NU Study Number: *NU 15B01*
Other Study Number: MedImmune # *ESR-14-10694 (D4190C00030)*

A SINGLE ARM PHASE II STUDY EVALUATING THE EFFICACY AND SAFETY OF DURVALUMAB (MEDI4736) IN COMBINATION WITH TREMELIMUMAB IN PATIENTS WITH METASTATIC HER2 NEGATIVE BREAST CANCER: TNBC EXPANSION COHORT

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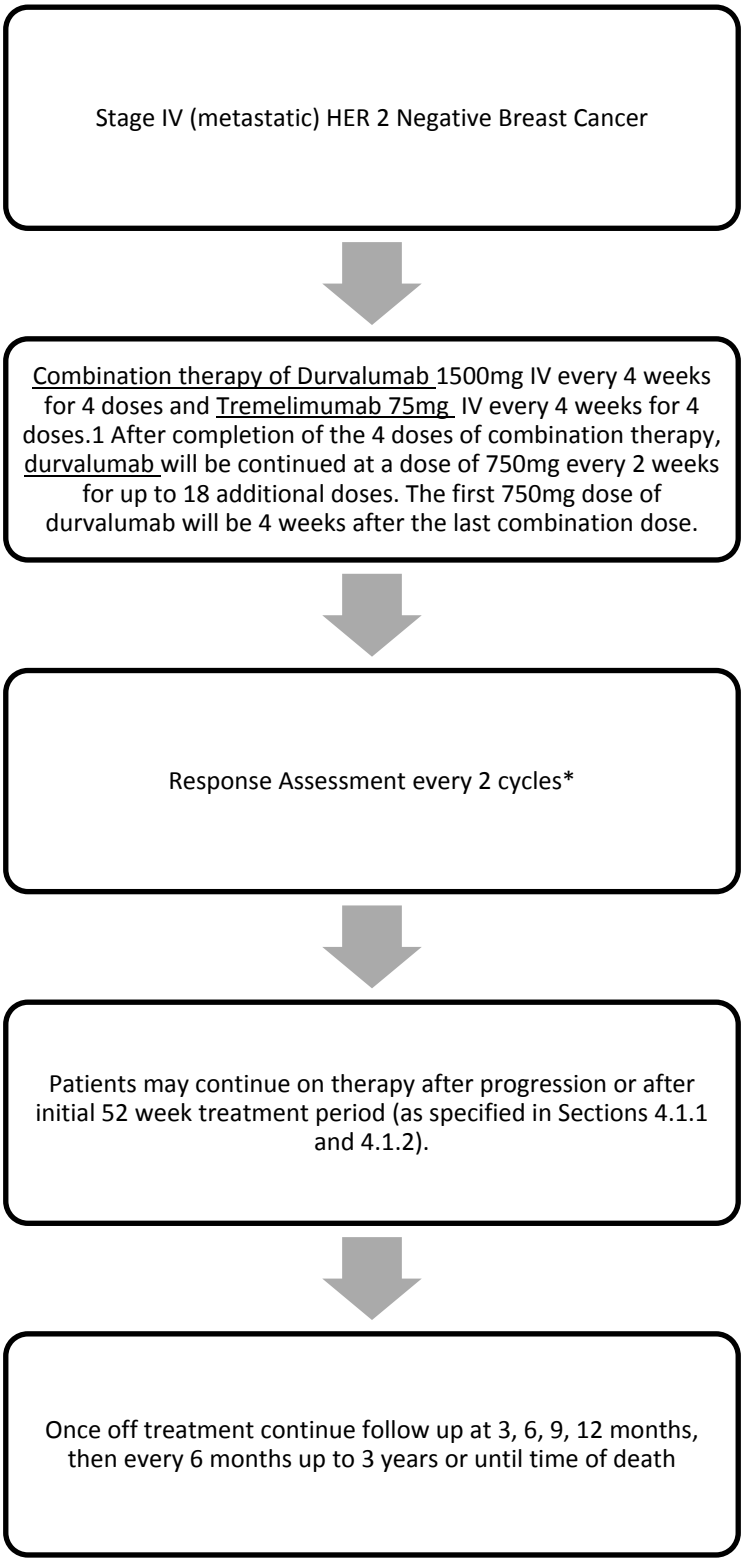
LIST OF ABBREVIATIONS

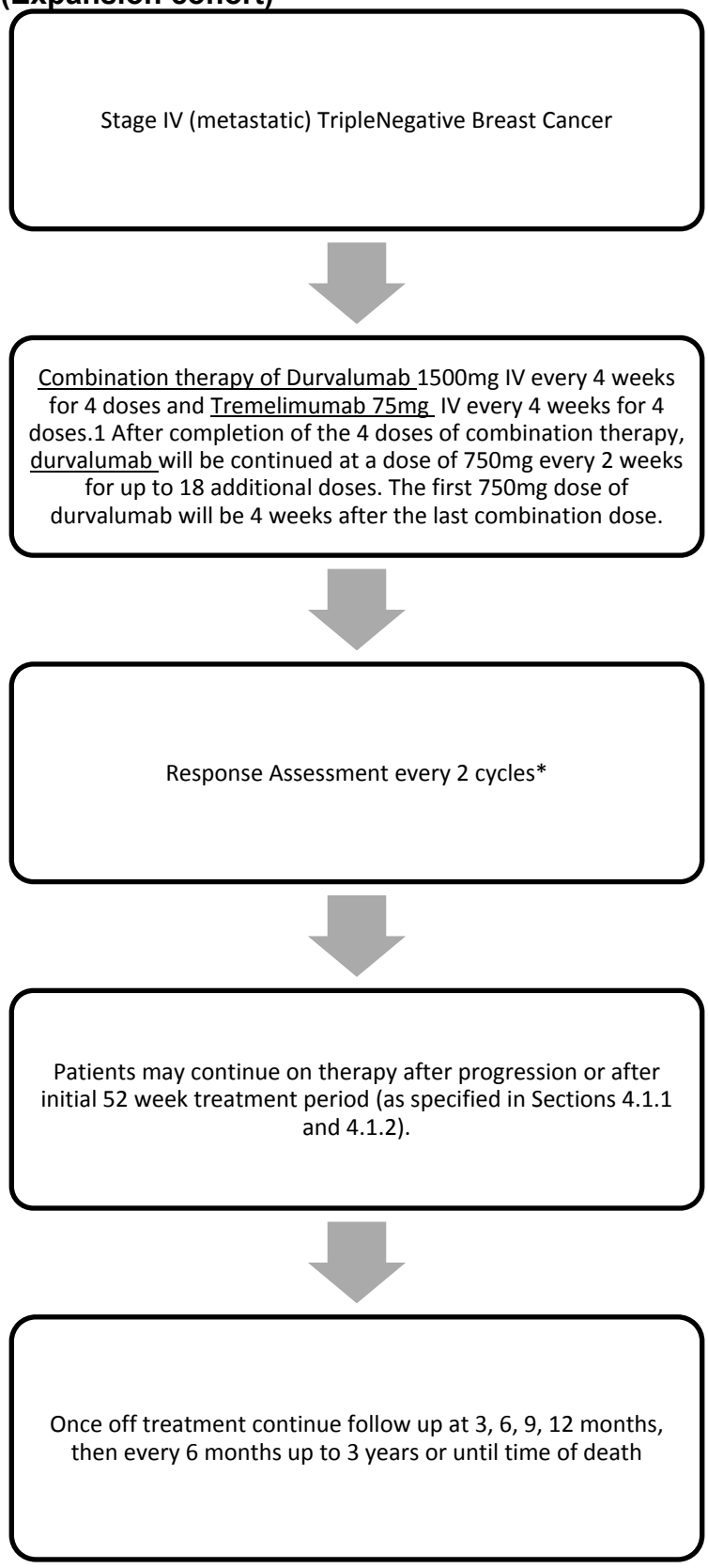
AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
H&PE	History & Physical Exam
IV (or iv)	Intravenously
ID	Infectious disease identifying data
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
WBC	White Blood Cells

STUDY SCHEMA (General cohort)



*Scans are to be completed every 8 weeks, regardless of drug holds or treatment delays

STUDY SCHEMA (Expansion cohort)



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STUDY SUMMARY

NU Study Number: *NU 15B01*
Other Study Number: MedImmune # *ESR-14-10694 (D4190C00030)*

Title	A Single Arm Phase II Study Evaluating the Efficacy and Safety of Durvalumab (MEDI4736) In Combination With Tremelimumab In Patients with Metastatic HER2 Negative Breast Cancer: TNBC expansion cohort
Short Title	Durvalumab and Tremelimumab in Metastatic Breast Cancer
Version	Amendment 12 dated 8.31.2020
Study Design	Phase II
Study Center	Northwestern University
Objectives	Primary Objective: To evaluate overall response rate (ORR) in patients with metastatic HER2 negative breast cancer treated with durvalumab in combination with tremelimumab. Expansion Cohort Objective: To evaluate overall response rate (ORR) in patients with metastatic triple negative breast cancer treated with durvalumab in combination with tremelimumab. Secondary Objectives: To evaluate PFS and OS in patients with metastatic HER2 negative breast cancer treated with durvalumab in combination with tremelimumab. To evaluate clinical benefit rate in this population. To evaluate safety and tolerability. Exploratory: To evaluate if serum and tissue-based immune-related biomarkers are modulated by therapy and predict response. (see Section 2.3 for details) To assess response rates to next line therapy after progression
Sample Size	A total of 30 patients (15 ER+, 15 ER-) with metastatic breast cancer which is HER2 negative will be enrolled into this study and receive durvalumab in combination with tremelimumab in order to get 28 evaluable (14 ER+,14ER-) for response. Expansion cohort based will enroll 20 additional patients with TNBC to determine the posterior Bayesian probability that the response rate exceeds 30%.
Diagnosis & Key Eligibility Criteria	Patients must have a histologically documented (either primary or metastatic site) diagnosis of breast cancer that is HER2 negative (expansion cohort only TNBC allowed). Patients must have stage IV disease and must have completed at least one line of chemotherapy. Only TNBC patients will be enrolled in the expansion cohort. Also, only PD-L1 negative patients in the front line setting will be enrolled. Beyond frontline setting, any PD-L1 status is acceptable. . Patients must be ECOG performance status of 2 or less and have normal organ function. Patients treated with previous immunotherapies are excluded.
Treatment Plan	Patients will be treated with durvalumab 1500mg intravenously (IV) every 4 weeks for a total of 4 doses, and tremelimumab 75mg IV every 4 weeks for a total of 4 doses. After completion of the 4 doses of combination therapy, durvalumab will be continued at a dose of 750mg every 2 weeks for up to 18 additional doses, or until progressive disease or unacceptable toxicity. The first 750mg dose of durvalumab will be 4 weeks after the last combination dose. Patients will be followed for 3 years for survival and progression of disease.

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Breast Cancer: All Subtypes Not Equal

Breast cancer is the most common non-dermatological malignancy in women with an estimated 232, 670 new diagnoses in 2014, and the second leading cause of cancer death in women with an estimated 40, 000 women in the United States succumbing to the disease in 2014 [1]. Breast cancer is a heterogeneous disease comprising of several molecular subtypes, which are commonly extrapolated into clinical subtypes, with significant prognostic implications [2, 3]. Significant advances have been made in certain subtypes of breast cancer, for example human epidermal growth factor 2-neu (HER2) receptor positive disease. In this subtype targeted therapies have changed the nature of the disease from an aggressive subtype to one which is highly curable in early stages, and in some patients with advanced metastatic disease treatable for many years [4]. The estrogen receptor (ER) and progesterone receptor (PR) positive subtypes also have several targeted therapies using hormonal manipulation, however, when the disease becomes metastatic all patients will eventually develop endocrine resistance and often require cytotoxic chemotherapy [5]. Similarly, patients with ER, PR, and HER2 negative, the so-called triple negative breast cancers (TNBC), biologically tend to display an aggressive phenotype, currently do not have targeted therapy options as a standard of care, and only have a limited amount of cytotoxic agents available to treat their disease [6] . Patients with metastatic ER positive breast cancer who have used all hormonal options, and those with TNBC, experience a poor prognosis with only a few treatment options.

1.2 Breast Cancer Immunology

The breast tumor microenvironment is often infiltrated by immune cells. The adaptive immune system can identify tumor antigens through immunosurveillence [7]. In this process, antigen-presenting cells present non-self antigens to T cells, which allow them to recognize and destroy cells expressing such antigens. A hallmark of oncogenesis is that tumor cells can develop mechanisms to evade such immune recognition [8, 9].

The presence of tumor infiltrating lymphocytes (TILs) has been associated with more favorable prognosis in breast cancer [10]. Paradoxically, TILs have been closely associated with ER negative subtypes, tumors with an aggressive biological behavior. However, this discrepancy may be due to the fact TILs are associated with better survival in basal-like rather than non-basal-like TNBC [11, 12]. Nevertheless, these results highlight the importance of immune regulatory mechanisms in the pathogenesis of breast cancer.

1.3 Immune Checkpoint Blockade in Breast Cancer

The success of immune checkpoint blockade in certain cancers has served as proof-of-concept that immune therapy is a viable therapeutic strategy. Cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitors have shown significant and sustained anti-tumor activity in melanoma [12]. While clinical data regarding CTLA-4 inhibition in breast cancer is limited, preclinical studies using mammary murine models using poorly immunogenic breast cancer cell lines failed to show single agent activity, however, in combination with radiation therapy improved survival related to a decrease in lung metastases [13]. Another study demonstrated significant tumor regression with the combination of a granulocyte-macrophage colony stimulating factor vaccine and CTLA-4 blockade [14]. A phase I clinical trial of 26 patients with hormone receptor positive metastatic breast cancer found that treatment with the a humanized immunoglobulin (Ig) IgG2 monoclonal antibody (mAb), tremelimumab and exemestane found that this treatment could illicit a robust immune response as measured by systemic immune effectors, and 42% of patients experienced disease stability for at least 3 months, thus demonstrating possible biological and clinical activity [15].

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling

T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T-cells[16]. It has 2 known ligands: PD-L1 (B7 H1; CD274) and PD-L2 (B7 DC; CD273) [17]. The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T-cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response. PD-L1 is constitutively expressed by B cells, dendritic cells, and macrophages [18].Importantly, PD-L1 is commonly over expressed on tumor cells or on non-transformed cells in the tumor microenvironment [19]. PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T-cells. These deactivated T-cells remain inhibited in the tumour microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity. In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T-cells and upregulated on activated T cells. Binding of CTLA-4 to CD80 or CD86 on IC leads to inhibition of T-cell activation [20]. The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on ICs. This activity overcomes PD-L1-mediated inhibition of antitumour immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

When this study was designed and launched (2015), the clinical scenario was that, blockade of the programmed cell death 1 (PD-1) and its ligand (PD-L1) had been found to have anti-tumor activity in certain cancers, with 6-17% overall response rates [21]. Approximately 20% of TNBC expresses PD-L1, suggesting that targeting the PD- 1/PD-L1 checkpoint may be an effective treatment strategy in this subtype [22, 23].
Expression of PD-L1 is known to be associated with poor prognosis in patients with breast cancer, particularly those with luminal B and basal-like subtypes [24], thus making aggressive phenotype ER positive and triple negative breast cancers attractive subtypes in which to investigate PD-L1 blockade. A subsequent phase 1B study presented at the 2014 San Antonio Breast Cancer Symposium demonstrated that in patients with heavily pretreated metastatic triple negative breast cancer (TNBC) treated with the humanized IgG4κ isotype mAb against PD-1, pembrolizumab, 16.1% had a partial response (PR), and 9.7% had stable disease (SD) [25].
Through the years, the clinical landscape has evolved. Original study (Santa-Maria et al Oncotarget 2018) found that patients who responded had only had 1 line of prior therapy. We thus want to limit to no more than 1 line of previous therapy in the metastatic setting. Indeed several studies have now shown that responses to immune checkpoint inhibition are mostly restricted to earlier lines settings (Santa-Maria et al JNCCN 2019).
Currently, atezolizumab in combination with nab-paclitaxel is FDA-approved for patients with no prior treatment for metastatic TNBC who are PD-L1 immune cell-positive. The ImPassion130 study (Schmid et al NEJM 2018) suggests that these patients benefit from the addition of atezolizumab to nab-paclitaxel in the front line setting. Therefore, now we wish to exclude patients who are PD-L1-positive in the front line setting. Patients who are PD-L1-negative are eligible for this protocol in the front line setting, if patients are enrolled in the second line setting, PDL1 status is not needed for enrollment.

Although effects of single agent checkpoint blockade are modest, with only a small fraction of patients having significant responses, recently combination checkpoint blockade with CTLA-4 and PD-1 inhibitors has demonstrated synergistic activity with an overall response rate of 40%, and 31% of patients achieving >80% reduction in their tumors by 12 weeks [26]. A recently presented phase 1 open-label study evaluating the anti-PDL1 inhibitor, durvalumab, in combination with tremelimumab in patients with advanced non-small cell lung cancer, revealed that the combination was well tolerated with 75% of reported adverse events (AEs) being low grade, and only 3/24 patients discontinuing therapy due to treatment-related AEs. Furthermore, patients experienced an

overall response rate (ORR) of 30% in the subset of patients that were PD-L1 negative [2 7] . These results suggest that combination immune therapy may improve anti- tumor responses.

1.4 Durvalumab (MEDI4736)

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

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 (MEDI4736) is a human IgG1κ monoclonal antibody directed against human PD-L1. Two monotherapy studies (NCT01693562 and NCT01938612), and one combination study (NCT02261220) investigating this drug are currently underway. NCT01693562 is a first- time-in-human, dose-escalation and dose-expansion study in adults with advanced solid tumors. NCT01938612 is a Phase 1, dose-escalation and dose-expansion study in Japanese adults with advanced solid tumors. NCT02261220, is a Phase 1 study investigating durvalumab in combination with MEDI6469, as well as other immune therapies, in patients with advanced malignancies.

1.5 Tremelimumab

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

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. As described above, tremelimumab has been safely administered in patients with metastatic breast cancer and, in combination with hormone therapy, associated with significant clinical benefit in terms of disease stability [15].

