**A Pilot Study of Brain Irradiation and Tremelimumab in Metastatic Breast Cancer**

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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**Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program**.

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# 1.1 PROTOCOL SUMMARY AND/OR SCHEMA

## 1.2 Brief Rationale

Breast cancer brain metastases commonly arise following multiple lines of cytotoxic chemotherapy. The standard-of-care is to suspend cytotoxic therapy, treat with brain radiotherapy (either whole brain or stereotactic), and subsequently treat with additional cytotoxic chemotherapy. Based on the premise that radiation therapy induces tumor antigen release, concurrent treatment with tremelimumab—a therapeutic immune checkpoint antibody—may induce anti-tumor immunity and systemic disease control. Thus, the overarching goal of this study is to utilize brain irradiation as a "window of opportunity" to provide effective immunotherapy, which may provide a period of respite from the cumulative toxicities of cytotoxic chemotherapy and potentially induce clinically significant systemic disease control in a patient population for whom few or no alternative effective therapies remain.

## 1.3 Protocol Summary

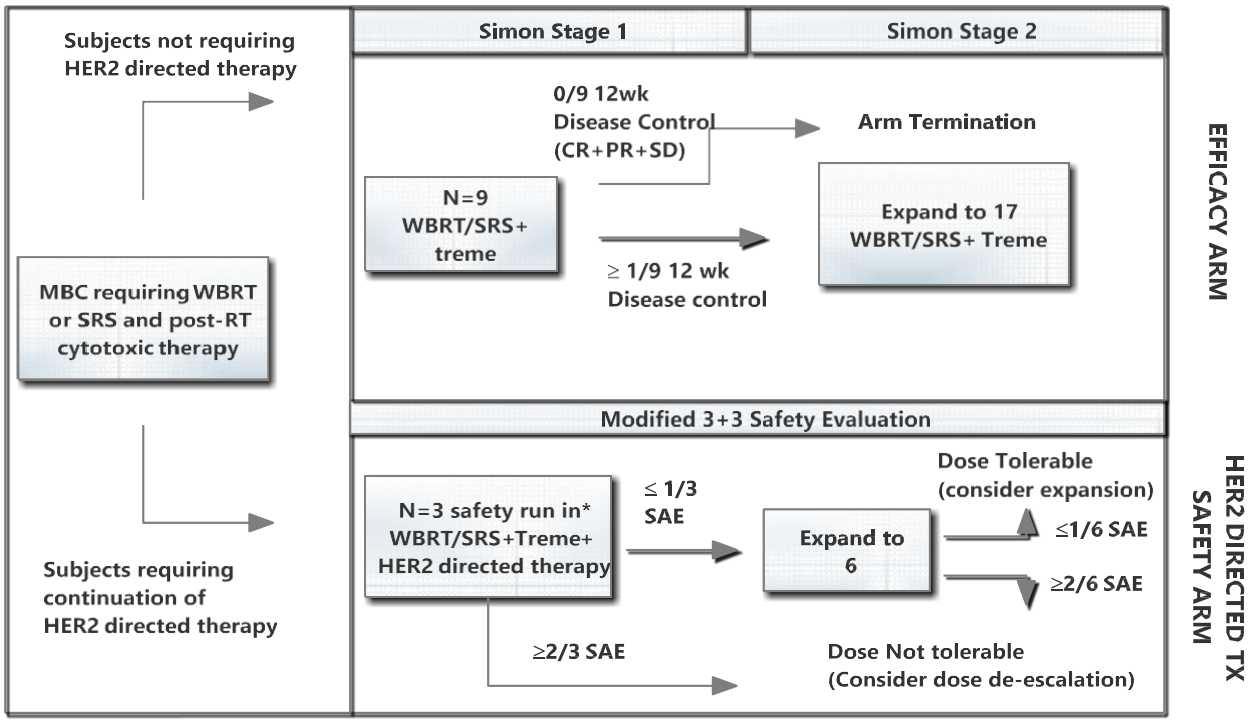
A single institution pilot study evaluated the combination of tremelimumab (treme) plus brain irradiation +/- HER2 directed therapy in breast cancer patients with brain metastasis (BCBM) for whom post-brain irradiation cytotoxic chemotherapy was planned. Subjects received either whole brain radiation treatment (WBRT) or stereotactic radiosurgery (SRS), as per standard of care, with tremelimumab administered at 10mg/kg every 28 days. All breast cancer subtypes were eligible for enrollment: subjects not requiring concurrent HER2 directed therapy such as trastuzumab (tras), were enrolled in a Simon 2-stage efficacy arm, whereas subjects with HER2-positive (i.e. HER2 overexpressing and/or amplified) disease requiring continuation of HER2 directed therapy were enrolled in a HER2 directed therapy safety arm designed to evaluate the safety of HER2 directed therapy and tremelimumab/RT co-administration. As of 3/1/2017, the 12 week disease control rate was 2/10 (10%) in the efficacy arm and 2/6 (33%) in the safety arm. One patient treated with concurrent HER2-directed therapy had a 57% partial response by RECIST v1.1 that was durable at 6 months. Overall, the regimen was well tolerated with 15 Grade 3 and no Grade 4 attributable toxicity events reported. The most comment treatment related AEs were diarrhea (12.9%), fatigue (9.7%), and colitis (6.5%). Thus, an expansion of the HER2 arm is planned in a parallel Simon two-stage design to evaluate efficacy of brain RT with checkpoint blockade and concurrent HER2-directed therapy. However, because of the diarrhea and colitis associated with tremelimumab mediated CTLA4 blockade when administered at 10mg/kg monthly (a well described class effect), a lower dose of tremelimumab will be co-administered with trastuzumab in the expansion study in combination with durvalumab, a PD-L1 directed antibody that is currently US FDA approved for other indications.

### 1.2.1 Protocol Expansion Summary

Given the safety and response demonstrated in the safety arm of patients treated with brain RT, checkpoint and HER2-directed therapy, this arm will be expanded to evaluate efficacy in a Simon two-stage design. In this expansion, we will evaluate the combination of tremelimumab (treme), durvalumab (durva), and HER2 directed therapy plus brain irradiation in breast cancer patients with brain metastases (BCBM) for whom post-brain irradiation cytotoxic chemotherapy is planned. Subjects will receive either whole brain radiation treatment (WBRT) or stereotactic radiosurgery (SRS), as per standard of care, with tremelimumab administered at 75 mg and durvalumab administered at 1500mg every 28 days for 4 cycles.

