. 90 and 120 minutes from the start of the infusion) (±10 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated.

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 electronic medical record. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 10.3. A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

8.2.5 Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments):

- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Pregnancy test (female subjects of childbearing potential only)
    - Urine human chorionic gonadotropin
- Thyroid Stimulating Hormone
    - free T3 and free T4 only if TSH is abnormal
- Other laboratory tests
    - Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
    - HIV antibody for patients with known history

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 haemoglobin concentration	

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 Screening, Day 1, and as clinically indicated.

Table 7. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells

8.3 Biospecimen collections

Blood and tissue specimens will be collected as specified in the Schedule of Study Assessments. Specimens will be de-identified and labelled with a unique study identification number for use in immune monitoring assays. Assays will be performed in research laboratories at the University of Texas MD Anderson Cancer Center to include the Immunotherapy Platform.

8.3.1 Tumor biopsies and surgical specimen

All patients will have biopsies performed before starting treatment with tremelimumab + durvalumab and post-treatment with tremelimumab + durvalumab (before starting neoadjuvant chemotherapy). These biopsies will be obtained by core needle using a needle gauge of 14 or larger, with up to five cores obtained at each time point. Surgical resection specimens will be obtained with the amount of tissue provided determined by the attending breast pathologist performing the gross sectioning at the time of surgical resection.

All samples will be collected and analyzed as per a separate IRB-approved lab protocol (PA13-0291). The Immunotherapy Platform will perform immune monitoring, including but not limited to evaluation of CD4 and CD8 T cells in available tumor samples as previously published (Liakou et al 2008; Carthon et al 2010; Tang et al 2013; Chen et al 2014; Eng et al 2015; Chen et al 2016; Subudhi et al 2016; Gao et al 2016).

8.3.2 Peripheral blood and serum samples

Multiple blood draws will be required for this trial (pre-treatment, post-treatment, at time of surgery). All blood collections will be compliant with the institutional safety standards and will not exceed the maximum blood draw per venipuncture policy. All samples will be collected and analyzed as per a separate IRB-approved lab protocol (PA13-0291). The Immunotherapy Platform will perform immune monitoring, including but not limited to evaluation of CD4 and CD8 T cells in available blood samples as previously published (Liakou et al 2008; Carthon et al 2010; Tang et al 2013; Chen et al 2014; Eng et al 2015; Chen et al 2016; Subudhi et al 2016; Gao et al 2016).

9. DISEASE EVALUATION AND METHODS

As this is a pre-surgical pilot study, evaluations will be done primarily by mammogram and breast ultrasound at baseline and then by ultrasound at the completion of the 2 cycles of investigational therapy.

At the time of surgery the residual tissue will be described by Residual Cancer Burden (RCB) (Symmans et al 2007). The RCB is a continuous variable derived from the primary tumor dimensions, cellularity of the tumor bed, and axillary nodal burden. RCB can be divided into four classes (RCB-0 to RCB-III) and will be collected as part of the study.

RCB-0 (pCR), Minimal RCB (RCB-I), Moderate RCB (RCB-II), and Extensive RCB (RCB-III)

The following parameters are required from pathologic examination in order to calculate

Residual Cancer Burden (RCB) after neoadjuvant treatment:

1. The largest two dimensions (mms) of the residual tumor bed in the breast (largest tumor bed if multicentric disease)
2. Submission of the entire largest cross-sectional area of the residual tumor bed for histologic mapping, with specific identification of those slides in the pathology report (e.g. "the largest cross-sectional area of primary tumor bed was submitted in cassettes A5 - A9")
    - If the residual tumor is large (i.e. largest diameter > 5 cm), then at least 5 representative cassettes from the largest cross-sectional area are sufficient, but should be identified in the original pathology report (e.g. "representative sections from the largest cross- sectional area of primary tumor bed were submitted in cassettes A5 - A9")
3. Histologic assessment of the percentage of the tumor bed area that contains carcinoma (all carcinoma, i.e. invasive and in situ), select one of the following:

    0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%

    - To assess cellularity it is helpful to scan across the sections of tumor bed and then estimate the average cellularity from the different microscopic fields.
    - When estimating percentage cancer cellularity in any microscopic field, compare the involved area with obvious standards, e.g. more or less than half, one quarter, one fifth, one tenth, one twentieth, etc.
    - Expect there to be variable cellularity within the cross section of any tumor bed, but estimate the overall cellularity from the average of the estimates in different microscopic fields of the tumor bed.
    - e.g. if cellularity in different fields of the tumor bed were estimated as 20%, 10%, 20%, 0%, 20%, 30%, then an average estimate of overall cellularity would be 20%.