Tremelimumab has been administered as monotherapy to subjects participating in 10 clinical studies, with over 1,000 subjects in a variety of tumor types. Across the clinical development program for tremelimumab and that of the related anti-CTLA-4 antibody ipilimumab, a pattern of efficacy has emerged that appears to be consistent across tumor types for this mechanism of action. Response rates to anti-CTLA-4 antibody monotherapy are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting months to years even in subjects with aggressive tumors, such as refractory metastatic melanoma. The most common treatment-related toxicity is diarrhea (41.2%), rash (27.2%), pruritus (25.1%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite (11.3%), headache (7.2%), pyrexia (7.0%), abdominal pain (6.7%), and colitis resulting in hypokalemia (5.5%).

1.6 Durvalumab in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity [19] 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.

1.7 Rationale for the Current Study

The association of the PD-1/PD-L1 axis in breast cancer, and early success of inhibitors of the PD1/PD-L1 axis in breast cancer, provides background rationale for the use of

durvalumab in patients with metastatic breast cancer. Recent studies published in melanoma suggest that the combination of the PD-1 inhibitor, nivolumab, in combination with the CTLA-4 inhibitor, ipilimumab, have improved progression free survival compared to single agent ipilimumab (11.5 months versus 2.9 months, respectively)[28]. Furthermore, a recent phase 1 study presented at the European Society for Medical Oncology (ESMO) found that in patients with metastatic lung cancer, the combination of durvalumab and tremelimumab found this combination was tolerable and associated with overall response rates of 28% [27]. The significant synergy in response rates observed with inhibition of CTLA-4 and the PD-1/PD-L1 axis in other malignancies supports the investigation of this combination in metastatic breast cancer.

1.7.1 Rationale for fixed dosing for durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors*). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg.. Simulation results demonstrate that body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady-state exposures and associated variability, supporting the potential switch of durvalumab from weight-based to fixed dose. Similar considerations hold for the Q4W dosing regimens (20 mg/kg Q4W versus 1500 mg Q4W).

A population PK model was developed for durvalumab using monotherapy data as detailed in Section 5.1.2 of the IB. Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤0.5). The impact of body weight--based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK concentrations exposures (AUCss,0-28, Cmax,ss, and Cmin,ss5th, median and 95th percentiles) using the population PK model.
A fixed dose of 750 mg Q2W was selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (based on median body weight of ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 120 110 kg. Simulation results demonstrate that body weight-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady-state exposures and associated variability, supporting the potential switch of durvalumab from weight-based to fixed dose.
Similar considerations hold for the Q4W dosing regimens (20 mg/kg Q4W versus 1500 mg Q4W).

Similar findings have been reported by others [29-32]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [31].

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

Fixed dosing of durvalumab and tremelimumab is recommend only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg will be excluded.

1.7.2 Rationale for dose and regimen selection

The dose levels selected for this combination of Durvalumab and Tremelimumab were based on a recent phase 1 study (Antonio et al. ESMO 2014, poster attached), which determined the maximal tolerated dose (MTD) of the combination. The combination was found to be safe and tolerable. Based on the phase 1 study of this combination (Antonio et al. ESMO 2014), we aim to treat for a total of 12 months of therapy. This regimen was associated with continued disease control at over 32 weeks (Figure 3 of abstract), and overall response rate of 28%. In light of this information, our treatment plan includes an induction period of 4 weeks of combination therapy, followed by maintenance monotherapy with durvalumab up to 12 months total (or approximately 18 doses).

The rationale for maintenance therapy with single-agent durvalumab is based on previous experience with immunotherapies. Response to immunotherapy may be delayed compared to conventional cytotoxic chemotherapy, and even appear as pseudoprogression (radiographic increase in the size of lesion due to T lymphocyte infiltration) before patients experience durable responses; to capture these delayed responses, the immune-related RECIST criteria have been developed (PMID 19934295). Because of the delayed response to immunotherapy, this study includes additional therapy using maintenance durvalumab after the 4 cycles of combination tremelimumab with durvalumab. Furthermore, in the phase 1 study where durvalumab was investigated with tremelimumab using various schedules (Antonio et al. ESMO meeting 2014), the regimen where there was least toxicity and greatest efficacy seen was when there was an induction of durvalumab with trememlimumab for 4 cycles, followed by durvalumab maintenance to complete 12 months of therapy. Continuing tremelimumab additionally for 12 months was associated with increased toxicity, therefore, we do not propose adding trememlimumab to durvalumab to the maintenance regimen in this study.

Pseudoprogression has been well-described in various studies in investigating checkpoint inhibitors, and refers to the inflammatory response that looks like progression of disease. This phenomenon is actually seen in the phase 1 study this proposal is based on (Figure 4 on abstract), but has also been observed in numerous other trials (PMID: 21785048). It crucial for drug development of immunotherapy to capture pseudoprogression in a safe manner, therefore this proposal has been designed to anticipate pseudoprogression and allow for continued treatment provided that very specific criteria are met.

1.7.3 Rationale for Expansion Cohort

Based on initial portion of the study where the first 18 evaluable patients were investigated, a striking difference between overall response rates in ER-positive and TNBC was observed (Table 1). The ORR in ER-positive was 0%, and in TNBC it was 42.9%. Furthermore, the TNBC group had 2 patients with SD (clinical benefit rate of 71.4%), and one of the patients listed as PD, in fact had pseudoprogression (after 2 months had sub-centimeter LNs enlarge to >15mm, captured as PD per RECIST, but afterwards experience stability in these lesions, and a PR in target lesions). While the numbers are small, there is a clear signal in the TNBC cohort since essentially 6 out of 7 patient experienced clinically relevant benefit. Immunotherapy is rapidly evolving in breast cancer, and these initial results show promise in this cohort of patients, and the rationale of the expansion cohort is to capitalize on this initial experience.

Table: Summary of responses by entire cohort and subtype of breast cancer

	All patients (n=18)	TNBC (n=7)	ER+ (n=11)
PR	3	3	0
SD≥2 months	4	2	2
PD	11	2*	9
ORR	16.7%	42.9%	0%
CBR	38.9%	71.4%	18.2%

*Includes one patient with pseudoprogression (enlargement of a LN with subsequent stability), while PD by RECIST, has otherwise experienced a PR based on target lesions and has been on study for 10 months (status post cycle 15)

1.8 Rationale for Exploratory Objectives

Immune-related biomarkers
Predictive biomarkers are needed to identify which patients are more likely to experience clinical benefit. A critical barrier in the development of immunotherapies for the treatment of cancer is the identification of predictive biomarkers to therapy since to date only a small proportion of patients derive benefit to immunotherapies. While some studies have shown PD-L1 overexpression by immunohistochemistry is associated with response, other studies have shown that patients with PD-L1 negative tumors may also exhibit significant response suggesting that PD-L1 expression alone may not fully predict response to therapy [33, 34]. Therefore, more accurate biomarkers predictive of response or urgently needed [35].

Immune cells identify cancer cells by detecting antigens, termed neoantigens, expressed on cancer cells. Higher mutational burden may correlate with more diverse neoantigen landscapes and predict responses to immunotherapy in patients with melanoma and lung cancer [36, 37]. Mutational burden may also be assessed on circulating tumor DNA. Similarly, patients with mismatch repair-deficient cancers have a higher number of somatic mutations compared to those who are mismatch repair-proficient, but furthermore, they have better responses to immune checkpoint blockade [11]. Diverse neoantigen landscapes are more likely to stimulate neoantigen-specific T cells, which can be measured through T cell receptor sequencing to quantify the clonality of the T cell receptor repertoire. Preliminary studies in patients with melanoma and lung cancer suggest that patients with oligoclonal T cell receptor repertoires are more likely to respond to immunotherapy [37, 38]. These immunopharmacogenomic biomarkers may, therefore, help identify patients with breast cancer more likely to benefit from immunotherapies.

The relationship between clonal expansion of the T cell receptor repertoire has been studied in patients receiving neoadjuvant therapy in early stage breast cancer. Matched samples of patients with early stage breast cancer of various subtypes and assessed the T cell receptor populations at baseline and after various chemotherapy regimens. Using the diversity index, which assesses T cell beta-receptor clonal diversity, clonal expansion was found to be associated with complete and partial responses [39]. In addition, gene expression profiling of immune relevant genes can be modulated by immunotherapy and be associated with outcomes, including CD8, granzyme A, and perforins (Santa-Maria, unpublished).

We therefore, plan to assess the various molecular and immunogenomic markers including: circulating tumor DNA, whole exome sequeincing to assess mutational and neoantigen burde, T cell receptor sequencing to assess T cell receptor repertoires, and immune-related gene expression analysis.

Response to next line therapy
We are adding a third exploratory objective in order to capture response and duration of response to next line therapy. This is based on the fact that significant responses have been recently documented, after progression when patients are started on next line of

chemotherapy.

Objective will be to determine the response rate (RR) and duration of response (DoR) of next line therapy after progression on durvalumab/ tremelimumab study regimen, for those patients who are able to submit detailed follow up data about subsequent treatment and response.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

To evaluate Overall Response Rate (ORR) in patients with metastatic HER2 negative breast cancer treated with durvalumab in combination with tremelimumab

The primary endpoint is ORR, defined as the number(%) of patients with one visit response orpartial response (PR) or a complete response (CR) in patients with metastatic HER2 negative breast cancer (TNBC in expansion cohort) treated with durvalumab in combination with tremelimumab using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (23).

Expansion cohort

To evaluate Overall Response Rate (ORR) in patients with metastatic TNBC treated with durvalumab in combination with tremelimumab.

The primary endpoint is ORR, defined as the number of patients exhibiting partial response (PR) or a complete response (CR) using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

2.2 Secondary Objectives & Endpoints

2.2.1 To evaluate PFS and OS in patients with metastatic HER2 negative breast cancer treated with durvalumab in combination with tremelimumab.

Secondary endpoints include PFS and OS, where PFS is defined as the time from date of treatment initiation to date of documented disease progression or death (by any cause in the absence of progression), and OS is defined as the time from date of treatment initiation until death due to any cause.

2.2.2 To evaluate safety and tolerability.

The endpoints will be the number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded.

2.2.3 To evaluate clinical benefit rate in this population.

Clinical benefit rate is defined as stable disease (SD) for ≥ 12 weeks + PR + CR.

2.3 Exploratory Objectives & Endpoints

2.3.1 To evaluate if serum and tissue-based biomarkers including: circulating tumor DNA, immunohistochemical expression of PD-L1; tumor infiltrating lymphocytes (TILs); changes in tissue and peripheral T cell receptor genotype; mutational and neoantigen burden; and immune-related candidate gene expression signatures predict response to durvalumab in combination with tremelimumab.

2.3.2. To determine the response rate (RR) and duration of response(DoR) of subsequent next line therapy after progression on durvalumab/ tremelimumab study regimen, for those patients who are able to submit detailed follow up data about subsequent treatment and response.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with stage IV (metastatic) HER2 negative breast cancer (both male and female patients are eligible). This will be a single-center trial conducted at Northwestern University. The expansion cohort will only include metastatic TNBC.

Eighteen patients will be added in the first stage. If 4 or more respond, then an additional 10 patients will be added for a total of 28. A total of 30 subjects (15 ER+, 15 ER) will be needed to obtain a total of 28 evaluable patients (14ER+ and 14ER-) for this trial. The expansion cohort will include 20 evaluable patients with TNBC. Approximately 5 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Massimo Cristofanilli at (312) 695-0990.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

3.1.1 For the expansion cohort: Only metastatic TNBC patients will be enrolled.
[Please note: the General cohort had enrolled patients with the following criteria: Patients must have a histologically documented (either primary or metastatic site) diagnosis of breast cancer that is HER2 non-overexpressing by immunohistochemistry, namely 0 or 1. If they have an equivocal immunohistochemistry, 2, the tumor must be non-gene amplified by FISH performed upon the primary tumor or metastatic lesion (ratio <2 and HER2 copy number <4). ER positivity is defined as 1% or greater (29). PR positivity will be defined as a result of greater than 10%.Documentation of ER and PR status should be available at registration.]
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3.1.2 Patients must have measurable disease by RECIST 1.1 criteria.

3.1.3 Patients must be one of the following :

- Have been treated with at least one prior chemotherapy regimen in the metastatic setting
- Within 12 months of their last adjuvant systemic treatment and are felt to be chemotherapy refractory.
- PD-L1-negative in the front line setting.
  [Note: Beyond frontline, any PD-L1 status is acceptable]

  Note: please submit the PD-L1 test with the pathology report at registration.

3.1.4 Completion of prior chemotherapy systemic anticancer therapy at least 2 weeks prior to study entry.

3.1.5 Radiation therapy must be completed at least 2 weeks prior to study entry. Radiated lesions may not serve as measurable disease unless they have been radiated ≥12 months prior to enrollment.

3.1.6 Patients may have parenchymal brain metastases if stable (no evidence of progression) for at least 1 month after local therapy (radiation or surgery). Leptomeningeal disease is excluded. Must have completed any prescribed

steroid taper prior to registration

3.1.7 Patients may have had a prior diagnosis of cancer if it has been > 3 years since their last treatment.(with the exception of squamous cell carcinoma or basal cell carcinoma of the skin or cervical intraepithelial neoplasia)

3.1.8 Patients must be age ≥ 18 years; both male and female are eligible.

3.1.9 Patients must exhibit an ECOG performance status of ≤2.

3.1.10 Patients must weigh greater than 30 kg.

3.1.11 Patients must have adequate organ and bone marrow function (transfusion permitted but not GCSF) within 14 days of first dose of study drug administration, as defined below:

Hemoglobin	≥9.0g/dl
absolute neutrophil count	≥ 1,500/mcL (1.5 x 109/L)
platelets	≥ 100,000/mcl
total bilirubin	≤1.5 times the institutional upper limit of normal (ULN) (or ≤3 times ULN in case of liver metastasis)
AST(SGOT)/ALT(SPGT)	≤ 2.5 X institutional ULN (or ≤5 times ULN in case of liver metastasis)
Serum creatinine	CL>40 mL/min by the Cockcroft-Gault formula (see appendix) or by 24-hour urine collection for determination of creatinine clearance

3.1.12 Female subjects must either be of non-reproductive potential (see definition below) or must have a negative serum pregnancy test within 7 days prior to registration on study.

Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. 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).

3.1.13 Female and male patients of reproductive potential must agree to use effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 180 days after the last dose of durvalumab monotherapy, whichever is the longer time period.[Refer Section 4.5.1]

Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately
Refer to section 4.5.1 for details.

3.1.14 Willingness to provide a fresh biopsy prior to study enrollment and after 2 cycles of treatment as clinically appropriate per PI discretion

3.1.15 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study. Written informed consent and HIPAA authorization will be obtained from the subject prior to performing any protocol-related procedures, including screening evaluations

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

3.2 Exclusion Criteria

3.2.1 Patients with documented HER2-positive metastatic disease based on most recent biopsy.

3.2.2 Patients with definite liver metastasis >1cm or signs of visceral crisis or impending visceral crisis at the clinical discretion of the treating physician.

3.2.3 Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the treating physician and/or PI.
- Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the treating physician and/or PI.

3.2.4 Patients who have had chemotherapy or radiotherapy within 2 weeks prior to entering the study.

3.2.5 Current or prior use of immunosuppressive therapy within 14 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.

3.2.6 Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 2 electrocardiograms (ECGs) using Bazett's formula. Two EKGs 5 minutes (+/-2 min) apart are mandatory.

3.2.7 Receipt of live attenuated vaccination within 30 days prior to registration.

NOTE: patients should also not receive such vaccination within 30 days of receiving durvalumab or tremelimumab.

3.2.8 Patients who are taking any herbal (alternative) medicines are NOT eligible for participation. Patients must be off any such medications by the time of registration for at least 2 weeks.
NOTE: Vitamin supplements are acceptable.

3.2.9 Patients may not have received any other investigational agents within 2 weeks or 5 half lifes prior to registration, whichever is shorter.

3.2 10Prior treatment with immune therapy (including but not limited to CD137, OX40, PD-1, PD-L1 or CTLA4 inhibitors such as durvalumab and tremelimumab).

Prior severe infusion reaction to a monoclonal antibody.

3.2.11 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

- Patients with vitiligo or alopecia
- Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician and/or PI.
- Patients with celiac disease controlled by diet alone

3.2.12 Known active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and positive TB test (PPD, Quantiferon)), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies).

- Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible.
- Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

3.2.13History of allogeneic organ transplant.

3.2.14 History of hypersensitivity to durvalumab or tremelimumab or any excipient.

3.2.15 Major medical conditions that might affect study participation (uncontrolled pulmonary, renal, or hepatic dysfunction, uncontrolled infection) are not eligible. Other significant comorbid condition which the investigator feels might compromise effective and safe participation in the study.

3.2.16 Patients who have an uncontrolled intercurrent illness including, but not limited to any of the following, are not eligible:

- Symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia
- Interstitial lung disease, serious gastrointestinal conditions associated with diarrhea
- Uncontrolled pulmonary, renal, or hepatic dysfunction
- Ongoing or active infection requiring systemic treatment
- Psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent
- Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints

3.2.17 Female patients who are pregnant or nursing are not eligible.

3.2.18 Patients who are involved in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrollment or randomization in the present study.

4.0 TREATMENT PLAN

4.1 Overview

Non-randomized, open-label, pilot phase II clinical trial of durvalumab in combination with tremelimumab in patients with stage IV HER2 negative breast cancer, with an expansion cohort of TNBC.

Patients will be treated durvalumab 1500mg intravenously (IV) every 4 weeks for a total of 4 doses, and tremelimumab 75mg IV every 4 weeks for a total of 4 doses. After completion of the 4 doses of combination therapy (induction phase), durvalumab will be continued at a dose of 750mg every 2 weeks for up to 18 additional doses (maintenance phase), or until progressive disease (see 4.1.1) or unacceptable toxicity. The first 750mg dose of durvalumab will be 4 weeks after the last combination dose. Patients may continue on therapy after progression or after initial 52 week treatment period as specified in Sections 4.1.1 and 4.1.2. Patients will be followed for 3 years or until time of death. Overall response rate (ORR), clinical benefit rate, PFS, and OS will be determined. In addition, patient's next line of therapy will be monitored for response rates and duration of clinical benefit to next line therapy.

Patients will undergo a fresh tissue biopsy prior to study enrollment and two months after treatment, unless deemed to be clinically inappropriate per PI or co-investigator, to evaluate pharmacodynamic changes in immune-related biomarkers. Correlatives will be assessed.