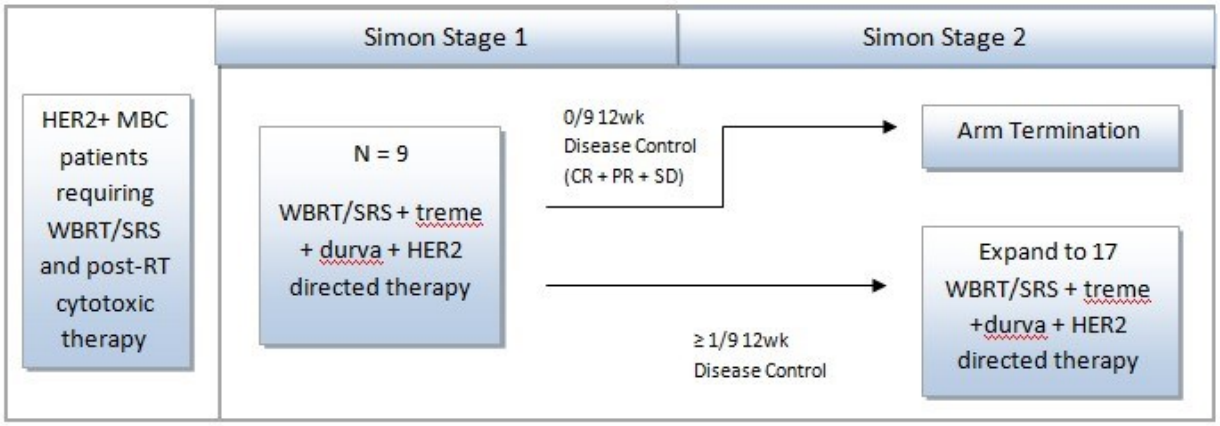
After the 4th cycle, patients will continue to receive 1500mg durvalumab every 28 days. Patients will continue to receive HER2 directed therapy at a NCCN-guideline-endorsed dose and schedule, as determined by the treating investigator. The same study design parameters will be applied to the expansion (Fig 1.2-2) as were previously applied to the completed efficacy cohort not requiring concurrent HER2 directed therapy (Fig 1.2-1).

**Figure 1.2-1: Design Schematic**




SAE: Serious adverse event requiring tremelimumab discontinuation
*Safety run-in: 6 week intra-subject enrollment hold across first 3subjects

Figure 1.2-2 Study Expansion Design Schematic



## 1.4 Efficacy Arm (Completed as of 3/1/2017)

The primary objective of the trial will be to evaluate non-CNS disease control of tremelimumab plus brain irradiation at 12 weeks, defined as either complete response (CR), partial response (PR), or stable disease (SD) by RECIST1.1 criteria. A Simon 2-stage design will be employed. A maximum of 17 subjects will be accrued to the efficacy arm. After the first 3 patients are enrolled in the efficacy arm, a 6 week enrollment hold will be conducted in order to ensure safety before additional patients are enrolled. An interim assessment will then occur after the first 9 subjects have enrolled, and the accrual to this arm will proceed only if a pre-specified futility threshold is met. Patients not requiring continuation of HER2 directed therapy will be enrolled in this arm.

After the first 3 patients in the efficacy arm complete the 6 week enrollment hold, safety will be assessed on a continuous basis, and enrollment will be suspended if toxicities exceed the pre-defined safety threshold.

## 1.5 HER2 directed therapy Co-administration Arm (Completed as of 3.1.2017)

Women with HER2-overexpressing breast cancer for whom continuation of HER2 directed therapy is indicated will be eligible to enroll in an arm that will enroll concurrently with the efficacy arm, but will evaluate the safety of HER2 directed therapy and tremelimumab co-administration.

Subjects in the co-administration arm will receive RT and tremelimumab at the same schedule and dose as the efficacy arm, but will continue to receive HER2 directed therapy at a NCCN-guideline-endorsed dose and schedule, as determined by the investigator. For heightened safety monitoring, a safety run-in will be performed, whereby each of the first 3 subjects will require a 6-week hold prior to enrollment of the subsequent subject. Accrual will follow a modified 3+3 design, to minimize drug exposure if the treatment is not tolerable.

## 1.6 Protocol Expansion (Planned as of 3.1.2017)

Subjects in the study expansion will be enrolled in a Simon two-stage arm, designed to evaluate the safety and efficacy of tremelimumab, durvalumab, HER2 directed therapy, and RT co-administration. A maximum of 17 patients will be accrued to this stage. After the first 3 patients are enrolled, a 6 week enrollment hold will be conducted in order to ensure safety before additional patients are enrolled. An interim assessment will then occur after the first 9 subjects have enrolled, and the accrual to this arm will proceed only if a pre-specified futility threshold is met. After the first three patients in this stage complete the 6 week enrollment hold, safety will be assessed on a continuous basis, and enrollment will be suspended if toxicities exceed the pre-defined safety threshold.

## 1.7 Drug administration and Radiation Initiation

1.6.1 Efficacy and HER2-directed Safety Arms (Completed as of 3.1.2017)

In both the efficacy arm and HER2 directed arms, tremelimumab was administered intravenously at 10mg/kg 2 days prior to the initiation of radiotherapy. In cases where this was not feasible, tremelimumab was administered at any time during a period of 5 days preceding the initiation of radiotherapy, to 3 days following initiation of radiotherapy. Subsequent doses of tremelimumab were administered every 28 days

+/- 1 week until progression or intolerable toxicity. The dosing schedule was based on a patient's first dose of tremelimumab.

1.6.1 HER2 Expansion (Planned as of 3.1.2017)

In the protocol expansion, tremelimumab will be administered at 75 mg and durvalumab will be administered at 1500 mg 2 days prior to the initiation of radiotherapy. In cases where this is not feasible, tremelimumab and durvalumab may be administered at any time during a period of 5 days proceeding initiation of radiotherapy to 3 days following initiation of radiotherapy. Subsequent doses of tremelimumab and durvalumab will be administered every 28 days +/- 1 week for 4 cycles. After the 4$^{th}$ cycle, durvalumab 1500 mg will be administered until disease progression or intolerable toxicity. The dosing schedule will be based on the patient's first dose of tremelimumab and durvalumab. Patients will receive HER2 directed therapy at the NCCN-guideline-endorsed dose and schedule, as determined by the investigator.

During tremelimumab +/- durvalumab administration, systemic therapy beyond HER2-directed therapy will be suspended until confirmed radiographic progression or clinical deterioration, at which ti me tremelimumab +/- durvalumab will be discontinued and systemic therapy may be initiated. Subjects who initiate non-study cancer-directed systemic therapy before the imaging assessment will be considered treatment failures when determining the primary endpoint.

Concurrent administration of bone modifying agents (i.e. Denosumab or zoledronic acid) is permitted on study.

Week 1 is the week of first treatment. Response assessment will occur 12 weeks thereafter (i.e. at week 13 +/- 1 week), with a confirmatory scan at 16 weeks (i.e. week 17 +/- 1 week ) in patients with evidence of radiographic progression at week 13 (Table 10.0-1). Responses will be determined by standard-of-care whole body imaging contrast-enhanced CT chest abdomen pelvis. For patients with bone metastases or with an appropriate clinical indication, concurrent bone scan or PET scan is recommended. Other imaging modalities will be performed as clinically indicated at the discretion of the investigator.

When feasible, subjects with symptomatic brain metastases will be managed conservatively without the use of steroids. Subjects requiring steroids for symptom management will be eligible for enrollment as outlined in section 9. CNS and systemic response assessments will be evaluated every 12 weeks starting at week 13 (i.e. 12 weeks after treatment in week 1). Research bloods will be obtained for immune monitoring.