4. Histologic estimate of the percentage of the carcinoma in the tumor bed that is in situ, select one of the following:
   0%, 1%, 5%, 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 100%
5. The number of positive (metastatic) lymph nodes
6. The largest diameter (mm) of the largest nodal metastasis

The RCB can be accessed online: www.mdanderson.org/breastcancer_RCB. The RCB will be determined using this online calculator and documented by the study staff in the patient's electronic medical record as part of the off study note.

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 Safety Parameters

10.1.1 Definition of adverse events

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

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

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

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product. Only AEs related to study drug (durvalumab + tremelimumab) will be followed. Non-treatment-emergent AEs will not be followed. In addition, AEs attributable to the preplanned neoadjuvant chemotherapy or surgery will not be collected.

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

10.1.2 Definition of serious adverse events

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

Results in death

Is immediately life-threatening

Requires in-patient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability or incapacity

Is a congenital abnormality or birth defect in offspring of the subject

Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above:

- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events, as defined above, also may be considered SAEs. Any important medical event can and will be reported as an SAE if deemed appropriate by the Principal Investigator or The University of Texas MD Anderson Cancer Center's IND Office.

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

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

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and The University of Texas MD Anderson Cancer Center IRB.

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

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

Reporting to FDA:

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

The Principal Investigator and research team will ensure SAEs are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

10.1.3 The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca. 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 AstraZeneca/MedImmune. 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 etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact Dr. Litton and/or Dr. Mittendorf.

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)
- Infusion related / Hypersensitivity / Anaphylactic reactions
- Other immune-mediated events that are rare could be reported (e.g. uveitis)

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 Appendix 1.

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 Appendix 1.

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 Appendix 1.

Lab abnormalities meeting the Potential Hy's Law criteria (increase in serum ALT or AST ≥ 3 x ULN together with total bilirubin ≥ 2 x ULN, irrespective of serum alkaline phosphatase, at any point during the study following the start of the immunotherapy agent) or Hy's Low (increase in serum ALT or AST

≥ 3 x ULN together with total bilirubin ≥ 2 x ULN, where no other reason can be found to explain the combination of increases, for example, elevated serum alkaline phosphatase indicating cholestasis, viral hepatitis, or another suspect drug) will be handled as per Astra-Zeneca standard operating procedures (Appendix 1).

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 Appendix 1.

Endocrine disorders

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

Pancreatic disorders

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

Neurotoxicity

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

Nephritis

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

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

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

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 (Weber et al 2012). 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).

10.2 If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact Dr. Litton and/or Dr. Mittendorf. 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 v4.03.
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 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. 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.

10.3 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 and recorded in RedCap for each AE:

- AE (verbatim)
- The date 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)
- Action taken with regard to durvalumab + tremelimumab/comparator/combination agent
- Outcome

In addition, the following variables will be collected and recorded in RedCap for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to <<criteria>>
- 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)

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 adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of first protocol intervention, throughout the treatment period and including the follow-up period (90 +/-7 days after the last dose of durvalumab + tremelimumab).

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 (90 days post End of Treatment) in the study are followed up by the investigator for as long as medically indicated, but without further recording. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune and the IND Office retain 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 The University of Texas MD Anderson Cancer Center and AstraZeneca/MedImmune Drug Safety.

10.3.2 Investigator Communications with AstraZeneca

All SAE reports and accompanying cover pages will be sent, by way of email, to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com.

***** A ***cover page*** should accompany the ***MD Anderson IRB SAE*** form indicating the following:

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

***** The University of Texas MD Anderson Cancer Center 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.

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 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 and/or Tremelimumab safety follow-up period will be documented, but will not be reported as an SAE. If the death is possibly related to durvalumab and/or tremelimumab, it will 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 University of Texas MD Anderson Cancer Center 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 University of Texas MD Anderson Cancer Center 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 The University of Texas MD Anderson Cancer Center 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, 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 Description of analysis sets

11.1.1 Safety analysis set

All patients who receive at least one dose of study drug will be included in the safety monitoring and safety analysis.

11.1.2 Efficacy analysis set

All enrolled patients will be included in the primary feasibility analysis. Only patients with surgical specimens and immune measures will be included in secondary and exploratory analyses requiring that information.