4.1.1 Continuation of Investigational Therapy after Radiographic Progression (Pseudoprogression)

Treatment may be continued in the setting of pseudoprogression (radiographic increase or new lesions felt to be due to inflammation/immune response) as long as all of the following criteria are met:

- Absence of clinical symptoms or signs indicating clinically significant PD.
- No significant decline in Eastern Cooperative Oncology Group (ECOG) performance status (PS >2 or as deemed by treating investigator).
- Absence of rapid PD or threat to vital organs/critical anatomical sites (e.g., spinal cord compression) requiring urgent alternative medical intervention

- Patients are made aware of the potential benefits and risks of continuing study therapy in the setting of Pseudo-Progression. Patients continuing therapy in the setting of suspected pseudoprogression should continue with treatment according to whether they in the induction phase (durvalumab 1500mg intravenously (IV) every 4 weeks for a total of 4 doses, and tremelimumab 75mg IV every 4 weeks for a total of 4 doses) or maintenance phase (durvalumab 750mg every 2 weeks). For example, a patient with suspected pseudoprogression after cycle 2 of durvalumab and tremelimumab would continue onto cycle 3 of durvaluamb and trememlimumab rather than durvalumab single agent portion of the regimen (maintenance phase).

4.1.2 Continuation of Investigational Therapy after 52 Weeks

- Patients who achieve clinical benefit (CR, PR, or SD) until the end of the 52 week period may enter a follow up phase or continue durvalumab as shown in table 5.1 for up to 52 more weeks as long as they are felt to be deriving clinical benefit.
- Patients who enter follow up phase will continue to be monitored. If during the first 6 months of follow-up, patients developing PD may be re-treated with

durvalumab as shown in table 5.1. Only one 52 week retreatment period will be allowed. Patients who are restarted on durvalumab after the initial 52 week period must meet the following criteria:

- Patients must have measurable disease by RECIST criteria.
- Have not received any additional anticancer therapy, radiation, or surgery since initially stopping immunotherapy
- No evidence or clinical concern of development or progression of CNS metastasis
- No secondary cancer
- Patients must exhibit an ECOG performance status of ≤2.
- Patients must have adequate organ and bone marrow function per section 3.1.10
- Meet eligibility criteria 3.1.11-3.1.15 as applicable
- None of the exclusionary criteria with the exception of 3.2.8 only for exposure to Durvalumab, as well as 3.2.18

4.2 Treatment Administration

Agent	Dose	Route	Schedule	Cycle Length
Durvalumab	1500mg (during combination therapy), 750 mg (during monotherapy)	IV	Day 1 of each cycle for 4 cycles (during combination therapy), then every 2 weeks for up to 18 additional doses of monotherapy. The first monotherapy dose of MEDI 4736 will be 4 weeks after the last combination dose.*	4 weeks (28 days)
Tremelimumab	75mg	IV	Day 1 of each cycle for a total of 4 doses	

*Patients may continue on therapy after progression or after initial 52 week treatment period as specified in Sections 4.1.1 and 4.1.2.
**On each treatment day, hematology and serum chemistry are to be resulted before treatment can begin

4.2.1 Monitoring of Dose Administration

On infusion days, patients receiving durvalumab + tremelimumab treatment will be monitored during and after infusion of IP as presented in the bulleted list below. Supine BP will be measured using a BP recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. BP and pulse will be collected from patients receiving durvalumab + tremelimumab treatment before, during, and after each infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]).
- Approximately 30 minutes during the infusion (**halfway** through infusion).
- At the end of the infusion (approximately 60 minutes ±5 minutes).
- A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab.

If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can

- be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).
- If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

The date and time of collection and measurement will be recorded on the appropriate eCRF. Additional monitoring with assessment of vital signs is at the

discretion of the Investigator per standard clinical practice or as clinically indicated. Body weight is also recorded along with vital signs. 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.

In the event of a Grade ≤ 2 infusion-related reaction, the infusion rate of durvalumab or tremelimumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) may be administered at the discretion of the investigator. If the infusion-related reaction is severe or prolonged (≥Grade 3), methylprednisolone 100 mg (or the equivalent) should be administered as well. Investigators may administer steroids per protocol guidelines (see Section 4.3) or at their discretion as clinically indicated in consultation with the study team.

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.

4.3 Toxicity Management & Dose Delays/Modifications

Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table). Toxicity will be assessed according to the NCI CTCAE V4.03.

Since the mechanism of action of both durvalumab and tremelimumab leads to T-cell activation and proliferation, immune related adverse events (irAE) may be observed, and be similar to that of other PD-1/PD-L1 checkpoint inhibitors, and may include immune-mediated pneumonitis, enterocolitis, dermatitis, hepatitis, and endocrinopathies (12, 16). Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (i.e. infection or PD), an immune-mediated etiology should be considered for signs or symptoms of pneumonitis, enterocolitis, dermatitis, hepatitis, and endocrinopathy. In addition to the dose modifications shown in Table 2, it is recommended that management of irAEs follow the guidelines outlined for other immune checkpoint inhibitors (31). These guidelines recommend the following:

- Subjects should be evaluated to identify any alternative etiology
- In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be 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 (i.e. infliximab, mycophenolate mofetil, etc.) should be considered for events not responding to systemic steroids

If the investigator has any question in regard to an AE being an irAE, the investigator should immediately contact the principal investigator. Treatment modifications will not be required for AEs that are clearly not attributed to investigational drugs (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Treatment modifications may be required in the event of treatment-related toxicity. General guidelines regarding treatment modification are provided in Table 2. **Doses may be held according to Table 2, there are no dose adjustments. Toxicities are attributed to respective drugs (durvalumab or tremelimumab).** All toxicities will be graded according to NCI CTCAE V4.03 (Appendix B).

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) 17 October 2019 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03 (unless indicated otherwise). In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2.0×ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis,	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – 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. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., 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 (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.

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) 17 October 2019 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	− With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. − Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., 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.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated 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/Interstitial Lung Disease (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 consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity 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 (e.g., 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 methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is 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-PJP treatment (refer to current NCCN guidelines for

			treatment of cancer-related infections)[a] – Consider Pulmonary and Infectious Disease consults. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., 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 (e.g., 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 patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of

		perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: symptomatic; medical intervention indicated*) * "medical intervention" is not invasive	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity 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 (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV 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 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day;	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days;	**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

	Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated) *This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective	study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	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 (e.g., 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. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	AST or ALT >ULN and ≤3.0×ULN if	• No dose modifications. • If it worsens, then treat as described	– Continue LFT monitoring per protocol.

baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB > ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal	for elevations in the row below.	
AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal	• Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal. • If toxicity worsens, then treat as described for elevation in the row below. • If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up 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 (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
AST or ALT >5.0×ULN if baseline normal, >5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal;	For elevations in transaminases ≤8×ULN and/or in TB ≤5×ULN if baseline normal, or for elevations in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal: • Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT	– 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 (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate.

>3.0×baseline if baseline abnormal	≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days For elevations in transaminases >8×ULN or elevations in TB >5×ULN if baseline normal, or for elevations in transaminases >8×baseline and/or TB >5×baseline if baseline abnormal, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

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 (e.g., 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 (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Grade 1 (Serum creatinine > 1 to 1.5×baseline; > ULN to 1.5×ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine >3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV

creatinine >6.0×ULN)			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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., 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, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – 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, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood

		sample for appropriate autoimmune antibody testing.
Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1.The event stabilizes and is controlled. 1. The patient is clinically stable as per investigator or treating physician's clinical judgement. 2. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[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	**For Grade 3 or 4:**

		than hypothyroidism and Type 1 diabetes mellitus, 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1.The event stabilizes and is controlled. 1. The patient is clinically stable as per investigator or treating physician's clinical judgement. 2. Doses of prednisone are ≤10 mg/day or equivalent.	– Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
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 (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology 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:** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., 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 (e.g., 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 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., 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 (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult.
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:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such

		decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be 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 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** − Consider, as necessary, discussing with study physician. − Recommend hospitalization. − Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory [e.g., BNP] or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.

	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation.

		– Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	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.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]	
Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]	

[a]ASCOEducational 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; imAE immune-mediated 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; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); 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 (e.g., 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 (e.g., 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 (e.g., 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 (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

4.4 Concomitant Medications/Treatments

The 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 appropriate eCRF. Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Table 2 for guidance on management of IP-related toxicities.

Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *short-term premedication for patients receiving combination agent where the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions* • *Use in patients with contrast allergies.* • *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc).*
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)

Rescue Medications

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

4.5 Other Restrictions During the Study

4.5.1 Birth control

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

Female patient of child-bearing potential

- 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 1) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. 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.

Male patients with a female partner of childbearing potential

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.
- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

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 1. Note that some contraception methods are not considered highly effective (eg. 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 1. Highly effective methods of contraception (<1% failure rate)

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

[a] This is also considered a hormonal method

4.5.2 Blood donation

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

4.6 Duration of Therapy

Patients may continue for 12 months of treatment or until any of the following occur:

- Disease progression
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the as a whole study
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.7 Duration of Follow Up

After patients come off treatment they will be followed up at 3, 6, 9, 12 months and then every 6 months for 3 years for survival and progression of disease.

4.8 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF. In general, patients who are permanently discontinued from receiving investigational product will be followed for disease progression, survival, and safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or administered subsequent therapy (see below). Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Patients will be permanently discontinued from study treatment and will not receive any

further investigational product if any of the following occurs for the subject in question:

- Patient voluntarily withdraws from treatment (follow-up observation is permitted)
- Patient is unable to comply with protocol requirements
- Patient experiences Grade ≥ 3 infusion reaction
- Patient experiences an adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant or intends to become pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study

Patients will not receive any further investigational product or further study observation if any of the following occurs for the subject in question:

- Patient becomes lost to follow-up (LTF)
- Patient withdraws consent
- Patient initiates an alternative anticancer therapy including another investigational agent

4.9 Patient Replacement

If a patient is enrolled in the study but comes off study before cycle 1 day 1 of treatment, the patient may be replaced.
A patient who does not reach the first imaging assessment at 2 months for reasons other than clinical progression will not be used toward assessment of the primary clinical endpoint (ORR), PFS or OS. However, they will be included in the final safety analysis. Additional patients may be added if needed for assessment of response.

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5.0 STUDY PROCEDURES

Visit Number	1	2	3	4	5	6	7	8	9	10	11	x	x + 1	x + 2	x + 3	x + 4
Procedure/Study Day	SV[9]	D1	D14 (±3D)	W4 (±3D)	W8 (±3D)	W12 (±3D)	W16 (±3D)	W18 (±3D)	W20 ** (±3D)	W22 (±3D)	W24 (±3D)	Off Treatment[8]	3M (±1 month)	6M ±1 month)	9M (±1 month	12M + q6M (±1 month)
Informed consent	X															
Durvalumab 1500mg		X		X	X	X										
Durvalumab 750mg							X	X	X	X	X					
Tremelimumab 75mg		X		X	X	X										
CT chest, abdomen, pelvis; nuclear bone scan[1, 9]	X				X		X				X	X				
Assessment of AEs/SAEs[15]		X	X	X	X	X	X	X	X	X	X	X	X			
Concomitant medications (including next line therapy after off treatment, response)	X	X	X	X	X	X	X	X	X	X	X	X	X			
Physical examination[10], weight	X		X	X	X	X	X		X		X	X	X	X	X	X
Height (prior to dosing)	X															
ECOG performance status	X			X	X	X	X		X		X	X	X	X	X	X
12-lead Electrocardiogram[11]	X															
Vital signs[12]	X	X	X	X	X	X	X	X	X	X	X	X				
Urinalysis[2]	X															
Hepatitis serologies[13]	X															
HIV antibody	X															
Pregnancy test[3]	X															
Serum chemistry[4]	X	X	X	X	X	X	X	X	X	X	X	X	X			
lactate dehydrogenase, GGT, lipase, uric acid and amylase[4]	X	X	X	X	X	X					X	X				
Hematology[5]	X	X	X	X	X	X	X	X	X	X	X	X	X			
Coagulation parameters[6]	X			X	X							X				
Thyroid function tests[7]	X	X		X	X	X					X	X				
Research blood samples[14]	X				X							X[18]				
Tumor biopsy[16]	X				X							X				

**** Visits 8 through 11 will repeat for a total of up to 18 doses of durvalumab, or until progressive disease (see 4.1.1) or unacceptable toxicity, with CTs and bone scan done every 8 weeks.** Scans are to be completed every 8 weeks, regardless of drug holds or treatment delays. **(Note: Bone scans will be done only if the patient has bone disease. PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a patient's disease. The same modality used at baseline should be used throughout). Patients may continue on therapy after progression or after initial 52 week treatment period as specified in Sections 4.1.1 and 4.1.2. Abbreviations: SV (screening visit)**

1 The same modality used at baseline should be used throughout. CT must have contrast, MRI with contrast is acceptable alternative if the patient is allergic to CT contrast. Scans are required to be completed every 8 weeks, regardless of drug holds or treatment delays.
(Note: Bone scans will be done only if the patient has bone disease. PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a patient's disease. The same modality used at baseline should be used throughout.) For patients with skin lesions, photographs may be taken on study-provided camera by study staff on a white background (wall of patient room) using a ruler measurement on a study supplied digital camera. Photographs should not include any identifying characteristics. (Please refer to section 6.1.1 for details)

2 Urinalysis will include color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin, and microscopy including WBC/high power field (HPF), RBC/HPF.

3 Serum beta-human chorionic gonadotropin (at screening only) for females of child-bearing potential (as indicated) within 7 days of registration.

4 Serum Chemistry Panel will include calcium, chloride, magnesium, creatinine, sodium, potassium, blood urea nitrogen, bicarbonate, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, total protein and creatinine clearance. . If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. Additional chemistry labs will include: lactate dehydrogenase (LDH), GGT, lipase, uric acid and amylase. During combination therapy, these labs should be monitored prior to each dose; during maintenance monotherapy, labs should be monitored every 8 weeks.

5 Hematology will include basophils, eosinophils, lymphocytes, platelet count, monocytes, neutrophils, red blood cell count, total white cell count, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, and hemoglobin.

6 Coagulation parameters will include prothrombin time, partial thromboplastin time, and fibrinogen.

7 Thyroid function tests will include thyroid stimulating hormone, free T3, and free T4. During combination therapy, these labs should be monitored prior to each dose; during maintenance monotherapy, labs should be monitored every 8 weeks.

8 Patients will be followed by routine clinic visit or phone call at 3, 6, 9, 12 months and then every 6 months for 3 years total from the end of treatment to document survival and disease progression.

9 The maximum time interval between Screening Visit/ baseline study procedures and the first dose of study drug will be 14 days. Systemic imaging (CTs, bone scan or PET-CT) and consent may be performed up to 28 days prior. Note: Bone scans will be done only if the patient has bone disease. PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a patient's disease. The same modality used at baseline should be used throughout.

10 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

11 Resting 12-lead ECGs (x2, 5 minutes [+/-2 min] apart) 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, 2 ECG's will be obtained on which QTcF must be <470 ms. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

12 Vital signs (blood pressure [BP], pulse, temperature) will be evaluated according to the assessment schedules outlined in Section 4.2.1).
13 Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
14 80 mL of whole blood should be collected in eight 10 mL plastic lavender top tubes (K2EDTA)
15 AE/SAE will be recorded from time of signature of informed consent, throughout treatment period, including the follow-up period (90 days after the last dose of durvalumab/tremelimumab)
16 tumor biopsy is mandatory prior to study enrollment and after 2 cycles of treatment (as clinically appropriate by PI discretion). At progression patients will be offered an optional biopsy. *(Note: If it is felt to be clinically inappropriate to biopsy the patient, then this should be clearly documented in the patient's chart and CRF. This documentation should also be printed and flagged in the patient's research chart)*.
[17] On each treatment day, hematology and serum chemistry are to be resulted before treatment can begin.

5.1 Study Procedures After 52 Weeks of study treatment

(For patients who are continuing treatment or re-starting treatment after progression of disease after 52 weeks, this table should not be used for patients who stay on therapy due to pseudoprogression)

Visit Number	1	2	3	4	5	6
Procedure/Study Day	Re-Evaluation before re-treatment	D1 **	D14 (±3D)	W4 (±3D)	W6 (±3D)	W8 *** (±3D)
Durvalumab 750mg*		X	X	X	X	X
CT chest, abdomen, pelvis; nuclear bone scan[1, 6]	X					X
Assessment of AEs/SAEs	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X
Physical examination[7], weight	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X
Vital signs[8]	X	X	X	X	X	X
Serum chemistry[2]	X	X		X		X
lactate dehydrogenase, GGT, lipase, uric acid and amylase[2]	X	X				X
Hematology[3]	X	X		X		X
Coagulation parameters[4]	X	X				X
Thyroid function tests[5]	X	X				X

* Treatment for this patient population will be Durvalumab monotherapy. On each treatment day, hematology, serum chemistry are to be resulted before treatment can begin.

**** The maximum time interval between re-evaluation study procedures and the first dose of study drug will be 14 days**

***** Visits 2 through 6 will repeat for a total of up to 26 doses of durvalumab (52 weeks of therapy total), or until progressive disease (see 4.1.1) or unacceptable toxicity, with CTs and bone scans done every 8 weeks**. Scans are to be completed every 8 weeks, regardless of drug holds or treatment delays.

[1] The same modality used at initial baseline should be used. Scans to be completed every 8 weeks, regardless of drug holds or treatment delays.

Note: Bone scans will be done only if the patient has bone disease. PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a

patient's disease. The same modality used at baseline should be used throughout. For patients with skin lesions, photographs may be taken on study-provided camera by study staff on a white background (wall of patient room) using a ruler measurement on a study supplied digital camera. Photographs should not include any identifying characteristics

[2] Serum Chemistry Panel will include calcium, chloride, magnesium, creatinine, sodium, potassium, blood urea nitrogen, bicarbonate, glucose, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), albumin, total protein and creatinine clearance. If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. Additional chemistry labs will include: lactate dehydrogenase, GGT, lipase, uric acid and amylase. During maintenance monotherapy, labs should be monitored every 8 weeks.

[3] Hematology will include basophils, eosinophils, lymphocytes, platelet count, monocytes, neutrophils, red blood cell count, total white cell count, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, and hemoglobin.

[4] Coagulation parameters will include prothrombin time, partial thromboplastin time, and fibrinogen.

[5]Thyroid function tests will include thyroid stimulating hormone, free T3, and free T4.

[6]Systemic imaging (CTs, bone scan or PET-CT) may be performed up to 28 days prior to D1. Refer to footnote 1 for instructions regarding bone scan, PET-CT and skin lesions.