## 2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

- To determine 12 week non-CNS disease control (CR + PR + SD) of the combination of tremelimumab plus brain irradiation (SRS or WBRT) by RECIST 1.1 criteria

- To determine 12 week non-CNS disease control (CR + PR + SD) of the combination of tremelimumab, durvalumab, and HER2 directed therapy plus brain irradiation (SRS or WBRT) by RECIST 1.1 criteria.

Secondary Objectives

- To determine the safety profile of tremelimumab +/- durvalumab and HER2 directed therapy co-administration plus brain irradiation
- To determine 12 week non-CNS objective response and disease control rate by immune related response criteria
- To determine non-CNS objective response, and progression free survival (PFS) by RECIST 1.1 criteria
- To determine overall survival
- To determine 24-week CNS objective response rate, 24-week CNS PFS, and CNS median PFS

Exploratory Objectives

- To evaluate the effect of tremelimumab +/- durvalumab + RT on: lymphocyte phenotype and serum cytokines, disease related biomarkers, humoral and cellular responses to tumor antigens and recall non-tumor antigens
- To evaluate serological and cellular immune correlates of toxicity and/or clinical activity
- To explore the radiologic changes by PET/CT with tremelimumab +/- durvalumab and RT administration
- To evaluate the efficacy of tremelimumab +/- durvalumab and HER2 directed therapy co-administration plus brain irradiation

## 3.1 BACKGROUND AND RATIONALE

### 3.2 Epidemiology of breast cancer brain metastases

Breast cancer is a global public health burden with more than 200,000 new cases diagnosed each year in the United States and more than one million new cases diagnosed worldwide each year (Society 2012). Despite effective screening and treatment, about one-third of women diagnosed with early stage disease develop lethal distant metastases. Furthermore, brain metastases are a relatively common and devastating complication of breast cancer. Hence, more effective approaches are needed. The uniqueness of tumors and hosts provides an opportunity for individualized treatment. Because the synergistic effect of radiotherapy (RT) and immunotherapy has been demonstrated in multiple preclinical studies and because RT combined with immunotherapy may confer an abscopal effect with regression of distant metastases, our proposed strategy uses immune stimulation to augment the therapeutic impact of whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS) on clinical outcomes for women with breast cancer brain metastases (BCBM). Thus, the central goal for this project is to make a major advance for women with BCBM by augmenting an effected individual's immune response to their existing tumor.

Brain metastasis is a relatively common and devastating complication of breast cancer. In fact, breast cancer is the second most common cancer associated with brain metastasis in the United States (Barnholtz-Sloan, Sloan et al. 2004). Both the incidence and prevalence of BCBM are rising (Frisk, Svensson

et al. 2012). Although brain metastases are diagnosed in approximately 15% of breast cancer patients, autopsy data suggest a prevalence of up to 30%-40% (Tsukada, Fouad et al. 1983). Brain metastasis secondary to breast cancer is an independent poor prognostic factor, with variable outcomes depending on histologic subtype.

### 3.2 Breast Cancer Brain Metastases at MSKCC

Because published outcomes data for women with BCBM treated in the modern treatment era are limited, we performed a retrospective study of our recent experience with this disease at Memorial Sloan-Kettering Cancer Center (MSKCC) (Morikawa, Diab et al. 2013). For women with newly diagnosed BCBM and treated with brain RT at MSKCC between January 2009 and December 2011, the median time from brain metastases to death for all patients was 15.3 months (10.9-18.2mo, 95% CI). The distribution by subtype was as follows: 28/113 (25%) HER2-positive (HER2+); 59/113 (52%) hormone receptor-positive, HER2-negative (HR+HER2-); and 26/113 (23%) hormone receptor-negative, HER2-negative, or "triple negative" (HR-HER2-). The majority (70%) were treated with WBRT. By subtype, the median time from brain metastases to death was 32.8 months for women with HER2+ disease; 12.7 months for women with HR+HER2- disease; and 11.3 months for women with HR-HER2- disease (p=0.001). The median time to death was 12.0 months for women treated with WBRT, and 23.0 months for women treated with SRS. These outcomes represent significant improvements when compared with published historical data, thereby implying that improvements in systemic and/or local therapeutic strategies have translated into improved survival for women with BCBM. However, despite these improvements, the prognosis for these women remains poor and further inroads are desperately needed.

### 3.3 Current Standard of Care for Treating Brain Metastases

Brain metastases are a particularly challenging clinical manifestation of breast cancer. Conventional systemic therapies have demonstrated limited effectiveness in preventing and treating brain metastases, as least in part because of the blood-brain barrier. For example, the successful development of trastuzumab in HER2+ breast cancer translated into an approximately 50% reduction in the risk of distant metastases when administered in the adjuvant setting (Slamon, Eiermann et al. 2011). However, in women with HER2+ metastatic breast cancer (MBC) treated with chemotherapy and trastuzumab, approximately 30% develop central nervous system (CNS) metastases (Gori, Rimondini et al. 2007). It was hoped that the small size of lapatinib, a tyrosine kinase inhibitor of EGFR and HER2, would permit CNS penetration and therefore, provide effective systemic treatment of brain metastases. However, studies of single agent lapatinib and lapatinib in combination with chemotherapy did not confer significant benefits (Lin, Carey et al. 2008). Response rates to systemic therapies have been similarly disappointing for other histologic subtypes. Consequently radiotherapy remains the cornerstone for the treatment of BCBM, palliating neurologic symptoms and potentially prolonging survival (Wong, Hird et al. 2009).

### 3.4 Rationale for Immunotherapy in Breast Cancer Brain Metastases

Despite promising initial response rates with brain radiotherapy, CNS failure is common (Ogura, Mitsumori et al. 2003). Therefore, local control in the brain could potentially be improved by combining radiotherapy with a systemic strategy that augments and prolongs the host immune response to radiotherapy-generated tumor-specific antigens. One such systemic strategy is the use of a therapeutic immunologic

checkpoint blockade antibody such as ipilimumab or tremelimumab. In melanoma patients with brain metastases, the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, ipilimumab, generated 14% disease control as monotherapy. (Margolin, Ernstoff et al. 2012)

Immunotherapy for the treatment of metastatic breast cancer has long been a goal of scientists and clinicians. However, numerous challenges to successful implementation have included limited numbers of viable targets as a consequence of tumor heterogeneity, limited efficacy of available agents, and the lack of sustained anti-tumor effects even in the face of increased immune responses. Despite these challenges, a recent and growing literature indicates that immune therapy for the treatment of breast cancer is a viable strategy. Studies have demonstrated the prognostic and predictive impact of tumor tissue infiltration by T effector (Teff) and T regulatory (Treg) cells in curable breast cancer (Bates, Fox et al. 2006, Ladoire, Mignot et al. 2011, Mahmoud, Paish et al. 2011). Furthermore, in the retrospective MSKCC study of outcomes after BCBM diagnosis in the modern treatment era, an absolute lymphocyte count ≥0.7/ul was associated with improved survival (Morikawa, Diab et al. 2013). Together, these data suggest that there is a critical relationship between the immune system and breast cancers, thereby supporting the pursuit of tumor-specific immunotherapy in this setting.