11.2 Goals

Since this combination has not been previously evaluated in the presurgical setting in hormone receptor positive, HER2 negative breast cancer, this trial will: 1) assess the feasibility of enrolling patients onto a trial evaluating investigational agents prior to initiating standard neoadjuvant chemotherapy, 2) determine the safety of durvalumab and tremelimumab in patients with hormone receptor positive, HER2 negative breast cancer, as well as 3) gather preliminary immunologic information for designing future trials.

11.3 Endpoints

11.3.1 Primary Endpoints

The primary endpoints will be
:

1. Feasibility. This will be measured by 2 achievements. If both are met, then upfront treatment with durvalumab plus tremelimumab will be feasible for future trials in these breast cancer patients. Otherwise, other strategies for implementing these treatments will need to be designed. The 2 measures are:

    a. Patients are willing to enroll: This will be established if we can enroll all 15 patients within 12 months of starting the study. The start date for measuring feasibility will be the date the first patient is screened.
    b. Patients can complete the protocol: If at least 10 patients complete the study and have available immune data the trial meets this feasibility criterion. If fewer than 8 finish then this dose/schedule is infeasible. If 8 or 9 complete the study with immune data then clinical judgment combining toxicity, efficacy, and physician

experience with the protocol will be used to determine whether adjustments to the treatment are needed before a future trial.

2. Adverse events will be recorded according to CTCAE 4.03.

11.3.2 Secondary Endpoint

Immune and molecular measures in peripheral blood and tumor tissues pre and post treatment.

11.3.3 Exploratory Endpoint

Pathologic response at surgery will be recorded for each patient.

11.4 Sample Size Considerations

The selection of 15 patients for this pilot trial is to provide preliminary information for feasibility and safety, as well as to have at least 10 patients with full immune measures pre and post treatment for hypothesis generation and testing in the next trial. An accrual rate of 2 patients per month is anticipated. A maximum sample size of 15 patients will be enrolled. No hypotheses will be formally tested, but with 15 patients we can determine whether an unreasonable proportion of patients have high grade toxicities and gather estimates of immune and molecular changes in tumor and peripheral blood. These measures will be used to design a larger, hypothesis-driven trial.

11.5 Interim Analysis: Safety Monitoring

Any patient who received the first dose of study medication will be included in the ongoing safety monitoring. For trial monitoring and decisions about future trials, a patient will be determined to have an extreme toxicity (ETOX) if either condition is met:

- The patient experiences any grade 3 or higher adverse event (AE) that is possibly, probably, or definitely related to therapy received on this protocol and occurs up to 90 days after the last dose of therapy (durvalumab + tremelimumab). As an exception, any such AE that is potentially treatable with steroids will only count as an ETOX if it does not improve to grade 1 or better within 2 weeks.
- The patient has a delay in surgery of 6 weeks or more due to AE, even if that AE does not meet the definition of ETOX.

Based on the method of Thall (1995)[9], we will monitor ETOX **continually after the 5th patient** receives treatment. Continuous monitoring will occur monthly. We assume $\Theta_T \sim$ beta (0.20, 0.8) for the current study, where Θ_T is the probability of a patient experiencing an ETOX. Our stopping rule is given by the following probability statement: $P_T(\Theta_T > 0.20 \mid \text{data}) > 0.90$. That is, we will stop the trial if, at any time during the study, we determine that there is more than an 90% chance that the ETOX rate is more than 20%.

The stopping boundaries for this toxicity rule are to terminate the trial if the number of patients with ETOX compared to the number of patients on trial exceed the limits in table 1, with

operating characteristics for this rule in table 2. After 5 patients, this table will be consulted prior to enrolling each patient. Enrollment will not require waiting for complete information for the previous patient, unless an ETOX in that patient would result in hitting the stopping rule. Boundaries and operating characteristics were calculated in Multc Lean v2.1.

Table 1. Stopping Criteria for Excessive Toxicities Based on ETOX

If there are this many patients with ETOX	3	4	5	6 or more
Stop if this many patients (or fewer) have been evaluated at least once for toxicity	6	10	13	15*

* The trial will stop at 15 patients, but if 6 or more patients experience ETOX, this regimen will be too toxic for further study in this population.