[7]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] Vital signs (blood pressure [BP], pulse, temperature) will be evaluated according to the assessment schedules outlined in Section 4.2.1.

6.0 ENDPOINT ASSESSMENT

6.1 Definitions

6.1.1 Measurable Lesions

Must be accurately measured in at least one dimension (greatest diameter) with a minimum size of 10mm by CT scan (cuts of 5mm or less), MRI, or physical exam (ideally using calipers). Bone only disease is allowed, however, must have an osteoblastic component that can be easily measured.

Note: In case of skin lesions, patients will have standardized digital photography of their disease site for disease assessment. Photographs will be taken at the same time points as the CT scans (as indicated in the study procedures table in Section 5). Frontal and lateral photographs will be taken by study staff on a white background (wall or curtain in patient room) using a ruler measurement on a study supplied digital camera. Photographs should not include any identifying characteristics.

6.1.2 Non-measurable Lesions

Defined as all other lesions less than 10mm. Examples of non-measurable lesions include leptomeningeal disease, ascities, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin or lung.

6.1.3 Response criteria

Complete Response - Disappearance of all lesions.

Partial Response - At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease - At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression.)

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

6.1.4 Immune-related RECIST

In addition to above, tumor response will be assessed by the irRECIST for investigational purposes, not assessment of primary objective (25). Tumor response by irRECIST is defined as an immune-related PR (irPR) or CR (irCR) over a period of at least 4 weeks. We will define immune-related clinical benefit rate as immune-related stable disease (irSD), irPR, or irCR.

6.2 Primary Endpoint

The primary endpoint is Overall Response Rate (ORR), defined as number (%) of patients with one visit response of partial response (PR) or a complete response (CR) in patients with metastatic HER2 negative breast cancer (TNBC in expansion cohort) treated with durvalumab in combination with tremelimumab using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (23). Patients who experience pseudoprogression and have subsequent response may count toward ORR. Evaluable patients must have had received 2 cycles of therapy and had 2 month scans.

6.3 Secondary Endpoints

Secondary endpoints include PFS and OS, where PFS is defined as the time from date of treatment initiation until date of documented disease progression or death (by any cause

in the absence of progression), and OS is defined as the time from date of treatment initiation until death due to any cause.

Clinical benefit rate will be assessed and defined as SD (for ≥ 12 weeks) + PR + CR. Any patient who has completed two months of study therapy is evaluable for this end point

The number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded. Any patient treated with minimum 1 dose of either study drug will be evaluable for toxicity.

6.4 Exploratory Endpoints

Biomarkers predictive of response include assessment of serum or tissue-based markers including but not limited to: circulating tumor DNA, immunohistochemical expression of PD-L1; TILs; changes in tissue and peripheral T cell receptor sequencing, mutational and neoantigen burden, and immune-related candidate gene signatures at baseline.

To determine the response rate (RR) and duration of response(DoR) of next line therapy after progression on durvalumab/ tremelimumab study regimen, for those patients who are able to submit detailed follow up data about subsequent treatment and response.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires high level monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for time points). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death.

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

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

7.2 Definitions & Descriptions

7.2.1 Adverse Event

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6 (R1) defines an adverse event (AE) as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the medicinal product.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement.

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

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

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

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

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4.03 is available at http://ctep.cancer.gov/reporting/ctc.html

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through 30 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in *death*.**
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is immediately life-threatening.**
  The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires *in-patient hospitalization* or *prolongation of existing hospitalization* for ≥ 24 hours.**
- ***Results in* persistent or significant disability or incapacity.**
- **Is a *congenital anomaly/birth defect.***
- **Is an *important medical event*.**
  Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".
  For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

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

7.2.4 Exceptions to AE and SAE definitions

Generally speaking, any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, as described above. Likewise, any condition responsible for surgery should be documented as an AE if the condition meets the criteria for an AE. However, for the purposes of this study, neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as AEs or SAEs under the following circumstances:

- Hospitalization or prolonged hospitalization is for a diagnostic or elective surgical procedure for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization is required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization is required for study-directed therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the principal investigator.
- Hospitalization or prolonged hospitalization is due to social reasons (i.e. awaiting transport home).
- Pregnancy is not considered a serious adverse event, any patients who become pregnant during the study should discontinue the study immediately. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant either during the treatment phase of the study or within 30 days or five half-lives after the treatment period, whichever is longer.

7.2.5 Durvalumab & Tremelimumab Adverse Events of Special Interest (AESI)

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

AESIs for durvalumab ± 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-mediated adverse event (imAE) is defined as an AESI 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 imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab ± tremelimumab include but are not limited to:

- Diarrhea/Colitis
- Intestinal perforation
- Pneumonitis
- ALT/AST increases/hepatitis/hepatotoxicity
- Neuropathy/neuromuscular toxicity (eg. Guillain-Barré syndrome, and myasthenia gravis)
- Myositis/polymyositis
- Endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, and hyper- and hypothyroidism, Type I diabetes mellitus)
- Rash/Dermatitis
- Myocarditis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)
- Other inflammatory responses that are rare with a potential immune-mediated etiology are also considered as AESIs and include, but are not limited to, pericarditis, sarcoidosis, and uveitis and other events involving the eye, skin, hematological and rheumatological events. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

The following are more details on specific AESIs:

7.2.5.1 Pneumonitis

Across the durvalumab monotherapy pooled dataset pneumonitis events observed (pneumonitis, ILD, acute interstitial pneumonitis and pulmonary fibrosis) were reported at a frequency rate of Common (98/1889; 5.2%). Adverse events of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with anti-PD-1 and anti-PD-L1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic
severe bacterial pneumonia [40]. Early consideration of pneumonitis should be realised when patients present with new onset or worsening of respiratory symptoms such as dyspnea or cough. Prompt treatment with steroids is important as per current established toxicity management guidelines. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Table 1.

7.2.5.2 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.

7.2.5.3 Hypersensitivity reactions

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

7.2.5.4 Hepatic Function Abnormality

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in bilirubin to greater than 2 × ULN. Examples of hepatitis abnormality are autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatoxicity resulting in hyperbilirubinemia. 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 investigational product. Guidelines for management of patients with hepatic function abnormality are provided in Table 1.

7.2.5.5 Gastrointestinal disorders

Diarrhea/colitis: is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy, but may also be related to durvalumab. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. There were no CTC Grade 4 or 5 events from the pooled dataset, however, fatal events of colitis have been reported with durvalumab in combination with tremelimumab. Guidelines on management of diarrhea and colitis in patients receiving tremelimumab are provided in Table 1.

- **Intestinal perforation**

  Across the durvalumab monotherapy pool of studies, intestinal perforation was reported at a frequency rate of Uncommon (2/1889; 0.1%); CTCAE Grades 2 and 4. There were no Grade 5 events.

  In the durvalumab + tremelimumab combination pooled dataset, intestinal perforation was reported in 3/1088 patients (0.3%; Uncommon) and large intestine perforation was reported in

4 patients (0.4%; Uncommon). All events were CTCAE Grade 4 or 5 in severity. One patient from study D4190C00010 died due to the event of intestinal perforation and had concurrent peritonitis/Grade 4 sepsis; autopsy was not performed. Another patient died due to the event of large intestine perforation and disease progression (Study D4190C00006). Both cases were not considered as treatment-related by the Investigator.

Monitor for symptoms that may be related to bowel perforation such as sepsis, peritoneal signs, and ileus (refer to the Toxicity Management Guidelines for diarrhoea/colitis). Investigators should adhere to the overall management for immune-mediated toxicities by performing a thorough evaluation to rule out alternative aetiologies and by initiating prompt treatment including steroids.

7.2.5.6 Endocrine disorders

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

7.2.5.7 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Pancreatitis is an inflammatory condition of the pancreas that typically manifests initially as asymptomatic elevations of amylase and lipase in patients treated with immune checkpoint inhibitors. Across the 1889 patients in the monotherapy program, events of pancreatitis were Uncommon to rare. Four patients (0.2%) experienced pancreatitis (CTC Grade 2, Grade 3 and Grade 4 in severity) and 1 patient (<0.1%) with CTC Grade 3 acute pancreatitis. Elevations in amylase and lipase were reported at a frequency rate of Uncommon (0.6% and 0.5%, respectively). In ongoing sponsored studies with durvalumab + tremelimumab therapy in 1088 patients, events of pancreatitis were Uncommon; pancreatitis was reported in 10 patients (0.9%) with 5 of these CTC Grade 3 in severity. Elevations in amylase and lipase were reported at a frequency of Common (91 patients; 8.4% and 101 patients; 9.3%, respectively). Most events of amylase increased were Grades 1 and 2 in severity while events of lipase increased tended to be more severe (Grade 3 and Grade 4) with the combination.
Patients should be monitored for signs and symptoms of pancreatitis including Grade 3 or 4
elevations in lipase and/or amylase. Close monitoring, early detection and prompt treatment of these events are important.

Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Table 1.

7.2.5.8 Neurotoxicity

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

Myositis/polymyositis

In the durvalumab pool of studies as of the DCO, 3 patients (0.2%) reported the event of myositis, including 1 CTCAE Grade 3 in severity. Outside of the pooled dataset, there were 2 fatal events of polymyositis considered as treatment-related by the Investigator.

In the durvalumab + tremelimumab combination pool, Grade 3 myositis event were reported in 1 patient (<0.1%). In addition, there were 4 SAEs of myositis reported from studies outside of the pooled dataset. Grade 2 polymyositis was reported in 1 patient (<0.1%) from the combination pooled dataset and 2 additional patients (1 each retrieved from the global safety database and a study outside of the pooled dataset). The severity of these events were Grade 3 and Grade 5 with the latter patient having died due to the event of polymyositis which was considered related by the Investigator. Autopsy showed polymyositis involving the diaphragm and chest wall muscles.

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative aetiologies and initiating prompt treatment with steroids and modification of study drug dose regimen depending on the severity of the event. Refer to the Toxicity Management Guidelines.

7.2.5.9 Nephritis

Immune-mediated renal events include nephritis. Management of patients with immune-related nephritis are provided in Table 1.

7.2.5.10 Dermatitis

Immune-mediated rashes can occur such as dermatitis. Management guidelines of immune-related dermatitis are reviewed in Table 1.

Myocarditis

Across the durvalumab monotherapy pool of studies, as of the DCO of 12 July 2017 there has been 1 serious report of CTC Grade 3 myocarditis and 2 additional cases (Grade 3 and Grade 4) outside of the pooled dataset. In all cases the patients recovered or were improving with corticosteroid therapy.

Across the durvalumab plus tremelimumab combination pool of studies as of 12 July 2017 there has been 1 report of myocarditis. In addition myocarditis has been reported in 4 patients from clinical studies outside of the pooled dataset: 3 patients receiving durvalumab plus tremelimumab (1 of which resulted in a fatal outcome not considered related by the Investigator) and 1 patient receiving durvalumab plus tremelimumab in combination with cytotoxic chemotherapy agents, etoposide and carboplatin (which resulted in a fatal outcome).

Investigators should be aware of such rare, but severe immune-mediated adverse events including myocarditis with its presenting signs/symptoms (eg, decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block).

For patients with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection) and the appropriate management that includes discontinuing drug (permanently if event progresses to Grade 3 or 4) and the prompt use of steroids or other immunsosuppressives.

For rapid recovery of Grade 1 and 2 events, re-expose with treatment is possible. Patients with pre-existing cardiac disorders should be closely monitored for deterioration in their cardiac condition, which could suggest new onset myocarditis.

7.2.5.11Immune-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).
- If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the treating physician.

7.2.5.12 Other rare or less frequent AESIs and immune-mediated adverse events

Events with an inflammatory or immune mediated mechanism could occur in nearly all organs.
Inflammatory events that are less frequent with a potential immune-mediated aetiology are also considered as AESIs and include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye (eg, keratitis and optic neuritis), skin (eg, scleroderma and vitiligo), haematological (eg, haemolytic anaemia and, immune thrombocytopenic purpura) and rheumatological events (polymyalgia rheumatic and autoimmune arthritis).

7.2.6 Other events requiring immediate reporting

7.2.6.1 Overdose

An overdose is defined as a patient 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 patient with the durvalumab + tremelimumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (refer section 7.3.3.4). If the overdose results in an AE, the AE must also be recorded on the AE eCRF. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

7.2.6.2 Pregnancy

Maternal exposure

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

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

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it. The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.(refer section 7.3.3.4).

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.
Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period 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.

7.2.6.3 Hepatic Function Abnormality

Hy's Law: Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs.
Hepatic function abnormality (as defined in Section 10.1.3.) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (refer section 7.3.3.4), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

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

no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay. Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor and AstraZeneca/MedImmune

7.2.8 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

1) Identify the type of adverse event using the NCI CTCAE v 4.03.
2) Grade the adverse event using the NCI CTCAE v 4.03.
3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
   - Definite: AE is clearly related to the study treatment.
   - Probable: AE is likely related to the study treatment.
   - Possible: AE may be related to the study treatment.
   - Unlikely: AE not likely to be related to the study treatment.
   - Unrelated: AE is clearly NOT related to the study treatment.
4) Determine the prior experience of the adverse event.
   Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
   - the current protocol
   - the drug package insert
   - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned Quality Assurance Monitor (QAM) within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required.

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- AE (verbatim)
- A description of the event, severity, treatment, and outcome (if known)
- The date when the AE started and stopped

- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

The following variables will be collected for SAEs as applicable:

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

7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs (if applicable).

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject while on treatment regardless of expectedness or relationship to study drug will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 5 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 Reporting to the FDA (completed by the NU QAM)

The NU QAM will handle all FDA reporting in accordance with the following:

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 Reporting to Medimmune

All deaths that occur during the study, or within the protocol-defined 30-day

post-last dose of durvalumab + tremelimumab safety follow-up period must be reported to AstraZeneca 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 AstraZeneca as a SAE within **24 hours** (see Section **Error! Reference source not found.** 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.

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

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

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

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-14-10694 (D4190C00030)

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

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

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the FDA.
Serious adverse events that do not require expedited reporting to the FDA still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

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

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

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.

8.0 DRUG INFORMATION

8.1 Durvalumab

8.1.1 Other names

MEDI4736

8.1.2 Classification - type of agent

Durvalumab is a human IgG1κ mAb.

8.1.3 Mode of action

Durvalumab, a human IgG1κ mAb directed against PD-L1, and with reduced binding to C1q and the Fcγ receptors

8.1.4 Storage and stability

All investigational products should be kept in a secure and dry place. Vials should be stored at 2°C to 8°C (refrigerated) and not be frozen.

8.1.5 Protocol dose specifics

Doses of 1500mg for patients (>30 kg) will be administered using an intravenous (IV) bag containing 0.9% (weight/volume) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) 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.

If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg Q4W. The appendix includes an example of a weight-based dose calculation. (Appendix C).

For 1500mg durvalumab dose (patients > 30kg), add 30.0 mL of durvalumab (MEDI4736) (ie, 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

For the 750mg durvalumab maintenance dose, add 15.0 mL of durvalumab (MEDI4736) (ie, 750mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 20 mg/mL, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag. Weight based dosing is not required for the 750mg durvalumab dose.

Patients will be treated with durvalumab 1500mg intravenously (IV) every 4 weeks for a total of 4 doses (along with tremelimumab 75mg IV every 4 weeks for a total of 4 doses). After completion of the 4 doses of combination therapy, durvalumab will be continued at a dose of 750mg every 2 weeks for up to 18 additional doses.

8.1.6 Preparation

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the investigator as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL.

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total in-use storage time from needle puncture of durvalumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

8.1.7 Route of administration for this study

The liquid product is to be diluted with 0.9% (w/v) saline or 5% (w/v) dextrose for IV infusion.

8.1.8 Incompatibilities

No formal drug-drug interaction studies have been conducted with durvalumab. There are no known clinically significant interactions of durvalumab with other medicinal products.

8.1.9 Availability & Supply

Durvalumab will be supplied by AstraZeneca as a 500-mg vial concentrate solution for infusion. Investigational products will be supplied by Medimmune in containers with identical appearances in coded kits for each product respectively. Each investigational product kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each container within the carton). Each carton and vial is labeled with the same unique sequence number range. MEDI4736 will be supplied in liquid form.

Durvalumab will be provided to Northwestern University by MedImmune, Northwestern University will request durvalumab submitted via email indicating the amount of bottles required to the contact below:

Linda M. Hall
Sr. Clinical Project Manager
HallL@medimmune.com
P: 301-398-5419| F: 301-398-9435

Please allow approximately 10 days for drug delivery.

8.1.10 Side effects

Below safety data from 393 subjects with various types of cancer who received Durvalumab alone is provided. **Related** side effects reported in subjects receiving durvalumab alone were:

Frequent - Expected to occur in 10% to 25% of people (10 to 25 out of 100 people): Fatigue (13.5%)

Not Frequent – Expected to occur in 2% to less than 10% of people (2 to less than 10 out of 100 people): Nausea (8.4%), Diarrhea (5.3%), Decreased appetite (5.3%), Rash (5.3%), Vomiting (4.8%), Itchiness (4.1%), Difficulty breathing (3.8%), Fever (3.1%), Low thyroid (2.8%), Increased liver enzymes (2.5%), Cough (2.5%), Muscle pain (2.3%), Stomach pain (2.0%), Dizziness (2.0%). In addition, productive cough,dysphonia, abdominal pain, blood TSH increase/decrease, hypophysitis, dysuria, night sweats, pyrexia, oedema peripheral, upper respiratory tract infections, pneumonia, oral candidiasis,dental and oral soft tissue infections, influenza, myalgia, myositis and polymyositis have been identified as adverse drug reactions.

Related and **serious** side effects reported in subjects receiving durvalumab alone were:

- Blockage in the urinary tract
- Fluid in the space surrounding the lung and inflammation of the lung
- Increase in calcium in the blood
- Joint pain
- Worsening of cancer
- Increase in liver enzymes and blockage of the tract between the liver and small intestine
- Spinal cord swelling
- Irregular heart beat or rhythm
- Chest pain and fluid in the abdomen
- Dehydration
- Disorder in the blood vessels of the organs
- Swelling of the tumor
- Lack of muscle control during walking or picking up objects

There was one death felt to be related to durvalumab when administered alone. The subject who had a prior history of cardiac illness including a prior heart attack died due to a disorder of the blood vessels. The Study Doctor also indicated possible other causes of the fatal event.