## 3.5 Anti-CTLA-4 therapy

CTLA-4 is a homolog of the co-activation receptor CD28 that, when bound to B7 ligands (CD80 and CD86), inhibits T-cell function by both intrinsic and extrinsic mechanisms (Krummel and Allison 1995). CTLA-4 induces inhibitory downstream T-cell receptor signaling, but also leads to up-regulation of CTLA-4 expression and competitive inhibition of CD28-mediated co-activation. CTLA-4 is also highly expressed on $CD25^{+}FOXP3^{+}$ T-regulatory ($T_{reg}$) cells and is instrumental in $T_{reg}$ function. CTLA-4 blockade been shown to promote T-cell activation, as well as depletion of intratumoral $T_{regs}$ (Quezada and Peggs 2013) Ipilimumab (IgG1) and tremelimumab (IgG2) are the two human anti-CTLA-4 antibodies that have undergone clinical evaluation.

## 3.6 Safety and Efficacy of Tremelimumab

### 3.6.1 Product Derivation

Tremelimumab is a human IgG2 mAb directed against CTLA-4. Tremelimumab has an overall molecular weight of approximately 149 kDa induding oligosaccharides. Cytotoxic T lymphocyte-associated antigen 4 is a critical regulatory signal for T-cell expansion and activation following an immune response, and it serves as a natural braking mechanism that maintains T-cell homeostasis. During T-cell activation, T cells upregulate CTLA-4, which binds to B7 ligands on antigen-presenting cells, sending an inhibitory signal that limits T-cell activation. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to B7, leading to prolongation and enhancement of T-cell activation and expansion.

#### 3.6.2 Summary of Nonclinical Experience

In vitro, specific mAbs directed against CTLA-4 enhance T cell function, measured by increased production of IL-2, IFN-γ, and other cytokines. In CTLA-4 knock-out mice, extensive, polyclonal lymphoproliferation

develops that is consistent with dysregulated activation of lymphocytes. Treatment of tumor-bearing mice with anti-mouse CTLA-4 mAb (9H10) can induce antitumor immunity and markedly enhance T cell-mediated killing of various mouse solid tumors. At a concentration of approximately 30 µg/mL 9H10, anti-tumor activity of 9H10 was observed in vivo. Thus, a concentration of ~ 30 µg/mL was identified as the target plasma concentration.

#### *3.6.2.1 Pharmacokinetics*

The pharmacokinetics (PK) of tremelimumab were evaluated in cynomolgus monkeys following single (0.75, 10, 30, and 100 mg/kg) and multiple (5 to 50 mg/kg weekly) intravenous (IV) administrations. The PK of tremelimumab is characterized by a low plasma clearance (CL = 4.32 mL/day/kg), small volume of distribution at steady-state ($V_{ss}$ = 53.8 mL/kg), and long half-life (t½ = 9.1 days). In toxicologic studies in cynomolgus monkeys, systemic exposures of tremelimumab, assessed by the mean peak observed concentration ($C_{max}$) and mean area under the concentration-time curve (AUC), increased dose-proportionally within the dose ranges examined following single or multiple IV administrations. No evidence of nonlinear PK or gender-related differences in exposures was observed. Anti-drug antibody (ADA) responses were detected in some animals from all dose groups following single or multiple IV administrations of tremelimumab. Finally, PK and ADA responses of clonally- and nonclonally-derived tremelimumab were comparable.

Population PK analysis of tremelimumab was performed on combined data from Phase 1, Phase 2, and Phase 3 studies (N = 654) in subjects with metastatic melanoma using nonlinear mixed-effects modeling in NONMEM software. A 2-compartment population PK model adequately described the plasma concentrations of tremelimumab following various dosing regimens. The population estimate for CL and central volume of distribution (V1) was 0.26 L/day and 3.97 L, respectively. The inter-individual variability in CL and V1 was modest (31.8% and 20.4%, respectively). Clearance was faster in males, subjects with higher values of creatinine clearance and endogenous Ig, and subjects with relatively poor baseline prognostic factors. Central volume of distribution was higher in males and subjects with higher body weight. No dose adjustment was needed based on the magnitude of the change in L(< 30%; Wang et al,

201 4). Preliminary population PK of tremelimumab was performed using data from two second-line, single-arm investigator-initiated Phase 2 studies (NCT01 649024 /N CT0 1655888) in subjects with malignant mesothelioma. A total of 40 subjects provided evaluable PK data following 15 mg/kg Q90D [NCT01649024] or 10 mg/kg Q4W for 6 months followed by 10 mg/kg Q12W [NCT01655888] dosing regimens. Tremelimumab PK exposure in mesothelioma subjects was similar to previous melanoma studies following 15 mg/kg Q90D. Following the 15 mg/kg Q90D, PK exposure was below the target trough level of approximately 30 µg/mL for about half of the dosing interval with almost all subjects below the lower limit of quantitation at the end of the 90-day dosing interval. Following more frequent dosing of 10 mg/kg Q4W, PK exposure was increased and maintained at or above the target level in the majority of subjects over the entire dosing interval. Tremelimumab PK was best described using a 2-compartment linear model with first order elimination. Following IV dosing, the typical CL and V1 were 0.2 L/day and 3.5 L, respectively. The between-subject variability for CL and V1 were 22% and 7%, respectively. The estimated typical PK parameters were similar to other mAbs without target mediated elimination. The baseline body weight and Eastern Cooperative Oncology Group (ECOG) performance status were identified as significant

covariates for CL, whereas only baseline body weight was significant covariate for volume of distribution. These correlations will be further validated using data from larger clinical studies.

#### *3.6.2.2 Toxicology*

The toxicology program conducted for tremelimumab consisted of in vivo general toxicology studies in cynomolgus monkeys for up to 6 months duration, an embryo-fetal development study in monkeys, tissue cross-reactivity studies in both monkey and human tissues, and blood compatibility studies. The cynomolgus monkey was considered to be the only pharmacologically relevant species for nonclinical safety testing of tremelimumab, based on similar binding and potency against cynomolgus monkey and human CTLA-4 and lack of binding to rodent CTLA-4-Ig. Overall, tremelimumab toxicities were consistent with inhibition of CTLA-4 and with clinical safety findings, and indicated that chronic clinical use of tremelimumab may lead to adverse effects on the gastrointestinal tract, skin, lymphoid organs, thyroid tissues, and hematological systems. Dose-limiting toxicities (DLTs) were identified in chronic toxicity studies in monkeys and include persistent diarrhea microscopically correlated with mononuclear cell inflammation in the cecum, colon, and/or duodenum, weight loss, and development of adverse skin conditions (scabbed areas; open sores; swollen eyelids; dry, scaly, or crusted skin; rash or reddened skin; yellowish skin) accompanied histologically with mononuclear cell inflammation. Most toxicities were reversible or showed a trend towards reversibility.

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

### 3.6.3 Summary of Clinical Experience: Monotherapy

As of November 12, 2014 (for all studies except D4190C00006 that has a cutoff date of December 4, 2014), 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 9 are ongoing. Tremelimumab has been administered as monotherapy to 973 subjects participating in 10 of the 22 clinical studies, 2 of which are ongoing. An additional 497 subjects have received tremelimumab or placebo in the ongoing double-blinded, Phase 2b mesothelioma study, D4880C00003 (DETERMINE; data remain blinded). Tremelimumab in combination with other anticancer agents has been administered to 208 subjects with a variety of tumor types in 12 of the 22 clinical studies, 7 of which are ongoing.