Table 2. Operating Characteristics for Toxicity Monitoring

True ETOX rate	Probability of Stopping Early	Median (25^{th} %ile, 75^{th} %ile)	Average Number of Patients	Average Number Patients with ETOX
0.05	0.003	15 (15, 15)	15.0	0.75
0.10	0.02	15 (15, 15)	14.8	1.5
0.20	**0.17**	**15 (15, 15)**	**13.7**	**2.7**
0.30	0.45	15 (6, 15)	11.6	3.5
0.40	0.72	8 (5, 15)	9.3	3.7

The Investigator is responsible for completing the summary report and submitting it to the IND Office Medical Monitor for review and approval. A Feasibility/Safety summary will be submitted after the first 5 evaluable patients complete study treatment, and monthly thereafter.

11.6 Analysis Plan

Feasibility will be assessed according to the endpoint definition provided above. Additionally, the total number of patients screened to achieve 15 enrolled patients will be reported. Since it is not known whether durvalumab plus tremelimumab can be safely used in the presurgical setting in patients with HR+, HER2- breast cancer, our other primary endpoint is safety. Adverse events will be tabulated by CTCAE grade and ETOX status. A 95% credible interval will be presented for the ETOX rate among patients in the safety analysis set. Surgery delay will be reported with the numbers of patients with any delay, as well as the median, IQR, min

and max for delay times. If 6 or more patients experience ETOX, then this combination will be determined to be too toxic for these patients.

For blood and tumor measures, descriptive statistics including plots, tabulations, mean, median and standard deviations will be used to summarize data. Differences and/or percent changes will be calculated between pre- and post-therapy samples from each patient and described as continuous measures.

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Appendix 1. 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 (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). − More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. − Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.
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.	

Appendix 1. 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
3. Doses of prednisone are at ≤10 mg/day or equivalent.	
Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	
Grade 4 Permanently discontinue study drug/study regimen.	
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.	
Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment (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 Dr. Litton and/or Dr. Mittendorf.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain pulmonary and infectious disease consult. − Hospitalize the patient. − Supportive care (eg, oxygen). − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Enterocolitis	**Any Grade**	General Guidance	**For Any Grade:**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – 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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeksa. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. − Consult Dr. Litton and/or Dr. Mittendorf if no resolution to Grade ≤1 in 3 to 4 days. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. − Monitor stool frequency and volume and maintain hydration. − Urgent GI consult and imaging and/or colonoscopy as appropriate. − If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** − Monitor and evaluate liver function test: AST, ALT, ALP, and TB. − Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** − Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × ULN)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to 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 Dr. Litton and/or Dr. Mittendorf. − 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 Dr. Litton and/or Dr. Mittendorf if mycophenolate mofetil is not available. **Infliximab should NOT be used.**

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in 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	**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 Dr. Litton and/or Dr. Mittendorf if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4.

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 4: serum creatinine >6.0 × ULN)		– If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, DR. LITTON AND/OR DR. MITTENDORF 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	**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 Dr.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		regimen after completion of steroid taper.	Litton and/or Dr. Mittendorf and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue 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]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with Dr. Litton and/or Dr. Mittendorf.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism,	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE	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.

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
hypopituitarism, and adrenal insufficiency)	v4.03 for defining the CTC grade/severity)		– Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than 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.	**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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		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.	relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.	**For Grade 3 or 4:** – Consult endocrinologist. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with Dr. Litton and/or Dr. Mittendorf.

Specific Immune-mediated Reactions

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

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	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 Dr. Litton and/or Dr. Mittendorf. – 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 ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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 Dr. Litton and/or Dr. Mittendorf. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Discuss with Dr. Litton and/or Dr. Mittendorf. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may

Specific Immune-mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			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 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 3 or 4 (severe or life-threatening events):** − Discuss with Dr. Litton and/or Dr. Mittendorf. − 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.

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.	○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* ○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. ○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

[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 AstraZeneca/MedImmune.).	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 Dr. Litton and/or Dr. Mittendorf."

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:

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

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

Example:

1. Cohort dose: 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 theoretical number of vials required for dose preparation:

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

Appendix 3. Durvalumab DOSE VOLUME CALCULATIONS

For durvalumab flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000 / 50 (mg/mL)

where 50 mg/mL is durvalumab nominal concentration.

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

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

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

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

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

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

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

Appendix 4. Tremelimumab DOSE CALCULATIONS

For tremelimumab dosing done depending on subject weight:

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

Number of vials = Dose (mL) / 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 theoretical number of vials required for dose preparation:

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

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

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

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

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

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

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