8.1.11 Nursing implications

Durvalumab will be administered as an IV infusion over approximately 1 hour in duration (± 5 minutes). If the infusion is less than 55 minutes or more than 65 it is considered a deviation. The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour (± 5 minutes) for each infusion. Refer to Section 4.2.1 for monitoring of vitals.

Since the compatibility of durvalumab with other IV medications and solutions, other than normal saline (0.9% [w/v] sodium chloride for injection) and 5% (w/v) dextrose, is not known, the durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered. No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. The date, start time, interruption, and completion time of

durvalumab administration must be recorded in the source documents.

In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

8.1.12 Return and Retention of Study Drug

All unused investigational products will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy.

8.2 Tremelimumab

8.2.1 Other names

n/a

8.2.2 Classification - type of agent

Tremelimumab is being developed as an immunotherapeutic agent for various cancers.

8.2.3 Mode of action

Tremelimumab is a human IgG2 anti-CTLA-4 mAb.

8.2.4 Storage and stability

Investigational product must be stored at 2 to 8 degrees Celsius and must not be frozen.

8.2.5 Protocol dose specifics

Tremelimumab 75mg IV every 4 weeks for a total of 4 doses for patients > 30kg.

A dose of 75 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 3.8 mL (ie,75 mg of tremelimumab, with the dose volume rounded to the nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 1mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of tremelimumab 75 mg Q4W. The appendix includes an example of a weight-based dose calculation. (Appendix D)

8.2.6 Preparation

The dose of 75 mg of tremelimumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total in-use storage time from needle puncture of tremelimumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2ºC-8°C (36ºF-46°F). If storage time exceeds these limits, a new dose must be prepared from new vials. The infusion solution in the prepared final IV bag should be equilibrated to room temperature prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

8.2.7 Route of administration for this study

IV

8.2.8 Incompatibilities

No formal drug-drug interaction studies have been conducted with tremelimumab. However, in RCC studies, acute renal failure has been reported with the combination of tremelimumab and sunitinib. It is unknown whether a similar reaction will be observed when tremelimumab is combined with other tyrosine kinase inhibitors.

8.2.9 Availability & Supply

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

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Tremelimumab will be provided to Northwestern University by MedImmune., Northwestern University will request tremelimumab submitted via email indicating the amount of bottles required to the contact below:

Linda M. Hall
Sr. Clinical Project Manager
HallL@medimmune.com
P: 301-398-5419 F: 301-398-9435

Please allow approximately 10 days for drug delivery.

8.2.10 Side effects

Below are safety data from 973 subjects with various types of cancer who received tremelimumab alone. Related side effects reported in subjects receiving tremelimumab alone were:

Very Frequent – Expected to occur in more than 25% of people (more than 25 out of 100 people): Diarrhea (41.2%), Rash (27.2%), Itching (25.1%)

Frequent - Expected to occur in 10% to 25% of people (10 to 25 out of 100 people): Fatigue (23.8%), Nausea (21.9%), Vomiting (13.5%), Decreased appetite (11.3%)

Not Frequent – Expected to occur in more than 5% to less than 10% of people (more than 5 to less than 10 out of 100 people): Headache (7.2%), Fever (7.0%), Stomach pain (6.7%), Inflammation of the large intestine (5.5%)

Related and serious side effects reported in more than 1% of people (more than 1 out of 100 people) receiving tremelimumab alone were: Diarrhea (9.2%), Inflammation of the large intestine (3.6%), Vomiting (2.3%), Nausea (1.8%), Dehydration (1.8%)

Deaths thought to be related to tremelimumab when given alone were reported in approximately 0.5% of subjects treated (approximately 1 out 200 people). There were five deaths reported that were thought to be related to side effects caused by tremelimumab. The deaths per subject are summarized with the causes noted (where known):

- Sudden death in a subject with advanced skin cancer who had a history of smoking. The subject had a family history of sudden cardiac death and had recently changed antidepressant medications. While on tremelimumab treatment, the subject had symptoms that might be consistent with decreased blood flow to the heart. However, the exact cause of death was not confirmed.
- Lack of oxygen to the brain due to sudden and unexpected loss of heart function in a subject whose skin cancer had spread to the lungs. The subject had a history of medical conditions that could increase the risk for heart problems including diabetes, increased blood pressure, elevated levels of fat in the blood and diarrhea. One week before loss of heart function, the subject experienced kidney failure, dehydration, fever and increased creatinine (a compound in the blood removed by the kidney that when high can indicate poor kidney function). The study doctor thought there was a possibility that the side effects and loss of heart function could be related to tremelimumab.
- Imbalance of essential minerals necessary for body function due to long lasting diarrhea in a subject with advanced skin cancer.
- Blood clot in the lungs in a subject with advanced skin cancer that had worsened.
- In a subject with advanced skin cancer, respiratory failure in relation to an infection that occurred after complications from surgery performed to treat inflammation and bleeding of the large intestine was the immediate cause of death. The study doctor thought the large intestine inflammation and complications that followed after surgery were related to tremelimumab.

8.2.11 Nursing implications

The first day of dosing is considered Day 1. Infusion duration for tremelimumab will be approximately 1 hour (± 5 minutes). If the infusion is less than 55 minutes or more than 65 it is considered a deviation. Tremelimumab will be administered first; followed by Durvalumab approximately 1 hour after the end of the tremelimumab infusion.

Each dose of investigational product should be administered using the following guidelines:

1. Investigational product must be administered at room temperature by controlled infusion into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion-related reaction due to the administration of the solution at low temperatures.
2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.
3. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2-µm in-line filters.
4. The duration of the investigational product administration will be recorded.

Tremelimumab will be administered as an IV infusion over approximately 1 hour (± 5 minutes). The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials.

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. Tremelimumab solution should not be infused with other solutions or medications.

8.2.12 Return and Retention of Study Drug

All unused investigational products will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy.

8.3 Combination of Durvalumab and Tremelimumab regimens

Patients in the durvalumab + tremelimumab combination therapy phase will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 750 mg durvalumab q2w starting on Week 16 for up to 8 months (18 doses) (see Figure 2). Fixed dosing is only for subjects with > 30kg body weight. Patients with a body weight ≤ to 30 kg will be excluded. If a patient becomes <30kg on study, please see additional dosing instructions per each agent

Tremelimumab will be administered first, followed by durvalumab. The duration for each will be approximately 1 hour (± 5 minutes). A 1-hour observation period is recommended 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).

8.3.1 Study drug preparation durvalumab and tremelimumab

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

8.3.2 Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.
In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) 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 (even during durvalumab monotherapy).

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

8.3.3 Side Effects when durvalumab and tremelimumab are given together (see current IB for full details)

Below are safety data from 61 subjects with lung cancer who received durvalumab

in combination with tremelimumab. Related side effects reported in subjects receiving the combination were:
Very Frequent – Expected to occur in more than 25% of people (more than 25 out of 100 people): Fatigue (26.2%)

Frequent – Expected to occur in 10% to 25% of people (10 to 25 out of 100 people): Diarrhea (21.3%), High level of amylase (increased amylase in your blood may indicate poor function of your pancreas; 13.1%)

Not Frequent – Expected to occur in 5% to less than 10% of people (5 to less than 10 out of 100 people): High level of alanine aminotransferase (ALT is a substance that is found in the blood and when high can indicate damage to the liver; 9.8%), Itching (9.8%), Decreased appetite (8.2%), High level of aspartate aminotransferase (AST is a substance that is found in the blood and when high can indicate damage to the liver; 8.2%), Inflammation of large intestine (8.2%), Rash (8.2%), Low level of blood thyroid stimulating hormone decreased (this may indicate that your thyroid is releasing too much thyroid hormone; 6.6%), High level of lipase (lipase is a substance that is found in the blood and when high can indicate damage to the pancreas; 6.6%). Intestinal perforation has been seen to occur in more increased frequency and severity when durvalumab and tremelimumab are used in combination.

Related and serious side effects reported in at least 2 subjects receiving the durvalumab and tremelimumab combination were: Diarrhea (8.2%), Inflammation of the large intestine (6.6%), Inflammation of the lung (3.3%), High level of AST (3.3%), High level of ALT (3.3%), High level of amylase (3.3%)

Related and serious side effects reported in at least 2 subjects receiving the durvalumab and tremelimumab combination were:

There was one death thought to be related to the durvalumab and tremelimumab combination treatment. The subject experienced myasthenia gravis and polymyositis. Myasthenia gravis and polymyositis are rare conditions that cause weakened muscles. They also cause swelling and tenderness. In this subject's case, the muscles responsible for swallowing and breathing as well as other muscles were affected. The subject declined treatment for the events. The polymyositis led to the subject's death approximately 2 months after receiving the first treatment with durvalumab and tremelimumab.

9.0 CORRELATIVES/SPECIAL STUDIES

Please refer to laboratory manual for additional details

9.1 Tissue sample collection guidelines

A fresh tissue biopsy of the primary tumor or a metastatic site at baseline and after 2 cycles of treatment will be collected. Re-biopsy after cycle 2 must be of the original biopsy site. In case of complete response, a biopsy of the original site will be re-biopsied, if feasible (i.e. chest wall metastasis), or another metastatic site may be used. The tumor lesion planned for biopsy must not be used as index lesion for assessment of disease unless there are no other lesions suitable for biopsy or the lesion used for biopsy is ≥ 2 cm in its longest diameter.

Fresh tissue biopsies will be performed using an image-guided core needle at the aforementioned time points (pretreatment, after 2 cycles) according to institutional practice. If clinically practical, subjects will undergo 4 core biopsies at each scheduled biopsy time point, ideally at least 3 core biopsies. Skin punch biopsies are acceptable, however, at least 2 punch biopsies that are at least 8mm in shortest diameter are necessary. All tissue samples will be immediately frozen in liquid nitrogen and then stored at -80°C, full details are provided in the lab manual. Collected tissues at baseline will undergo a touch prep to be sent to pathology for standard of care testing.

Tumor samples will be stored and may be used for additional correlative studies at a later date such as, but not limited to, immunohistochemistry, tumor mutation analysis and proteomic analysis.

9.2 Blood sample Collection Guidelines

Research blood samples will be collected at baseline and 2 months, and at end of study or time of discontinuation)..
80 mL of whole blood should be collected per lab manual instructions. Please ensure that tubes are completely filled at time of collection.

9.3 Sample Processing, Storage, and Shipment

Refer to the lab manual for sample processing, storage, and shipment information.

9.4 Assay Methodology

See lab manual for details.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This will be a single-arm, open-label, pilot phase II study to assess the efficacy and safety of durvalumab in combination with tremelimumab in patients with stage IV breast cancer which is HER2 negative. Patients who have completed the week 16 CT or nuclear bone scan will be evaluable for response endpoints. *(Note: Bone scans will be done only if the patient has bone disease. PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a patient's disease. The same modality used at baseline should be used throughout.)*

The **primary endpoint** is ORR, defined as number (%) of patients with at least one visit response of partial response (PR) plus complete response (CR) in patients with metastatic HER2 negative breast cancer treated with durvalumab in combination with tremelimumab using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (23).Any patient who has completed two months of study therapy is evaluable for this end point.

Secondary endpoints include PFS and OS, where PFS is defined as the time from date of treatment initiation until date of documented disease progression or death (by any cause in the absence of progression), and OS is defined as the time from date of treatment initiation until death due to any cause. Clinical benefit rate (SD for ≥ 12 weeks + PR + CR) will be assessed. Any patient who has completed two months of study therapy is evaluable for this end point.

The safety endpoints will be the number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded. Any patient treated with minimum 1 dose of either study drug will be evaluable for toxicity.

The expansion cohort will follow a similar design but only include patients with metastatic TNBC. Responses will be captured by RECIST v1.1.

Exploratory endpoints include serum and tissue-based biomarkers including: circulating tumor DNA, immunohistochemical expression of PD-L1; TILs; changes in tissue and peripheral T cell receptor sequencing, mutational and neoantigen burden, and immune-related candidate gene signatures at baseline.

Based on the fact that significant responses have been recently documented after progression when patients are started on next line of chemotherapy; a third exploratory objective is being added in order to capture response and duration of response to next line therapy.

Objective: To determine the response rate (RR) and duration of response(DoR) of next line

therapy after progression on durvalumab/ tremelimumab study regimen, for those patients who are able to submit detailed follow up data about subsequent treatment and response.

10.2 Sample Size and Accrual

A total of 35 patients (as needed)with metastatic breast cancer which is HER2 negative will be enrolled into this study and receive durvalumab in combination with tremelimumab, in order to get 28 evaluable for response. 15 patients with ER-positive disease and 15 patients with ER-negative disease will be enrolled (i.e. 2 cohorts with 14 evaluable each). Patients who have completed the week 8 CT or nuclear bone scan will be evaluable for response endpoints. Bone scans will be done only if the patient has bone disease. PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a patient's disease. The same modality used at baseline should be used throughout.
Using a Simon's two-stage design, we assume the undesirable overall response rate (null hypothesis) to be approximately 10%, and the alternate hypothesis to be approximately 30% based on previously published and presented data. Eleven patients will be added in the first stage. If 2 or more respond, then an additional 16 patients will be added for a total of 27. If 6 or more respond, then the hypothesis that the response rate is at least 30% is supported. This design has a Type I error rate of 4% and 80% power, and has a 70% chance of stopping early for futility after the first stage if the true response rate is 10%. The design is based on the complete sample and is not stratified by estrogen receptor status. ORR will also be calculated separately by receptor status, but the study is not powered for analyses within these subgroups.

For the expansion cohort we expect the ORR based on RECIST v1.1 to exceed 30% given our preliminary data. Using a Bayesian design assuming a prior beta distribution with parameters 0.3 and 0.7, there is a posterior probability of 0.81 that the ORR exceeds 30% if 8 or more responses out of 20 evaluable patients are observed.

10.3 Data Analyses Plans

The primary analysis will be on the intent-to-treat (ITT) population, including all evaluable patients. Best ORR defined as will be defined as number (%) of patients with at least one visit response of complete or partial response by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1). Best objective response prior to disease progression will be used. The overall response rate will be estimated by the proportion of overall response, and its 80% confidence interval (CI) and 95% CI will be estimated using the exact binomial distribution.

Additionally, we will evaluate clinical benefit rate, defined as stable disease for ≥ 12 weeks complete or partial response using RECIST 1.1 guidelines in a similar manner. We will also perform similar analyses using Immune Related RECIST (irRECIST).

PFS is defined as the time from date of treatment initiation until date of documented disease progression or death (by any cause in the absence of progression). OS is defined as the time from the date of start of treatment until death due to any cause. For patients alive at the time of data cut-off, PFS and OS will be censored as of the last tumor assessment date or known to be alive, respectively. The PFS and OS will be estimated using the Kaplan-Meier method. The number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded.

Baseline percent PDL1 expression, TILs (sTILs, iTILs, and their ratio), and changes in T cell subpopulations will be used as a continuous variable to predict clinical benefit or overall response rates using appropriate statistical summaries. Cox proportional hazards regression will be used to compare how these biomarkers are associated with PFS and OS as well.

Changes from baseline in these biomarkers will also be analyzed to assess for pharmacodynamic effects of treatment. Continuous variables will be analyzed using either paired t-tests, signed rank tests or repeated measures analysis of variance.

For analysis of each T cell receptor clonotype, we will apply a newly-developed algorithm Bowtie2 aligner (Ref; Nature methods 2012; 9:357-9), in collaboration with Profs. Miyano and Yamaguchi in Human Genome Center, The University of Tokyo. We will assign each of V, (D), J and C segments in the TCRA and TCRB reference sequences provided by IMGT/GENE-DB (Ref; Nucleic acids research 2005; 33:D256-61). By our approach, we will also identify novel exons that are not deposited in the reference sequence database. After decomposition of T cell receptor sequencing reads into V, (D), J and C segments, we will determine amino acid sequences of CDR3 (complementarity determining region 3), which plays a critical role in recognition of antigen. We will also calculate the diversity index (inverse Simpson's index) in CDR3 sequences to assess overall diversity and clonality in the T cell receptor clonotyes. Descriptive statistics will be used to assess differences from baseline to two months, and their relationship with clinical endpoints.

Determination of response rate to subsequent next line therapy will be determined in a similar manner as to the primary objective when feasible, where ORR is defined as number (%) of patients with at least one visit response of PR or CR. In instances where data for this post-hoc analysis cannot be obtained and only clinical responses can be obtained (ie patient followed up at an outside institution and only clinical radiograph reports are available), these will be used. Best objective response prior to disease progression will be used. Response rates will calculated using proportions and the 80% and 95% confidence intervals will be estimated using the exact binomial distribution. Duration of response to next line therapy will be defined as date from next line therapy until date of last dose of next line therapy. The Kaplan-Meier method will be used to assess duration of response to next line therapy.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by MedImmune Scientific Affairs. In the event that external participating sites are added, amendments will be distributed by the lead institution (Northwestern) to all external sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

For potential patients for phase II studies, study teams are asked to inform the assigned QAM (croqualityassurance@northwestern.edu) of the date and time that the patient will

need to be registered.

BEFORE a patient can be treated on study, the following items must be completed and submitted to confirm eligibility and receive a subject identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Copy of the pathology report (upload to NOTIS)
- Signed and dated Eligibility Checklist (upload to NOTIS and keep original hard copy in a secure location/study chart)

The assigned QAM will review the registration documents. Once review is complete, he or she will register the patient, assign a subject identification number, provide a cohort assignment (as applicable) and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Data collection for this study will be done through NOTIS. Access to the trial in NOTIS is granted to appropriate roles identified at the time of participating site activation, or upon request. Site users will not be able to access the study in NOTIS until all required and study specific trainings are completed.

Once a patient is confirmed and registered to the study, eCRFs should be submitted according to the study procedures table. Generally, for all phase II patients, data are due with 10 days of a visit or end of cycle. A set amount of data may also be requested for any screen failures, as is defined by the study. In most instances, this will include collection of adverse events and baseline data from the time of registration to the date of screen failure.

11.5 Instructions for Participating Sites

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Trials Office at Northwestern University (as applicable):

- Completed feasibility assessment(s) to verify site's capacity to support a Northwestern sponsored trial
- Signed copy of Northwestern University's Data Participating Site Acknowledgement which details data submission guidelines
- Draft consent form for review and approval prior to submission to the local IRB
- A copy of the official IRB approval letter for the protocol and informed consent
- A copy of the IRB approved informed consent
- Pertinent credentials (CVs, MLs, CITI & GCP Training and FDFs) for the local PI and any sub-investigators who will be involved in the study at the site
- Form FDA 1572 appropriately filled out and signed with appropriate supporting certifications

Additional activities may be required prior to site activation (i.e. contract execution, study-specific training, and delegation of authority log). Full requirements will be outlined in the study start-up packet upon successful completion of a feasibility assessment.