#### *3.6.3.1 Efficacy*

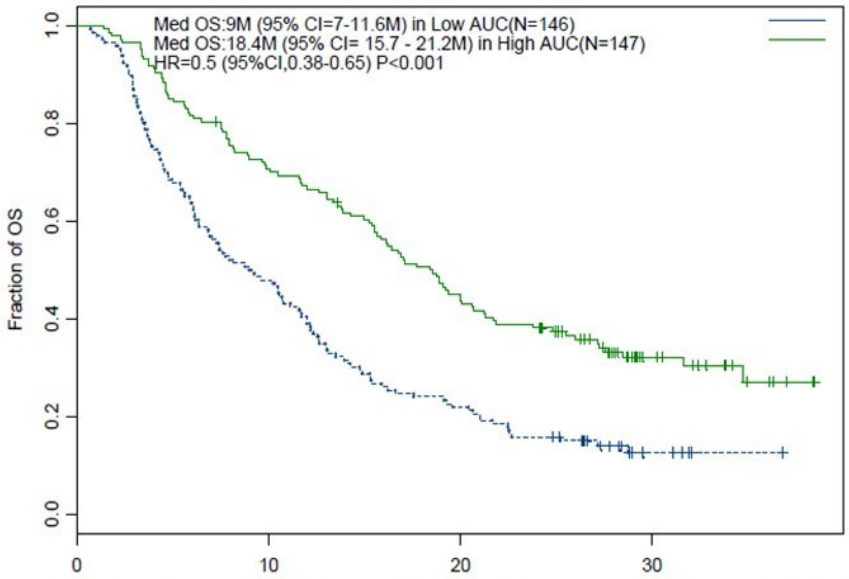
Across the clinical development program for tremelimumab, a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this mechanism of action. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in patients who respond, the responses are generally durable, lasting several months even in those with aggressive tumors such as refractory metastatic melanoma. Moreover, survival benefit was reported even in subjects without radiographic regression in tumor burden. In a single-arm Phase 2 study (Study A3671008) of tremelimumab administered at 15 mg/kg Q90D to subjects with refractory melanoma, a response rate of 7% and median OS of 10 months in the second-line setting

(as compared to approximately 6 months with BSC reported from a retrospective analysis; (Korn, Liu et al. 2008) was observed (Kirkwood, Lorigan et al. 2010). In a randomized, open-label, first-line Phase 3 study of tremelimumab (administered at 15 mg/kg Q90D) versus chemotherapy (DTIC or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed a response rate of 11% and median OS of 12.58 months in this first-line setting (as compared to 10.71 months with standard chemotherapy)(Ribas, Kefford et al. 2013). Additionally, in a Phase 2 maintenance study in NSCLC, PFS at 3 months was 22.7% in the tremelimumab arm compared with 11.9% in the BSC arm (Study A3671015).

Survival analysis of 293 subjects treated with tremelimumab in a Phase 3 study in melanoma showed better OS in subjects with higher exposure. The median OS was 18.4 months for the high AUC (≥ 123,665 µg·hour/mL) group compared to 9.0 months for the low AUC (< 123,665 µg·hour/mL) group (HR 0.5; $p < 0.001$) as shown in Figure 3.6.3.1. Higher rates of 1-year survival (67% vs 56%) and 2-year survival (16% vs 5%) were observed in the high versus low AUC groups, respectively. It is possible that the lower OS in the low AUC90 group is due to less favorable prognostic features in that group. Subjects who had an AUC90 below the median were more likely to have baseline characteristics that predict poor prognosis, including M1c (67% vs 47%), LDH > ULN (30% vs 17%), ECOG performance status > 0 (42% vs 21%), and CRP > 1.5 × ULN (40% vs 18%). However, subjects who were able to achieve a higher AUC despite the presence of poor prognostic features had a better survival outcome than those who did not, suggesting that maximizing exposure could improve the survival outcome with tremelimumab.

Preliminary data are available for the ongoing study, D4190C00006, which is evaluating MEDI4736 in combination with tremelimumab. As of the data cutoff date of 04Dec2014, a total of 31 of 61 subjects were evaluable for efficacy with at least 8 weeks of follow-up. Of these, 8 subjects had PR, 11 subjects had stable disease, and 12 subjects had PD.

**Figure 3.6.3.1: Kaplan-Meier curve of survival stratified by drug exposure in a phase III melanoma trial**




$AUC_{90}$ = area under the plasma concentration-time curve; CI = confidence interval; HR = hazard ratio; OS = overall survival.

Note: High AUC subjects had $AUC_{90}$ above the median value while low AUC subjects had $AUC_{90}$ below the median value.

#### *3.6.3.2 Safety*

The profile of adverse events (AEs) and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. Based on integrated data from the completed and rollover tremelimumab monotherapy studies (N = 973), AEs (all grades, regardless of severity) reported in > 10% of subjects were diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.8%), pruritus (27.3%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15.0%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.2%; see Section 5.3.2.1 for details). Integrated data from completed studies of tremelimumab in combination with other agents (N = 116) showed that AEs (all grades, regardless of causality) reported in > 15% of subjects (all grades, regardless of causality) included diarrhea (54.3%); nausea (40.5%); fatigue (38.8%); rash (35.3%); pruritus, decreased appetite (30.2% each); vomiting (27.6%); pyrexia (26.7%); influenza like illness (20.7%); arthralgia (19.8%); constipation (19.0%); thrombocytopenia, injection site reaction (18.1% each); and increased aspartate aminotransferase (15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations.

Events reported in > 5% of subjects treated with tremelimumab monotherapy and assessed by the investigator as treatment related (listed in descending order of frequency) were diarrhea, rash, pruritus, fatigue, nausea, vomiting, decreased appetite, headache, abdominal pain, and colitis.

In an integrated analysis of tremelimumab monotherapy studies, 944 of the 973 subjects (97.0%) treated with tremelimumab monotherapy experienced at least 1 AE (Table 3.6.3.2). The events resulted in discontinuation of tremelimumab in 10.0% of subjects, were serious in 36.5%, were ≥ Grade 3 in severity in 49.7%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of subjects.

The frequency of any AEs and ≥ Grade 3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of subjects in the 10 mg/kg Q28D and 15 mg/kg Q90D groups compared with the All Doses < 10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product, and deaths.

A total of 944 subjects (97.0%) experienced at least 1 event for a total of 10,341 events. Adverse events (all grades) reported in > 10% of subjects (in decreasing order of frequency) were diarrhea, fatigue, nausea, rash, pruritus, decreased appetite, vomiting, pyrexia, cough, constipation, abdominal pain, headache, dyspnea, and decreased weight. The frequencies of these AEs were higher in the 10 and 15 mg/kg dose groups than the All Doses < 10 mg/kg group. Notably, for all of these frequent AEs (all grades), excœpt for diarrhea, abdominal pain, headache, and dyspnea, the incidence was higher in the 10 mg/kg group than the 15 mg/kg group.

Approximately half of the subjects experienced AEs of ≥ Grade 3 severity. The most frequent ≥ Grade 3 AEs reported in ≥ 2% of subjects (in decreasing order of frequency) were diarrhea, fatigue, colitis, disease progression, dyspnea, dehydration/nausea/vomiting, abdominal pain, decreased appetite, and asthenia. The events of diarrhea, abdominal pain, and colitis occurred at a higher rate in the 10 mg/kg group, whereas fatigue, disease progression, dehydration, nausea, vomiting, decreased appetite, and asthenia were reported more frequently in the 15 mg/kg group.

Adverse events were considered to be treatment related in 770 subjects (79.1%). Treatment related AEs were reported at similar rates in the 10 and 15 mg/kg groups (81.8% and 80.0%, respectively), and were mostly Grade 1 or 2 in severity (≥ Grade 3 treatment-related AEs reported in 26.1% of subjects). The most frequent treatment-related AEs (in > 5% of subjects) were diarrhea (41.2%), rash (27.2%), pruritus (25.1%), fatigue (23.8%), nausea (21.9%), vomiting (13.5%), decreased appetite (11.3%), headache (7.2%), pyrexia (7.0%), abdominal pain (6.7%), and colitis (5.5%).

**Table 3.6.3.2: Adverse Events Associated with Tremelimumab**

| System Organ Class Preferred Term (MedDRA V16.0) | Tremelimumab (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All<10 (n=33) n(%) | | 10 (n=77) n(%) | | 15 (n=866) [a] n(%) | | Total (N=973) n(%) | |
| | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 |
| Total number of events | 238 | 30 | 1088 | 107 | 9021 | 1107 | 10347 | 1244 |
| Subjects reporting ≥ 1 event | 32 (97.0) | 13 (39.4) | 77 (100) | 35 (45.5) | 837 (96.7) | 437 (50.5) | 944 (97.0) | 485 (49.8) |
| **Blood and Lymphatic System Disorders** | **4 (12.1)** | **1 (3.0)** | **15 (19.5)** | **1 (1.3)** | **94 (10.9)** | **28 (3.2)** | **113 (11.6)** | **30 (3.1)** |
| Anemia | 2 (6.1) | 1 (3.0) | 12 (5.6) | 0 (0.0) | 52 (6.0) | 15 (1.7) | 66 (6.8) | 16 (1.6) |
| **Gastrointestinal Disorders** | **21 (63.6)** | **6 (18.2)** | **61 (79.2)** | **21 (27.3)** | **614 (70.9)** | **175 (20.2)** | **696 (71.5)** | **202 (20.8)** |
| Diarrhea | 10 (30.3) | 3 (9.1) | 32 (41.6) | 15 (19.5) | 399 (46.1) | 108 (12.5) | 441 (45.3) | 126 (12.9) |
| Nausea | 10 (30.3) | 0 (0.0) | 33 (42.9) | 2 (2.6) | 273 (31.5) | 26 (3.0) | 316 (32.5) | 28 (2.9) |
| Vomiting | 5 (15.2) | 0 (0.0) | 26 (33.8) | 2 (2.6) | 188 (21.7) | 26 (3.0) | 219 (22.5) | 28 (2.9) |
| Constipation | 2 (6.1) | 1 (3.0) | 16 (20.8) | 1 (1.3) | 122 (14.1) | 4 (0.5) | 140 (14.4) | 6 (0.6) |
| Abdominal pain | 1 (3.0) | 0 (0.0) | 7 (9.1) | 3 (3.9) | 127 (14.7) | 23 (2.7) | 135 (13.9) | 26 (2.7) |
| Colitis | 0 (0.0) | 0 (0.0) | 9 (11.7) | 4 (5.2) | 49 (5.7) | 32 (3.7) | 58 (6.0) | 36 (3.7) |
| Abdominal pain upper | 0 (0.0) | 0 (0.0) | 4 (5.2) | 0 (0.0) | 47 (5.4) | 0 (0.0) | 51 (5.2) | 0 (0.0) |
| **General Disorders and Administration Site Conditions** | **19 (57.6)** | **1 (3.0)** | **53 (68.8)** | **5 (6.5)** | **543 (62.7)** | **133 (15.4)** | **614 (63.1)** | **139 (14.3)** |
| Fatigue | 8 (24.2) | 0 (0.0) | 40 (51.9) | 1 (1.3) | 317 (36.6) | 46 (5.3) | 365 (37.5) | 47 (4.8) |
| Pyrexia | 4 (12.1) | 0 (0.0) | 14 (18.2) | 1 (1.3) | 131 (15.1) | 9 (1.0) | 149 (15.3) | 10 (1.0) |
| edema peripheral | 5 (15.2) | 0 (0.0) | 14 (18.2) | 2 (2.6) | 78 (9.0) | 8 (0.9) | 97 (10.0) | 10 (1.0) |
| Asthenia | 6 (18.2) | 0 (0.0) | 6 (7.8) | 0 (0.0) | 71 (8.2) | 19 (2.2) | 83 (8.5) | 19 (2.0) |
| Chills | 0 (0.0) | 0 (0.0) | 7 (9.1) | 1 (1.3) | 48 (5.5) | 0 (0.0) | 55 (5.7) | 1 (0.1) |
| Disease progression | 0 (0.0) | 0 (0.0) | 1 (1.3) | 1 (1.3) | 32 (3.7) | 32 (3.7) | 33 (3.4) | 33 (3.4) |