11.6 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to the CTO website for additional information). The level of risk attributed to this study requires high level, as outlined in the DSMP. The assigned QAM, with oversight from the Data and Safety Monitoring Committee, will monitor this study in accordance with the study phase and risk level. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

11.7 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.7.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.7.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Reportable New Information (RNI) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.8 Investigator Obligations – Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection. The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all

the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Clinical Trial Audit Committee (CTAC), as outlined in the DSMP.

11.9 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the DSMC Data Release Policies and Processes. The assigned QAM will prepare a preliminary data set for DSMC approval no later than 3 months after the study reaches its primary completion date, as defined by ClinicalTrials.gov. This is the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated. If the investigator would like data release to be approved by the DSMC prior to when study design specifies, and/or prior to three months after a study's primary completion date, the PI must send a written request for data approval to the QAM which includes justification. Requests must be made a minimum of six to eight weeks in advance of the expected deadline. The request will be presented to the DSMC at their next available meeting. Any DSMC decisions regarding data release will be provided to the PI. If the request is approved, the QAM will present the data set to the DSMC for approval. A final, DSMC-approved dataset, as applicable, will then be released 6-8 weeks after the request was made. The investigators are expected to use only DSMC-approved data and statistical analyses any time they are disseminating trial data. The investigators must send a copy of the draft abstract/poster/manuscript to the study's biostatistician and assigned QAM to confirm that the DSMC-approved data and statistical analyses are used appropriately. Once the biostatistician and QAM gives final approval, the publication may be submitted to external publisher.

11 APPENDICES

APPENDIX A- EFFECTIVE METHODS OF CONTRACEPTION

Please refer to section 4.5.1 for details

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APPENDIX B- COMMON TOXICITY CRITERIA FOR ADVERSE EVENTS

Toxicity will be graded according to the NCI's Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE version 4.0 can be accessed at the following link:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

APPENDIX C – Durvalumab weight based dose calculation

For durvalumab dosing done depending on subject weight. Weight-based dosing should be utilized for patients whose weight decreased to ≤ 30 kg who would otherwise be receiving the durvalumab 1500mg Q4W fixed dose:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

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

4. Dose to be added into infusion bag:

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

Where 50 mg/mL is durvalumab nominal concentration.

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

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

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

Example:

1. Cohort dose: 20 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 600 mg = 20 (mg/kg) × 30 (kg)

4. Dose **to be added into infusion bag:**

Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

5. The number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

APPENDIX D – Tremelimumab weight based dose calculation

[Note: Cohort Dose X = 1 mg/kg]

For Tremelimumab, dosing done depending on subject weight. Weight-based dosing should be utilized for patients whose weight decreased to ≤ 30 kg:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

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

4. Dose to be added into infusion bag:

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

where 20 mg/mL is tremelimumab nominal concentration.

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL).
Dose adjustments for each cycle are only needed for greater than 10% change in weight or if patient's weight improves to >30kg. Once a patient's weight improves to >30kg, patient should start receiving the fixed dosing of tremelimumab 75mg Q4W

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

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

Example:

1. Cohort dose: 1 mg/kg

2. Subject weight: 30 kg

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

4. Dose to be added into infusion bag:

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

5. The number of vials required for dose preparation:

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

APPENDIX E – Protocol Summary of Changes

Original Protocol – June 10, 2015			
Amendment 1 – July 20, 2015 *Changes Requested During FDA Review of IND*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Face Page (PI address, IND number, IND holder, version date, amendment number)	N/A	PI address corrected, IND number and IND holder added, amendment number updated	Administrative
Section 1.6 (Rationale for the current study)	N/A	Clarified rationale for the study, justification for choosing the proposed doses and schedule of MEDI4736 and tremelimumab therapy and rationale for administering 18 additional doses of MEDI4736	Per FDA reviewer recommendations
Sections 3.0 (Patient eligibility) & 3.1 (Inclusion Criteria)	Target population was females with Her2-negative breast cancer	Modified to include both female and male	Per FDA reviewer recommendations
Section 3.1 (Inclusion criteria)	Stated that ER+ patients ositive must have progressed through standard hormone therapy & received at least one line of chemotherapy in the metastatic setting.	Modified to require *progression through prior therapy with Palbociclib* in addition to standard chemotherapy and hormone therapy	Per FDA reviewer recommendations
Section 3.2 (Exclusion criteria)	N/A	Added exclusion criteria to exclude patients with documented Her2-positive metatstatic breast cancer regardless of Her2-negative status of primary tumor	Per FDA reviewer recommendations
Section 4.1 (Treatment plan)	N/A	Added a statement regarding continued safety monitoring in case of decision to continue therapy on patients who develop disease progression while on study	Per FDA reviewer recommendations
Table 2	• Treatment allowed to resume for G3 hepatitis as well as for G3 immune-mediate neurotoxicity and G3 immune-mediated peripheral	Dose modification and toxicity management in Table 2 modified as follows: • Added statement regarding ruling out infections etiologies for G2 diarrhea/enterocolitis	Per FDA reviewer recommendations

	neuromotor syndromes • Stated that treatment could resume for G3 non-immune mediate AEs that downgrade to ≤ G2 within 7 days or resolve to ≤ G1 or baseline within 14 days,	• Requires treatment discontinuation for G3 (or higher) hepatotoxicity, immune mediated neurotoxicity, and immune-mediate peripheral neuromotor syndromes. • Requires that G3 non-immune mediated reactions downgrade to ≤ G2 with 7 days AND resolve to ≤ G1 or baseline within 14 days.	
Section 5.0 (Study Procedures)	• Imaging for RECIST response required only at baseline, W16, and off-study. • No reference was made to the time between screening procedures and first dose of study drug. • Less frequent monitoring of thyroid, liver, and chemistry tests required.	• Amended to reflect that imaging for RECIST response will be performed every 2 cycles (8 weeks) while patients are receiving therapy • Amended to clarify that the maximum time interval between Screening Visit/ baseline study procedures and the first dose of study drug will be 14 days. • Modified to reflect that thyroid function, liver function, and clinical chemistries will be done prior to each dose during combination therapy and then every 4 weeks during maintenance therapy.	Per FDA reviewer recommendations
Amendment 2 – July 25, 2015 *Changes Requested by IRB*			
Section(s) Affected	***Prior Version***	***Amendment 1 Changes***	***Rationale***
Section 4.4 (Concomitant medications/treatments)	Stated that herbal therapies “should be avoided.”	Modified section to clarify concomitant use of herbal during therapy and make section consistent with exclusion criteria	Per IRB reviewer suggestion
Section 8.0 (Drug Information)	Formulation of investigational drugs referenced both	Clarified the formulation of investigational drugs (MEDI4736 and	Per IRB reviewer suggestion

	lyophilized and liquid formulations; shipment of agents to other sites mentioned.	Tremelimumab) supplied by MedImmune. Clarified that Northwestern University is the only site for shipment purposes	

Original Protocol – June 10, 2015			
Amendment 3 – Oct .9. 2015 *Changes Requested by Astrazeneca*			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Title	A single arm phase II study evaluating the efficacy and safety of MED14736 in combination with tremelimubab in patients with metastatic HER2 negative breast cancer	A single arm phase II study evaluating the efficacy and safety of **Durvalumab** (MED14736) in combination with tremelimubab in patients with metastatic HER2 negative breast cancer	**Per new IB**
Signature page	Present	Removed	New NU IIT protocol template
Throughout	Drug referred to as MEDI4736	MED14736 drug name Durvalumab added.	Per new IB
Study summary; Sec 2.0,4.1	Primary endpoint was defined as Clinical Benefit Rate,	Primary endpoint changed to Overall Response ate(ORR) Clinical benefit rate added as the secondary endpoint	Per sponsor Astrazeneca, based on recent study's
Study summary; Section3.0 ;	N/A	Accrual: two cohorts of 15 pts, ER+ and ER-	Ensure equal subgroups
Section 3.0 (patient eligibility)	Stated as 'Stage IV'	Word 'metastatic' added	For clarification
Section 3.1.7	Exceptions to" prior diagnosis of cancer not specified."	**Exceptions stated:** squamous cell carcinoma or basal cell carcinoma of the skin or cervical intraepithelial neoplasia	**Per PI** **To increase clarity for inclusion criteria**
Section 3.1.10 (incl. criteria)	N/A Creatinine ≤2ng/ml ANC≥1000 Platelets≥50,000/mcl	**Laboratory parameters:** Added Hb level ≥9.0g/dl Serum Creatinine: new assessment criteria ANC≥1500/mcL(1.5x10L) Platelets≥100,000/mcl	Per new IB

Section 3.1.10	Transfusion and GCSF detail not included	**Added " transfusion permitted but not GCSF" for the laboratory values**	Per PI. To increase clarity of eligibility criteria
Section 3.1.11 (incl.criteria)	Required pregnancy test Required only negative pregnancy test	Requires ***Serum*** pregnancy test Added " females of non-productive potential" (with definition) **OR** negative **serum** pregnancy test	For clarification Per Astrazeneca
Section 3.1.12 (incl. criteria)	Addressed females of reproductive potential Methods of birth control were stated ; duration was 'study participation'	Addressed " male patients of reproductive potential" in addition to females Birth control methods and duration changed Added statement for female patients to report new or suspected pregnancy during study participation	Per Astrazeneca
Section 3.1.14 (incl. criteria) Section 3.1.15 (incl. criteria)	Requirement of consent before registration N/A	Added statement clarifying time-point for consent Added statement for subject willingness for study compliance	For clarification Per revised NUIIT protocol template
Sections in Excl. criteria 3.2.4 3.2.5, 3.2.10 3.2.11 3.2.12 3.2.16	N/A	Added ECG specifications; vaccine prohibitions; Inflammatory bowel disease; Organ transplant; hypersensitivity to durvalumab or excipient; Exclude any study staff (who may also be patients) to avoid potential conflict of interest.	Per Astrazeneca
Section 3.2.3 (Excl.criteria)	Use of Immunosuppressive therapy	Timepoint changed; exceptions stated	Clarification-per Astrazeneca
Section 3.2.4	Number of EKGs required was not stated.	Added " 2 EKGs 5 mins apart is mandatory"	Per PI . For clarity and confirmation of EKG findings

Study Schema; Study summary; Sec 4.2	Only weight based dosing	Change in dosing for Durvalumab and Tremelimubab: **Fixed dosing** regimen and **weight based** dosing	Per new IB
Section 1.4 (Durvalumab/MEDI4736)	N/A	Information regarding drug Durvalumab added to existing information	Per new IB
Section 1.5 (Tremelimumab)	N/A	Information regarding drug Tremelimubab added to existing information	Per new IB
Section 1.6 (Durvalumab in combination with Tremelimumab)	N/A	This section is a new addition and describes the synergistic/additive Combination of Durvalumab and tremelimubab	Per Astrazeneca
Section 1.7.1 (Rationale for fixed dosing)	N/A	This is a new section describing : Rationale for fixed dosing for durvalumab and tremelimumab	Per Astrazeneca and new IB
Section 4.1 Section 4.1.1	Provision for optional biopsy at progression Provision of separate ICF at PD	Provision removed Provision removed	Per PI. Per PI
Section 4.2.1 (Monitoring of dose administration)	N/A	Details for monitoring of subjects for infusion-related reactions have been added	For clarity
Section 4.2.1	Grade 3 reaction not clarified, even though description was there	Description now classified as " ≥Grade 3 reaction" in the paragraph about modification of infusion rate	Per PI. To increase clarity
Section 4.3 (Toxicity Management)	Dose reduction tables present for both drugs. "Modifications should be implemented only if toxicities are attributed to respective drugs"	Dose reductions tables for both drugs deleted. Statement inserted "Doses may be held according to Table 2, there are no dose adjustments. Toxicities are attributed to respective drugs (durvalumab or tremelimumab)"	Per Astrazeneca and new IB

Table 2 (Immune related Adverse Events)	The term 'study physician' was used.	The term 'study physician' was replaced with 'treating physician'	For clarity and logistical convenience
Section 4.4 (Concomitatnt Medications/Treatment)	List of concomitant medications and prohibited treatments referred to were limited.	List of concomitant medications and prohibited treatments while the patient is on the study has been expanded.	Per Astrazeneca
Section 4.5 (Other Restrictions)	This section number was associated with 'Duration of therapy in the previous' in the previous version. New section number is 4.6.	New section has been added to detail other restrictions during the study that includes birth control and blood donation while on the study	Per Astrazeneca
Section 4.6 (Duration of therapy - previously section 4.5)	Duration of therapy was 14 months	Duration reduced to 12 months.	Clarification, per Astrazeneca
Section 4.8 (Removal of subjects - previously section 4.7)	N/A	Revised previous criteria/added new criteria for subject removal from the study or stopping treatment. Re-defined conditions for permanent discontinuation vs. stopping of IP administration to the subject.	Per Astrazeneca
Section 5.0 (Study procedures – Main study table)	Previous table had descriptions for dose/body weight. Hepatitis and HIV tests were not included.	Updated table to describe fixed doses for Durvalumab (Medi4736) and Tremelimumab. Added new screening tests to include Hepatitis & HIV. Expanded lab tests to add. Footnotes updated.	Per Astrazeneca

Section 5.0 (Study procedures – Main study table)	Previous table +/- 7 days window for visit At 3M,6M,9M, 12M	Added a window of +/- 1 month for all said visits	Per PI and QA . To increase scheduling flexibility and ensure patient compliance
	Tumor biopsy at 12 wk	Tumor biopsy at 8 wk.	Error correction
	Column heading" Off study"	Column heading " OFF treatment"	
	Optional biopsy at end of treatment	Optional biopsy at treatment removed	Per PI
	Concomitant medications review not marked at all visits	Concomitant medication review marked for all visits	Per QA
	Assessment of AE/SAE s not included in 9M and 12 M visit	Assessment of AE/SAEs included in 9M and 12 M visit. Footnotes added" AE/SAE to be followed up until resolved or patient off study"	Per QA
Section 5.1 (Study procedures – additional study table)	N/A	Additional study table added for patients continuing treatment/re-starting treatment after disease progression.	Per suggestions from QA team
Section 6.2 (Primary endpoint)	Primary endpoint was Clinical benefit rate	Primary endpoint changed to Overall Response Rate (ORR).	Based on new literature reports using this drug combination.
	N/A	Evaluable patient defined	Per PI
Section 6.3 (Secondary Endpoints)	N/A	Added Clinical benefit rate as a secondary endpoint	To retain Clinical benefit rate as one of the study goal.
		Evaluable patient defined	Per PI

Section 7.0 (Adverse events)	N/A	1. 7.1 AE monitoring section elaborated. 2. 7.2.1 AE definitions elaborated. 3. 7.2.3 Added a statement about causality assessment and communication with sponsor. 4. 7.2.25 AE of Special Interest (AESI) was elaborated. 5. 7.2.6 Other events requiring immediate reporting expanded 6. 7.3.3 Expedited Reporting of SAEs/Other events elaborated	Per Astrazeneca
Section 8.0 (Drug information)	N/A	1. 8.1.5 Dose specifications for Durvalumab to be used in the protocol elaborated. 2. 8.1.6 – Durvalumab preparation and reconstitution updated. 3. 8.1.9 Durvalumab availability and supply updated. 4. 8.2.6 Preparation of Tremelimumab described. 5. 8.2.9 – Tremelimumab availability and supply updated. 6. 8.3 Dose specifications for the combination of Durvalumab plus Tremelimumab elaborated. New sections added to detail drug preparation for the combination, monitoring of the administered dose.	Updated based on IB v8.0 dt 09.01.15.

Section 8.1.11	N/A	Details about infusion schedule and monitoring of vitals added.	Per QA. For clarity
Section 8.2.9; 8.1.9	N/A	Updated drug availability information	Per new IB
Section 9.0 (Correlative/Special Studies)	1. N/A 2. End of study biopsy	1. Reference to lab manual for details was added	1. Per QA recommendation 2. Feasibility and funding will be insufficient for end of study biopsy
Section 9.2	"Blood samples will be collected at end of study"	Added" "Blood samples will be collected at end of study or time of discontinuation"	Per QA.
Section 10.0 (Statistics)	N/A	1. 10.1 – Clinical benefit rate added to secondary endpoint. 2. 10.2 Sample size updated. 3. 10.3 Data analyses plan modified to define ORR as the primary endpoint 4. Evaluable patients defined.	Based on changes to the primary and secondary endpoints.

Section 11.3 (Registration Procedures)	This section had references to eligibility confirmation by QAM and to eCRF training.	Section related to eligibility confirmation by QAM and eCRF training deleted.	Per QA
Section 11.7 (Investigator obligations)		Statement referring to the study being conducted under ICG/GCP added.	Per Astrazeneca
Amendment 3 – Oct 9, 2015			
Amendment 4 – Dec 8, 2015			
Section(s) Affected	***Prior Version***	***Amendment 3 Changes***	***Rationale***
Section 3.1.12 (Inclusion Criteria)	Previous version stated that the use of effective birth control while on the study to be 180 days after the last dose of combination and 90 days after the last dose of Durvalumab monotherapy	Period for use of effective birth control while on the study changed to 180 days after the last dose of combination therapy and 180 days after last dose of Durvalumab monotherapy	Per updated recommendations from MedImmune
Section 3.2.4 (Exclusion criteria)	Previous version stated: '… calculated from 3 ECGs'	Corrected to '… calculated from 2 ECGs'	To correct for error.
Section 4.3 (Toxicity management and dose delays/modifications)	N/A	Dose Modification description in Table 2 updated	To reflect the updated IB for Durvalumab
Section 4.4 (Concomitant Medications)	Previous version incorrectly stated 'Refer to section 5.6'	Corrected to read 'Refer to Table 2'	Correction for error
Section 7.2.5 (Adverse Events of Special Interest)	N/A	Section updated to add descriptions related to Nephritis and Dermatitis	To reflect the updated IB for Durvalumab

Section 8.2.11 (Nursing implications)	Previous version incorrectly indicated that Tremelimumab will be administered after Durvalumab	Sequence and duration of infusion for Tremelumumab and Durvalumab was clarified	To correct discrepancy between section 8.1.11 and 8.2.11
Section 9.0 (Correlatives/Special studies)	Sec 9.1 (Tissue sample collection guidelines) previously specified different sample processing instructions for different biopsies Sec 9.4 (Assay Methodology) had detailed methodology for various assays to be used for correlative studies	Sec 9.1 (Tissue sample collection guidelines) changed to clarify that **all tissue** samples will be immediately frozen in liquid nitrogen Sec 9.4 (Assay Methodology) – detailed methodology was replaced by statement 'See lab manual for details'	For clarity For simplicity and clarity.
Amendment 5 – Feb 8, 2016			
Section(s) Affected	***Prior Version***	***Amendment 4 Changes***	***Rationale***
Section 3.1 (Inclusion Criteria) Sec 3.1.3	Previous version stated prior therapy with Palbociclib as an inclusion criteria for patients with ER positive breast cancers	Removed prior therapy with Palbociclib as an inclusion criteria for patients with ER positive breast cancers. Replaced with clinical resistance and progression through endocrine therapy as a criteria	Eligibility changed to reflect endocrine resistance more dynamically, this wording reflects biology more accurately and will enhance accrual.
Sec 3.1.7	Prior diagnosis of cancer > 5 years	Replaced with prior diagnosis > 3 years	Will enhance accrual, consistent with many cancer protocols.