**Table 3.6.3.2 (continued): Adverse Events Associated with Tremelimumab Monotherapy**

| System Organ Class<br>Preferred Term (MedDRA V16.0) | Tremelimumab (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All<10<br>(n=33)<br>n (%) | | 10<br>(n=77)<br>n (%) | | 15<br>(n=866) [a]<br>n (%) | | Total<br>(N=973)<br>n (%) | |
| | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 |
| **Investigations** | **8 (24.2)** | **1 (3.0)** | **23 (29.9)** | **4 (5.2)** | **205 (23.7)** | **49 (5.7)** | **236 (24.3)** | **54 (5.5)** |
| Weight decreased | 4 (12.1) | 0 (0.0) | 12 (15.6) | 1 (1.3) | 83 (9.6) | 6 (0.7) | 99 (10.2) | 7 (0.7) |
| **Metabolism and Nutrition Disorders** | **3 (9.1)** | **0 (0.0)** | **38 (49.4)** | **6 (7.8)** | **287 (33.1)** | **76 (8.8)** | **328 (33.7)** | **82 (8.4)** |
| Decreased appetite | 3 (9.1) | 0 (0.0) | 29 (37.7) | 0 (0.0) | 190 (21.9) | 23 (2.7) | 222 (22.8) | 23 (2.4) |
| Dehydration | 0 (0.0) | 0 (0.0) | 13 (16.9) | 4 (5.2) | 61 (7.0) | 24 (2.8) | 74 (7.6) | 28 (2.9) |
| **Musculoskeletal and Connective Tissue Disorders** | **13 (39.4)** | **1 (3.0)** | **31 (40.3)** | **3 (3.9)** | **309 (35.7)** | **50 (5.8)** | **353 (36.3)** | **54 (5.5)** |
| Arthralgia | 4 (12.1) | 0 (0.0) | 8 (10.4) | 1 (1.3) | 79 (9.1) | 8 (0.9) | 91 (9.4) | 9 (0.9) |
| Back pain | 1 (3.0) | 0 (0.0) | 7 (9.1) | 2 (2.6) | 75 (8.7) | 13 (1.5) | 83 (8.5) | 15 (1.5) |
| Pain in extremity | 1 (3.0) | 0 (0.0) | 8 (10.4) | 0 (0.0) | 69 (8.0) | 11 (1.3) | 78 (8.0) | 11 (1.1) |
| Myalgia | 2 (6.1) | 0 (0.0) | 11 (14.3) | 0 (0.0) | 57 (6.6) | 3 (0.3) | 70 (7.2) | 3 (0.3) |
| Musculoskeletalpain | 2 (6.1) | 1 (3.0) | 3 (3.9) | 2 (2.6) | 50 (5.8) | 7 (0.8) | 55 (5.7) | 10 (1.0) |
| **Nervous System Disorders** | **13 (39.4)** | **3 (9.1)** | **26 (33.8)** | **1 (1.3)** | **274 (31.6)** | **40 (4.6)** | **313 (32.2)** | **44 (4.5)** |
| Headache | 7 (21.2) | 1 (3.0) | 10 (13.0) | 0 (0.0) | 117 (13.5) | 8 (0.9) | 134 (13.8) | 9 (0.9) |
| Dizziness | 4 (12.1) | 0 (0.0) | 5 (6.5) | 1 (1.3) | 61 (7.0) | 2 (0.2) | 70 (7.2) | 3 (0.3) |
| **Psychiatric Disorders** | **9 (27.3)** | **0 (0.0)** | **15 (19.5)** | **1 (1.3)** | **154 (17.8)** | **19 (2.2)** | **178 (18.3)** | **20 (2.1)** |
| Insomnia | 5 (15.2) | 0 (0.0) | 6 (7.8) | 0 (0.0) | 77 (8.9) | 0 (0.0) | 88 (9.0) | 0 (0.0) |
| **Respiratory, Thoracic and Mediastinal Disorders** | **9 (27.3)** | **4 (12.1)** | **30 (39.0)** | **5 (6.5)** | **316 (36.5)** | **55 (6.4)** | **355 (36.5)** | **64 (6.6)** |
| Cough | 3 (9.1) | 0 (0.0) | 12 (15.6) | 0 (0.0) | 131 (15.1) | 4 (0.5) | 146 (15.0) | 4 (0.4) |
| Dyspnea | 2 (6.1) | 1 (3.0) | 9 (11.7) | 2 (2.6) | 110 (12.7) | 26 (3.0) | 121 (12.4) | 29 (3.0) |
| Oropharyngealpain | 2 (6.1) | 0 (0.0) | 5 (6.5) | 0 (0.0) | 51 (5.9) | 0 (0.0) | 58 (6.0) | 0 (0.0) |

**Table 3.6.3.2 (continued): Adverse Events Associated with Tremelimumab Monotherapy**

| System Organ Class<br>Preferred Term (MedDRA V16.0) | Tremelimumab (mg/kg) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | All<10<br>(n=33)<br>n (%) | | 10<br>(n=77)<br>n (%) | | 15<br>(n=866) [a]<br>n (%) | | Total<br>(N=973)<br>n (%) | |
| | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 | All Grades | ≥ Grade 3 |
| **Skin and Subcutaneous Tissue Disorders** | **14 (42.4)** | **0 (0.0)** | **53 (68.8)** | **2 (2.6)** | **504 (58.2)** | **22 (2.5)** | **571 (58.7)** | **24 (2.5)** |
| Rash | 7 (21.2) | 0 (0.0) | 29 (37.7) | 2 (2.6) | 244 (28.2) | 10 (1.2) | 280 (28.8) | 12 (1.2) |
| Pruritus | 3 (9.1) | 0 (0.0) | 33 (42.9) | 1 (1.3) | 230 (26.6) | 3 (0.3) | 266 (27.3) | 4 (0.4) |

MedDRA = Medical Dictionary for Regulatory Activities.

Note: This table includes data from Studies A3671001 (single-dose study), A3671002, A3671008, A3671009, A3671011 (single-dose study), A3671014, A3671015, A3671022, and A3671024 (D4881C00024).

[a] Includes 3 subjects who were initially treated at 10 mg/kg in one of the legacy studies and subsequently treated at 15 mg/kg in the rollover study (D4881C00024).

The highest incidence of serious AEs (SAEs) occurred in the 10 mg/kg group (42.9%), followed by the 15 mg/kg (36.0%) and All Doses < 10 mg/kg (30.3%) groups. Serious adverse events experienced by > 1% of subjects were diarrhea, colitis, vomiting, disease progression, dehydration, pyrexia, nausea, abdominal pain, dyspnea, pneumonia, and confusional state. The majority of these events was ≥ Grade 3 in severity and reported at a higher rate in the 15 mg/kg group. A total of 451 SAEs in 197 subjects (20.2%) were assessed as related to investigational product by the investigator. Treatment-related SAEs were reported in more subjects in the 10 mg/kg group compared with the 15 mg/kg group (29.9% vs 20.0%, respectively), and were ≥ Grade 3 in severity in the majority of subjects (84.8%). The most frequent treatment related SAEs (occurring in > 1% of subjects) were diarrhea (9.2%), colitis (3.6%), vomiting (2.3%), and nausea and dehydration (1.8% each).

A total of 97 subjects (10.0%) experienced 140 AEs that resulted in discontinuation of tremelimumab. The highest frequency of such AEs occurred in the 10 mg/kg group (16.9%) followed by the 15 mg/kg (9.8%); none of the AEs reported in the All Doses < 10 mg/kg group resulted in discontinuation of tremelimumab. Adverse events that resulted in discontinuation of tremelimumab in ≥ 3 subjects (≥ 0.3%) were diarrhea, colitis, abdominal pain, dehydration, hypophysitis, renal failure, and asthenia. Of the 97 subjects with AEs resulting in treatment discontinuation, 72 subjects (74.2%) had 98 events that were ≥ Grade 3 in severity and 84 subjects (86.6%) had 118 events that were assessed as treatment related by the investigator. Treatment-related AEs resulting in discontinuation of tremelimumab in ≥ 3 subjects (≥ 0.3%) were diarrhea (3.4%), colitis (1.4%), asthenia (0.5%), and hypophysitis, dehydration, and abdominal pain (0.3% each). As of August 2013, 659 subjects (67.7%) who received tremelimumab monotherapy have died due to a number of causes, including 0.5% which was attributed to tremelimumab.

### 3.6.4 Summary of Clinical Experience: Combination Therapies

116 subjects with a variety of tumor types have received tremelimumab in combination with other anticancer agents in 5 of the 15 clinical studies. Overall, 114 of 116 subjects (98.3%) treated with tremelimumab in combination with other agents experienced at least 1 adverse event. The frequency of events overall was similar across the combination therapy arms. Adverse events resulted in discontinuation of tremelimumab in 25.9% of subjects, and were serious in 39.7%, fatal in 45.7%, ≥ Grade 3 in severity in 62.9%, and considered to be treatment related in 70.7% of subjects. Adverse events reported in > 10% of subjects overall were diarrhea, nausea, fatigue, rash, decreased appetite, pruritus, vomiting, pyrexia, influenza-like illness, arthralgia, constipation, injection site reaction, thrombocytopenia, aspartate aminotransferase increased, peripheral edema, alanine aminotransferase increased, back pain, dysgeusia, headache, dyspnea, and cough. Most of these events occurred at a higher rate with tremelimumab + sunitinib compared with the other combinations.