Section 3.2 (Exclusion Criteria) 3.2.1 3.2.7	 Previous version stated: 'even if their primary breast cancer was Her2-negative Prior treatment with investigation agents 4 weeks before registration was a criteria for exclusion	 Replaced with: 'based on most recent biopsy' Replaced with prior treatment with investigational agents 'within 2 weeks of 5 half lives'	 For clarity
Table 1 (Immune-mediated reactions) – Dose Modifications for Hepatitis	Previous version incorrectly stated transaminases ≤ 8 x ULN or bilirubin ≤ 5 x ULN	Corrected to read transaminases ≥ 8 x ULN or bilirubin ≥ 5 x ULN	Corrections
Section 5.0 (Study table) Thyroid function tests Footnote 11 Footnote 14	 Previous versions were missing the required 'X' for Thyroid function tests at W4 and W8 Previous version stated 'a single ECG' will be obtained at screening Previous version stated 36 ml	 Added 'X' for W4 and W8 Changed to state '2 ECGs' will be obtained at screening Changed to 80 ml	 Corrections Corrections Correlative analysis requires additional blood testing.
Section 8.3 (Combination of Durvalumab and Tremelimumab regimens)	Previous dose for durvalumab monotherapy after week 16 was incorrectly stated at 1500 mg	Dose for durvalumab monotherapy starting week 16 changed to 750 mg.	Corrections
Section 9.0 (Correlatives/Special studies) 9.1 Tissue sample collection 9.2 Blood sample collection guidelines	 N/A Previous version stated 40 mL volume for research blood samples to be collected	 Skin punch biopsies added as an alternative to core needle biopsy Revised to state 80 mL will be collected	 Some patients may have skin disease, offer guidance to tissue needed. Correlative analysis requires additional blood testing.

Amendment 6– July 1st, 2016			
Section(s) Affected	***Prior Version***	***Amendment 6 Changes***	***Rationale***
Cover page	NU Sub-Investigators listed	**Removed** B.carneiro,MD; Y.Chae,MD; J.Kaplan,MD; A.Williams, H.Garrett, Ellen Dammrich Megan Sullivan **Added:** Massimo Cristofanilli,MD; Luis Blanco, MD	Per PI
Section 1.7.3	N/A	**Section added: Ratiobale for Exploratory Objectives:** Three exploratory objectives have been explained. The third objective is a new one that is being added in this amendment**.**	Section was not included earlier in the protocol. Inclusion of this section will increase clarity and improve protocol structure.
Section 2.3.3 Section 6.4.3 Section 10.1	N/A	Added third exploratory endpoint. “To determine the response rate (RR) and duration of response(DoR) of next line therapy after progression on durvalumab/ tremelimumab study regimen, for those patients who are able to submit detailed follow up data about subsequent treatment and response”.	This is based on the fact that significant responses have been recently documented, after progression when patients are started on next line of chemotherapy.
Exclusion criteria 3.1.10	Patients must have adequate organ and bone marrow function (transfusion permitted but not GCSF) within 14 days prior to registration.	Patients must have adequate organ and bone marrow function (transfusion permitted but not GCSF) within 14 days of first dose of study drug administration.	Modified to be consistent with instructions in the study procedures table

Section 4.1	Treatment overview	Added terms: "Induction phase" and "Maintenance Phase". Also added: In addition patient's next line of therapy will be monitored for response rates and duration of clinical benefit to next line therapy.	For clarity In keeping with the addition of the 3rd exploratory endpoint.
Section 4.1.1	**Section heading:** Continuation of Investigational Therapy after Progression.	**Section heading changed to**: Continuation of Investigational Therapy after Radiographic Progression (Pseudo-progression). Language added stating treatment regimen for patients continuing therapy with suspected pseudo-progression. Language indicates that patients should continue with treatment according to whether they in the induction phase or maintenance phase	To separately state the treatment regimen for pseudo-progression as opposed to subjects who continue treatment beyond 52 weeks , which is described in section 4.1.2
Section 4.1.2 Continuation of Investigational Therapy After 52 Weeks	1. Patients who achieve clinical benefit (CR, PR, or SD) until the end of the 52 week period may enter a follow up phase or continue durvalumab as shown in table 5.1 for up to 52 more weeks as long as they are felt to be deriving clinical benefit. 2. During follow-up ,patients develop who PD may be re-treated with Durvalumab. Only 52 week	1. Patients who achieve clinical benefit (CR, PR, or SD) until the end of the 52 week period may enter a follow up phase or continue durvalumab as shown in table 5.1 for up to 52 more weeks as long as they are felt to be deriving clinical benefit. 2. Patients who enter follow up phase will continue to be monitored. If during the first 6 months of	To clearly state the different scenarios and course of action for subjects who continue investigational therapy after 52 weeks.

	retreatment period will be allowed.	follow-up, patients developing PD may be re-treated with durvalumab as shown in table 5.1. Only one 52 week retreatment period will be allowed. Patients who are restarted on durvalumab after the initial 52 week period must meet the following criteria: Criteria have been listed	
Section 5.0 Study procedures	Concomitant medication schedule	Modified to: Concomitant medications (including next line therapy after off treatment, response data).Same schedule as previously followed for concomitant medication	In order to capture the data for next line therapy in keeping with the 3rd exploratory objective.
	Footnote 1 regarding imaging: The same modality used at baseline should be used throughout.	Added to footnote 1 CT must have contrast, MRI with contrast is acceptable alternative if the patient is allergic to CT contrast	In order to provide patients with a safe alternative in case of allergy to CT contrast.

	N/A	Added footnote 16: tumor biopsy is mandatory prior to study enrollment and after 2 cycles of treatment (as clinically appropriate by PI discretion).	For clarity
Section 5.0-Study procedures table footnote 11; Eligibility Criteria 3.2.4	2 EkGs 5 mins apart	2 EKGs 5 minutes(+/-2 mins) apart	Window inserted for logistical convenience, so that patients may not be deemed ineligible for very minor time deviations.
Section 5.1	Section heading: Study procedures (For patients who are continuing treatment or re-starting treatment after progression of disease.	Section heading modified: **Study Procedures After 52 Weeks of study treatment** (For patients who are continuing treatment or re-starting treatment after progression of disease after 52 weeks, this table should not be used for patients who stay on therapy due to pseudo-progression). Other minor edits made in the footnotes in order to increase clarity.	For clarity
Section 10.2 Sample size and accrual(statistics section)	Patients who have completed the week 16 CT or nuclear bone scan will be evaluable for response endpoints.	Patients who have completed the week 8 CT or nuclear bone scan will be evaluable for response endpoints	Error correction. Week 16 changed to week 8 to be consistent with the rest of the protocol.
Section 10.3 Statistical data analyses plans	Data analyses plans explained	**Added paragraph for 3rd exploratory objective**: Determination of response rate to next line therapy will be determined in a similar manner as to the primary objective when feasible, where ORR is defined as PR or CR. In instances where data for this post-hoc analysis cannot be obtained and only clinical responses can be obtained (ie patient followed up at an outside institution and only clinical radiograph reports are	Per PI and statistician, in keeping with the addition of the 3rd exploratory objective.

		available), these will be used. Maximum response prior to disease progression will be used. Response rates will be calculated using proportions and the 80% and 95% confidence intervals will be estimated using the exact binomial distribution. Duration of response to next line therapy will be defined as time next line therapy begins, and last dose of next line therapy. The Kaplan-Meier method will be used to assess duration of response to next line therapy.	
	Amendment 7	September 26th ,2016	
Section 5.0 (Study Procedures)	Thyroid function tests scheduled every 4 weeks during maintenance. But it was marked at W16, W18 and W20 in the table. Footnote **(under W20 in the table)read: *Visits7 through 9* will repeat for a total of up to 18 doses of durvalumab, or until progressive disease (see 4.1.1) or unacceptable toxicity, with CTs and bone scan done every 8 weeks. Footnote 16 states details about tumour biopsy	The 'X' indicating the W18 thyroid function test removed from the table. The Footnote has been modified to indicate that *Visits 8 through 9* will be repeated. Added a note to footnote 16: *"Note: If it is felt to be clinically inappropriate to biopsy the patient, then this should be clearly documented in the patient's chart and CRF.This documentation should also be printed and flagged in the patient's research chart)."*	***For accuracy, consistency and clarity***

Section 5.0(Study procedures) and Section 5.1 **(**Study Procedures After 52 Weeks of study treatment)	Respiration rate included as part of vital signs.	Respiration rate removed from vital signs.	***Respiration rate is not routinely done in clinic every time as part of vital signs. Hence, removed to prevent protocol deviations.***

Amendment 8 April 26th , 2017(with additional updates after initial SRC approval)

Section(s) Affected	***Prior Version***	***Amendment 8 Changes***	***Rationale***
Protocol title page and throughout	Original title	Added: TNBC expansion cohort	***An expansion cohort for TNBC patients has been added to this study***
	PI credentials	Updated PI credentials by adding MSCI along with MD	***To be consistent with current PI credentials***
List of abbreviations	previous list	Added: ID: Infectious disease identifying data	***For clarity***
Study schema	Had only one schema which illustrated the study	Two schemas: 1. For general cohort with Her2 negative breast cancer patients 2. For Expansion cohort-with Triple negative breast cancer patients. Added footnote that scans are to be completed every 8 weeks, regardless of drug holds or treatment	***An expansion cohort for TNBC patients has been added to this study***

		delays. All other details about this cohort is similar to the general cohort.	
Study summary and Section 2.1 (Primary objectives and endpoints)	Primary, secondary and exploratory objectives listed.	Added Expansion cohort objective to the Primary Objective, stating the evaluation of ORR in TNBC patients with the same drug and dose combination. Exploratory objective modified as explained in section 2.3	***In order to accommodate and analyze the expansion cohort of TNBC patients***
Study schema: sample size section(statistics)	Details about the 30 patients in the general cohort.	**Added language**: "Expansion cohort based will enroll 20 additional patients with TNBC to determine the posterior Bayesian probability that the response rate exceeds 30%."	***In order to accommodate and analyze the expansion cohort of TNBC patients***
Study schema : diagnosis and key Eligibility criteria and Section 4.1 treatment overview	Criteria listed briefly	**Added language:** (expansion cohort only TNBC allowed)	***In order to accommodate the expansion cohort of TNBC patients***
Section 1.7.1 rationale for fixed dosing for durvalumab and tremelimumab	Patients with a body weight ≤30kg should be dosed using a weight based dosing schedule.	Patients with a body weight ≤ 30kg will be excluded.	***Study is for adult population, data for <30kg patients primarily in pediatrics.***
Section 1.7.3 Rationale for expansion cohort	N/A	A new section added explaining the rationale for inclusion of the TNBC expansion cohort:	**A striking difference between response rates in ER-positive (0%) and TNBC(42.9%) was observed. Essentially 6 out of 7 patients in TNBC cohort experienced clinically relevant benefit.**
Section 1.8 Rationale for Exploratory Objective	N/A	A new section added to explain rationale for exploratory objectives	***For clarity***

Section 2.2.1 Secondary objective and Section 6.3 Secondary Endpoints	Statement of objective PFS and OS along with definitions	PFS definition modified : "from date of treatment initiation to date of documented disease progression or death(by any cause in the absence of progression)." OS definition reworded for clarity	***For increased clarity***
Section 2.1 and Section 6.2 Primary Objective and Endpoint	ORR listed as primary endpoint with definition.	ORR definition updated to read; "ORR defined ***as number (%) of patients with one visit response*** of partial response (PR) or a complete response (CR) in patients with metastatic HER2 negative breast cancer (TNBC in expansion cohort) treated with durvalumab in combination with tremelimumab using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1" Language added for evaluable patients and pseudoprogression.	***Clarified how ORR determined and evaluated***
Section 2.3.1 Exploratory endpoint and Sections 6.4.1	To evaluate if tissue-based immunohistochemical expression of PD-L1; tumor infiltrating lymphocytes (TILs); peripheral T cell subpopulations; changes in tissue and peripheral T cell receptor genotype; human leukocyte antigen (HLA) genotype; and immune-related candidate gene signatures predict response to durvalumab in combination with tremelimumab.	Modified to add: serum biomarkers as well. Biomarkers will also include circulating tumor DNA and mutational and neoantigen burden	***As decided after internal review by sponsor and PI*** ***To assess response rates to next line therapy after progression***

Section 3.0 Patient eligibility overview	Previous details	Added language that states that the expansion cohort will include only metastatic TNBC patients and this cohort will include 20 evaluable patients with TNBC.	***In order to accommodate the expansion cohort of TNBC patients.***
Eligibility criteria 3.1.1	Description of histological criteria for general cohort.	Added language: PR positivity will be defined as a result of greater than 10%. Documentation of ER and PR status. The expansion cohort will only include Her-2 negative, ER and PR-negative patients.	***For clarity, and in order to accommodate the expansion cohort of TNBC patients.***
Section 3.1.10 Inclusion criteria	N/A	New criteria included which states that patients must weigh >30kgs for them to be included in the study	***Study is for adult population, data for <30kg patients primarily in pediatrics.***
Section 3.1.12 Inclusion criteria	Details about pregnancy test requirements.	Added language regarding age specific requirements.	***According to updated language per sponsor.***
Section 3.2.2	N/A	New exclusion criteria added stating that patients with visceral crisis or impending visceral crisis will be excluded at the clinical discretion of the treating physician. Excludes patients with definite liver metastsis >1cm	***Immunotherapy takes several weeks to work.So, patients with rapidly progressive disease unlikely to benefit.*** ***This subset of patients did exceptionally poor in the first cohort***
Section 3.2.3 Exclusion criteria	N/A	New exclusion criterion added with details regarding unresolved toxicity from previous anti-cancer therapy	***To avoid compounded toxicity with investigational drugs.***

Section 3.2.5 Exclusion criteria	Current or prior use of immunosuppressive therapy within 28 days prior to the first dose of durvalumab or tremelimumab	Updated from 28 days to 14 days.	***Sufficient time for washout. Window narrowed to expedite enrollment***
Section 3.2.6 Exclusion criteria	Mean QT interval corrected for heart rate using Bazett's correction	Changed to: Mean QT interval corrected for heart rate using Fridericia's correction.	***Current studies have used this correction model.***
Section 3.2.8 Exclusion criteria	Prior treatment with immune therapy (including but not limited to CD137, OX40, PD-1, PD-L1 or CTLA4 inhibitors)	Updated to : "Prior treatment with immune therapy (including but not limited to CD137, OX40, PD-1, PD-L1 or CTLA4 inhibitors such as durvalumab and tremelimumab)	***For added clarity***
Section 3.2.10 Exclusion criteria	N/A	New exclusion criteria added for prior documented autoimmune or inflammatory disorders with some exceptions listed.	***Immunotherapy may adversely affect autoimmune or inflammatory disease.***
Section 3.2.11 Exclusion criteria	N/A	New criterion added which includes TB, HIV, HCV and Hep B infections and the criterion for exclusion of patients with these infections.	***Immunotherapy not studied in patients with these immunodeficient states, unclear effects on ID or anti-cancer effects.***
Exclusion criteria 3.2.13	History of hypersensitivity to durvalumab or any excipient.	Updated to : Hypersensitivity to durvalumab or tremelimumab or any excipient	***Prevent allergic reactions***

Exclusion criteria 3.2.15	Previous list of uncontrolled intercurrent illness that excluded patients from the study.	Added: 1. Symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia 2. Interstitial lung disease, serious gastrointestinal conditions associated with diarrhea 3. Psychiatric illness/social situations that substantially increase risk of incurring AEs or compromise the ability of the patient to give informed consent.	***For added safety and clarity***
Section 4.1.1 (Pseudoprogression)	Pseudoprogression defined as: radiographic increase felt to be due to inflammation/immune response. Criteria for continuation of treatment in case of pseudoprogression included "No decline in Eastern Cooperative Oncology Group"	Added language to state radiographic increase or "new lesions" felt to be due to inflammation/immune response. Modified to No '**significant'** decline in Eastern Cooperative Oncology Group(PS>2 or as deemed by treating investigator)	***Per PI*** ***For clarity and specificity***
Section 4.2 Treatment administration	Tabular details about treatment administration	Added language as footnote stating labs required to start treatment "On each treatment day, hematology and serum chemistry are to be resulted before treatment can begin"	***For clarity***

Section 4.2.1 Monitoring of dose administration	Investigators may administer steroids at their discretion as clinically indicated and per their institutional guidelines	Modified to: "Investigators may administer steroids per protocol guidelines (see Section 4.3) or at their discretion as clinically indicated in consultation with the study team."	***For safety and convenience***
Section 4.3 Table 1-Immune mediated reactions	Previous table with details of overall management of Immune –mediated reactions	Updated to current instructions for overall management of Immune –mediated reactions	***Based on current IB***
Section 4.4 Concomitant medications/treatments	Previous language including table for rescue medications	Added table detailing "prohibited concomitant medications'	***As mandated by sponsor AstraZeneca***
Section 4.5.1 Birth control	Previous language	Added language describing various scenarios and age related restrictions Some repetitive language deleted. Reference to this section added to eligibility criteria 3.1.13 as well.	***As decided after internal review by sponsor and current Durvalumab IB***
Section 4.9 Patient replacement	Previous language: If a patient is enrolled in the study but comes off study before cycle 1 day 1 of treatment, the patient may be replaced.	Added language; A patient who does not reach the first imaging assessment at 2 months for reasons other than clinical progression may be replaced. They will not be used toward assessment of the primary clinical endpoint (ORR), PFS or OS. However, will be included in the final safety analysis	***For clarity***
Section 5.0 Study procedures table	Tabular listing of study procedures with footnotes	Modifications done: 1. Removed Con-meds and general chemistry , hematology and thyroid tests review from the	***For safety, clarity and convenience***

		6,9 and 12 mths follow-up visits 2. Additional labs of LDH,GGT,lipase ,uric acid and amylase along with coagulation and thyroid tests can be done every 2 months in the monotherapy phase 3. Week 22 column created which is similar to week 18. 4. Week 24 column created to illustrate tests done every 2 months in the monotherapy phase. 1. Footnote with ** updated to state that visits 8 through 11 will be repeated. Alsoa dded language to state that scans are to be done every 8 weeks regardless of treatment dealys or drug holds 5. Footnotes 1 and 9: language added to state that bone scans will be done only if the patient has bone disease. 6. Footnote 4 updated to move creatinine clearance from additional chemistry labs to serum chemistry panel. Also language added to state that if total bilirubin is ≥2xULN (no evidence of	

		Gilbert's syndrome) then fractionate into direct and indirect bilirubin. Additional chemistry labs to be monitored every 8 weeks instead of 4 weeks. 7. Footnote 15 updated to state that AE/SAE will now be followed up until 90 days after last dose of either drug. 8. Footnote 16 updated along with corresponding position in the tale, to state that at progression, patients will be offered an optional biopsy. 9. Footnote 17 added to state the labs required to be resulted to start treatment on each treatment day.(this matches with section 4.2) 10. Footnote 18 Language added for a research sample to be collected for all patients on therapy for >12 months (between 12-24 months).	***In order to do additional correlatives to assess long term responders***.
Section 5.1 (table) Study Procedures After 52 Weeks of study treatment	Tabular listing of study procedures with footnotes	Modifications done: 2. Additional labs of LDH,GGT,lipase ,uric acid and amylase along with coagulation and thyroid tests	***For clarity, convenience and consistency***

		can be done every 2 months in the monotherapy phase 3. Footnotes 1 :language added to state that bone scans will be done only if the patient has bone disease. 4. Footnote*** and 1:Added language to state that scans are to be done every 8 weeks regardless of treatment dealys or drug holds 5. Footnote * : added language to state the labs required to be resulted to start treatment on each treatment day.(this matches with section 4.2 and 5.0) 6. Footnote 2 updated to move creatinine clearance from additional chemistry labs to serum chemistry panel. Additional chemistry labs to be monitored every 8 weeks instead of 4 weeks. 7. Removed 'X' from the first row of the table that earlier would have indicated Informed consenting again. 8. Footnote 9 Language added for a research sample to be	***In order to do additional correlatives to assess long term responders***.

		collected for all patients on therapy for >12 months(to be collected between 12-24 months)	
Section 5.0 Footnote 1, 5.1 Footnote 1 and 6 and Section 6.1.1 Endpoint Assessment	No language regarding skin lesion photography	Language inserted regarding photography of skin lesions for disease assessment.	***For convenience and to be complaint with ethical requirements***
Section 6.1.1 Endpoint definitions	Measurable lesions definition: "Must be accurately measured in at least one dimension (greatest diameter) with a minimum size of 10mmx10mm by CT scan (cuts of 5mm or less), MRI, or physical exam (ideally using calipers)"	Updated 10x 10mm to 10mm	***Correction of error***
Section 7.2.5 Durvalumab and Tremelimumab AESI	Different AESIs listed and described individually	Added introductory language for AESIs	***Per sponsor AstraZeneca***
Section 7.2.6.3 Hepatic Function Abnormality(under AESIs)	Previous details	Added Hy's law to this for assessment of cases and categorizing as SAE.	***As decided after internal review by sponsor and PI***

Section 7.3.3.4 Reporting to Medimmune	Previous details	Added language with instructions for reporting of all deaths that occur during the study, or within the protocol-defined 30-day post-last dose of durvalumab + tremelimumab safety follow-up period, to AstraZeneca	***As mandated by sponsor AstraZeneca.***
Section 7.3.3.5 study recording period and follow-up for AEs and SAEs	N/A	New section added with language describing the recording and follow-up of AEs and SAEs	***As decided after internal review by sponsor and PI***
Section 8.1.5 protocol dose specifics	Previous details	New language for preparation, dilution and weight based dosing inserted. Reference to appendix c is made, which contains more details about weight based dosing.	***Based on current Durvalumab IB***
Section 8.1.6 Durvalumab drug preparation	A concentrate for solution will be supplied by AstraZeneca	This has been removed. Now a 500mg vial solution for infusion will be provided and it has to be diluted before use.	***Based on current Durvalumab IB***
Section 8.1.7 Route of administration	For Iv infusion; reconstituted solution (for lyophilized product) was to be diluted with 0.9%(W/v) saline	Reconstituted solution (for lyophilized product) has been removed and the drug is described as 'liquid solution'. 5% (w/v) dextrose can also be used for dilution	***Based on current Durvalumab IB***
Section 8.1.9 availability and supply of Durvalumab	previous details which included description of each vial containing drug product	Description of each vial removed. Drug product will now be supplied as a liquid solution that needs to be diluted before infusion.	***Based on current Durvalumab IB***
Section 8.1.11 Nursing implications for Durvalumab	previous language	New details about infusion windows, incompatibilities and maximum time between doses have been inserted	***Based on current Durvalumab IB***

Section 8.2.5 protocol dose specifics for Tremelimumab	Previous language	New language on dose preparation and weight based dose calculation inserted. Reference to Appendix D made which contains further details	***Based on current Durvalumab IB***
Section 8.2.6 preparation of Tremelimumab	Previous storage details	storage details have been modified	***Based on current Durvalumab IB***
Section 8.2.9 Availability and supply of tremelimumab	Tremelimumab will be supplied as a sterile solution, packaged in 20-mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL of tremelimumab (with a nominal fill of 400 mg per vial) in 20 mM histidine buffer, pH 5.5, with 84 mg/mL of trehalose dihydrate, 0.2 mg/mL polysorbate 80, and 0.1 mg/mL disodium-EDTA dihydrate.	Removed this language. The standard supply of tremelimumab is delivered in a white carton with 16 vials of tremelimumab within foam inserts.	***Based on current Tremelimumab IB/procedures***
Section 8.2.11 Nursing implications for Tremelimumab	Previous information	New details about infusion windows inserted. Maximum time between infusions have been stated. Incompatibilities of Tremelimumab have been clarified	***For increased safety and clarity***
Section 8.3 and 8.3.1	Study drug preparation durvalumab and tremelimumab This included instructions for dose volume calculation for patients <30 kgs, for both drugs	Removed the instructions for dose volume calculation for patients ≤30kgs body weight. Patients with a body weight ≤ to 30 kg will be excluded.	***Since a new inclusion criteria states that patients must weigh greater than 30kgs***
Section 8.3.2	Monitoring of dose administration (instructions apply to both drugs-combination regimen)	Modified language to say that , If the infusion-related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued and this is will apply during Durvalumab monotherapy as well.	***For clarity***

Section 8.3.3	Side Effects when durvalumab and tremelimumab are given together	Added language; **(see current IB for full details)**	***For clarity***
Section 9.2 Research blood sample collection	previous details	Added language: For a research sample to be collected for all patients on therapy for >12 months(to be collected between 12-24 months)	***In order to do additional correlatives to assess long term responders***.
Section 10 Statistics	Details about design, sample size and analysis	Added language for TNBC expansion cohort sating that it will have similar design as general cohort and responses will be captured by RECIST 1.1. In addition, it states the use of Bayesian design for analysis. Other language modified to align with the new updates. Sample size and accrual language modified to state: Eleven patients will be added in the first stage. If 2 or more respond, then an additional 16 patients will be added for a total of 27. If 6 or more respond, then the hypothesis that the response rate is at least 30% is supported. This design has a Type I error rate of 4% and 80% power, and has a 70% chance of stopping early for futility after the first stage if the true response rate is 10%.	***In order to accommodate and analyze the expansion cohort of TNBC patients***

Section 11.8 Publication policy	Previous details	Added language: "All clinical data, all blood and tissue samples, and publication/authorship rights will be under the direct supervision of Dr. Massimo Cristofanilli. Any use of data or resultant publication must be approved directly by Dr. Cristofanilli"	***Per PI, for clarity***
Appendix A	Table containing acceptable methods of contraception	Table removed. Reference made to section 4.5.1 for contraception details	***Due to repetition of information. Section 4.5.1 contains current sponsor approved language***
Appendix C	N/A	New appendix added which describes "Durvalumab weight based dose calculation"	***For added clarity and convenience***
Appendix D	N/A	New appendix added which describes "tremelimumab weight based dose calculation"	***For added clarity and convenience***
Amendment 9 October 20th, 2017(re-submitted to SRC with version date 12.7.17)			
Section(s) Affected	***Prior Version***	***Amendment 9 updates***	***Rationale***

Section 1.3 Section 1.7.1	Referenced outdated data for durvalumab and tremelimumab dosing.	Deletes old data and replaces with new data about the PD-L1 blockade mechanism, durvalumab fixed dosing (versus weight-based dosing),	***Updated per durvalumab IB edition 12***
Section 1 References	n/a	Updates all reference numbers and bibliography to incorporate EndNote and correct numbering of references in order of appearance.	***Administrative document update and to account for new data from durvalumab IB edition 12***
Study procedure tables Section 5.1 footnote **, 1 and 9 and Section 5.2 Footnote 1 and 6	Note: Bone scans will be done only if the patient has bone disease.	Added language:"PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a patient's disease. The same modality used at baseline should be used throughout."	***For safety and flexibility***
Section 7.2.5	n/a	Adds new AESI's related to durvalumab +/- tremelimumab as well as additional data for existing AESI's. New AESI's include: • Intestinal perforation • Myositis/polymyositis • Myocarditis • Other inflammatory responses	***Updated to align with durvalumab IB edition 12***
Section 10 Statistics	Patients who have completed the week 8 CT or nuclear bone scan will be evaluable for response endpoints.	Added language: "Bone scans will be done only if the patient has bone disease. PET-CT is acceptable in place of bone scan, if a bone scan is contra-indicated for a patient's disease. The same modality used at baseline should be used throughout."	***To be in alignment with the updates made to Section 5***

References	The section heading was missing	References heading added	***Correction of error***

Amendment 10– 1.10.19

Section(s) Affected	***Prior Version***	***Amendment 10 Changes***	***Rationale***
Section 4.3 Toxicity management and dose delays/modifications	Previous management details based on earlier toxicity tables received from AstraZeneca	Updated with most current toxicity management and dose modifications tables received from AstraZeneca dated Nov 2017. In addition, the cardiac toxicity details have been updated based on Durvalumab ***action letter*** dated 8.6.18	***To be in alignment with most current specifications from AstraZeneca***
Section 5 Study procedures table	AEs/SAEs were indicated to be assessed at the 6, 9 and 12 month visits (after last dose of treatment) as well.	Updated to indicate that AEs/SAEs will only be followed up till the 3 month visit (after the last dose of treatment)	***Correction of discrepancy since the rest of the protocol states that AEs/SAEs are to be followed up for 90 days after the last dose of treatment***.
Section 7.2.6. Other events requiring immediate reporting	Incorrect reference to section 10.3 for contact information	Correct reference to section 7.3.34 for contact information regarding Safety e-mailbox for AstraZeneca	***Correction of error***

Amendment 11– 10.29.19			
Section(s) Affected	***Prior Version***	***Amendment 11 Changes***	***Rationale***
Title page	Massimo Cristofanilli, MD was still listed as Sub-I	Removed Dr.Cristofanilli and added Claudia Tellez, MD as sub-I	***Administrative update [Dr.Cristofanilli is the PI for this study].***
		Added affiliate PI: Cesar A.Santa-Maria, MD from Johns Hopkins	***On boarding of first affiliate site for this study.***
	Alfred Rademaker, PhD still listed as biostatistician	Removed Alfred Rademaker and added Masha Kocherginsky, PhD as biostatistician	***Change of statistician. Alfred Rademaker is no longer at NU.***
	MedImmune listed as funding source	Specified that MedImmune is only drug source.	***MedImmune is only supplying drug for this study.***

Section 1.3 Background: Immune Checkpoint Blockade in Breast Cancer	Previous language regarding immune checkpoint blockade	Updated with current developments in immune checkpoint blockade in breast cancer. This language serves as rationale for modification to the eligibility criteria which now facilitates the enrollment of PD-L1 negative patients in the front line setting only into the trial. It has been clarified that beyond frontline, any PD-L1 status is acceptable. this will give the study some wriggle room for enrollment	***Updates made based on evolving clinical landscape. Reference provided.***
Section 3.1.1 Inclusion criteria and Study summary	Criteria stated requirements for both general and expansion cohort. Expansion cohort included. The expansion cohort will only include HER2-negative, ER and PR-negative patients.	The general cohort details are now included as a note. The Expansion cohort will now enroll only metastatic TNBC patients.	***Enrollment to general cohort is done. Only expansion cohort is now enrolling patients. TNBC patients alone are being enrolled. Rationale explained in section 1.7.3***
Section 3.1.3 Inclusion criteria and Study summary	Along with other requirements, patients with ER positive disease were included.	Patients with ER positive disease removed and PD-L1 negative patients in the front line setting are now eligible. A note has been inserted to clarify that beyond frontline, any PD-L1 status is acceptable	***Based on current clinical landscape, explained in the background section.***
Section 3.2.6 Exclusion criteria	For ECGs the Friderica's Correction was listed	Friderica's correction replaced by Bazett's formula.	***To align with standard procedures used at NU***

Section 3.1.13 Inclusion criteria	Criteria regarding birth control	Inserted Appendix A	***For clarity and consistency***
Section 4.3 Toxicity Management & Dose Delays/Modifications	Previous version of toxicity management guidelines	Removed previous version. Inserted : Updated toxicity management guidelines (dated Oct 2019)	***Based on information received from AstraZeneca***
Section 4.9 Patient replacement	A patient who does not reach the first imaging assessment at 2 months for reasons other than clinical progression may be replaced. They will not be used toward assessment of the primary clinical endpoint (ORR), PFS or OS. However, they will be included in the final safety analysis	Previous language has been reworded to state: "A patient who does not reach the first imaging assessment at 2 months for reasons other than clinical progression will not be used toward assessment of the primary clinical endpoint (ORR), PFS or OS. However, they will be included in the final safety analysis. Additional patients may be added if needed for assessment of response."	***For increased clarity***
Section 5.0 Study procedures table	Discrepancy between the footnotes and the 'X' in the table for Thyroid tests and LDH , GGT, lipase, uric acid and amylase Research blood sample collection had a follow-up sample that was stated in footnote 18 and indicated in the table	Corrected the discrepancy by moving the 'X's to the right columns. This 'X' has been removed and footnote 18 has been removed as well.	***Correction of discrepancy*** ***This sample is no longer being collected.***

Section 5.1 Study Procedures After 52 Weeks of study treatment	Research blood sample collection indicated in the table along with footnote 9	This has been removed	***This sample is no longer being collected.***
Section 8.2.9 Tremelimumab Availability and supply	Previous language. Tremelimumab was being supplied as a 400mg vial solution.	Replaced by updated language as mandated by AstraZeneca. Tremelimumab will now be supplied as either 400mg or a 25mg vial solution for infusion after dilution.	To add flexibility for AstraZeneca to send smaller vials of tremelimumab.
Section 9.2 Blood sample Collection Guidelines	Another research sample will be collected at 12 months. If the sample is not collected at 12 months, it can be collected anytime between 12-24 months, while the patient is in therapy	This has been removed	***To align with updates made to the rest of the protocol. {This sample is no longer being collected}.***
Exclusion criteria	Numbering of criteria was wrong. There were two 3.2.2	Numbering had been corrected	***Correction of error***
Throughout	N/A	Minor language updates made for clarity	***For increased clarity and consistency across the protocol.***

Section 11.3 Study Management 'Registration procedures'	Standard language from old protocol template	Replaced by standard language from current protocol template	***Administrative update***
Section 11.4 Study Management 'Data submission'	Standard language from old protocol template	Replaced by standard language from current protocol template	***Administrative update***
Section 11.5 Instructions for participating sites	N/A	New sub-section added	***Since affiliate sites are now joining the study.***
Section 11.6 Study management 'Data management and Monitoring/Auditing	This was previously section 11.5. It contained standard language from old protocol template	This is now section 11.6 since we have a new section 11.5 dedicated as described above. This now contains standard language from current protocol template	***Administrative update***
Section 11.9 Study Management 'Publication policy'	This was previously section 11.8. It contained standard language from old protocol template	This now contains standard language from current protocol template	***Administrative update***

Appendix D Tremelimumab weight based dose calculation	Previous language	Language updated to align with Section 8.2.9	***For clarity and consistency***
Amendment 11 dated 10.29.19 [version 11.1]			
Section(s) Affected	***Prior Version***	***Amendment 11.1 Changes***	***Rationale***
Title page	Added Masha Kocherginsky, PhD, as biostatistician replacing Alfred Rademaker	Removed Masha Kocherginsky, PhD, as biostatistician and added Borko Jovanovic, PhD as biostatistician	***Re-assignment of statistician***
Amendment 12 dated 8.31.2020			
Title page	Inclusion of Johns Hopkins as an affiliate site with Dr.Cesar Santa-maria as PI	Removal of Johns Hopkins as an affiliate site	***Johns Hopkins will no longer join the study as an affiliate site. This study was closed on 7.20.2020 due to low accrual, as decided by PI in agreement with SRC sub-committee for Accrual Review***

Section 3.1.13 Inclusion criteria regarding use of birth control	Reference to Appendix A made here for details	Reference to Appendix A has been replaced with reference to Section 4.5.1	***For convenience.*** ***Section 4.5.1 contains the specified information. Appendix A also refers to this section***
Exclusion criteria	Numbering was incorrect. There was a repetition of number 3.2.7 after 3.2.8 which made the rest of the numbering incorrect	Numbering has been corrected	***Correction of error***

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