Of the subjects who experienced AEs, 73 (62.9%) had events of ≥ Grade 3 severity. The most frequently reported ≥ Grade 3 treatment emergent AEs (TEAEs) (in > 3% of subjects) were diarrhea (14.7%), fatigue (7.8%), hypertension (5.2%), disease progression and dyspnea (4.3% each), and nausea, alanine aminotransferase increased, lipase increased, and dehydration (3.4% each). Adverse events were considered to be treatment related in 82 subjects (70.7%). The most frequent treatment-related TEAEs (occurring in > 10% of subjects) were diarrhea (44.0%), pruritus (25.0%), fatigue (24.1%), rash (23.3%), nausea (19.8%),

decreased appetite (18.1%), vomiting and pyrexia (12.9% each), and thrombocytopenia (10.3%). Of note, thrombocytopenia was reported with tremelimumab + sunitinib (10 subjects) and tremelimumab + gemcitabine (2 subjects).

A total of 30 subjects (25.9%) experienced 52 AEs that resulted in discontinuation of tremelimumab. The highest frequency of such AEs occurred with tremelimumab + sunitinib and tremelimumab + neoadjuvant androgen ablation (42.9% each). Adverse events that resulted in discontinuation of tremelimumab in ≥ 2 subjects (> 1%) were diarrhea, pyrexia, acute renal failure, colitis, rash, disease progression, dyspnea, and edema. A total of 25 subjects (21.6%) had 32 AEs that were ≥ Grade 3 in severity and 19 subjects (16.4%) had 35 AEs that were assessed as treatment related by the investigator. Treatment related AEs that resulted in discontinuation of investigational product in ≥ 2 subjects (> 1%) were diarrhea (6.0%), pyrexia (3.4%), colitis (2.6%), and rash, edema, and acute renal failure (1.7% each). The cause of death was ascribed to the investigation product in 0.9%.

#### *3.6.4.1 Summary of Tremelimumab in Breast Cancer*

In the only reported study of anti-CTLA-4 therapy in breast cancer, tremelimumab with exemestane proved safe in women with heavily pre-treated hormone receptor-expressing advanced breast cancer, conferring a 42% 12-week disease control rate across multiple doses (Vonderheide, LoRusso et al. 2010). The MTD was determined to be 6mg/kg q90d, however, dose escalation at the q28d schedule was aborted when the first subject receiving 6mg/kg q28d developed dose-limiting diarrhea. The effect of exemestane on the rate of adverse effect profile, or the disease control rate, is unknown.

### 3.6.5 Tremelimumab Dose & Schedule

For future clinical studies, tremelimumab will be administered IV at a dose of 10 mg/kg Q4W for the first 6 doses, followed by one dose Q12W until disease progression. The proposed dose and schedule is informed by PK, safety, and efficacy data on tremelimumab.

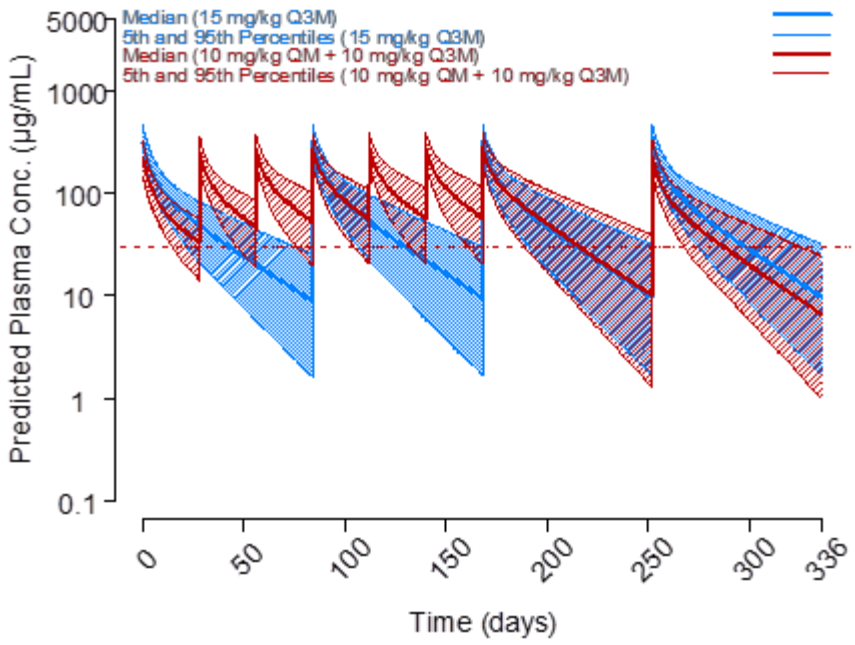
In an early small Phase 2 study (A3671002), 2 dosing regimens of tremelimumab were compared in subjects with melanoma: 15 mg/kg Q90D (N = 45) and 10 mg/kg Q28D (N = 44). Comparable efficacy and overall AE rates were observed in both arms; however, the rate of treatment-related CTCAE Grade 3 or 4 AEs was higher in the 10-mg/kg Q28D arm (27%) compared to the 15-mg/kg Q90D arm (13%).

Subsequently, 2 pivotal tremelimumab studies (Phase 2 Study A3671008 and Phase 3 Study A3671009) in subjects with melanoma used the regimen 15 mg/kg Q90D. Although neither study met its primary endpoint, the observed response rate and OS clearly indicate activity of tremelimumab in melanoma. Retrospective exposure-survival analyses of these studies suggest better OS in subjects with higher tremelimumab exposure (see Section 3.6.3.1). In the Phase 3 trial, there was no difference in the incidence of ≥ Grade 3 AEs between low and high exposure groups of tremelimumab.

Tremelimumab at a concentration of 30 µg/mL enhanced IL-2 release (in vitro) and showed antitumor activity (in vivo), and was consequently identified as the target concentration. Pharmacokinetic simulations indicate that following a dose of 10 mg/kg Q28D for 6 months, approximately 90% of subjects are expected to be above the target level of 30 µg/mL during the induction phase (See figure 3.6.5.1). In the Phase 3 melanoma

trial with less frequent dosing of 15 mg/kg Q90D, only approximately 50% of the subjects treated with tremelimumab were above the target concentration, for only half of the dosing interval.

**Figure 3.6.5.1: Predicted Plasma Tremelimumab Concentration-time Profiles for 10 mg/kg Q28D (induction phase) followed by 10 mg/kg Q90D (maintenance phase), versus 15 mg/kg Q90D**




Q28D = once every 28 days; Q90D = once every 90 days.

Note: The horizontal line represents the target level of 30 µg/mL.

Tremelimumab at a dose of 10 mg/kg QM for 6 months followed by 10 mg/kg Q3M is expected to yield PK exposures similar to those of the related anti-CTLA-4 mAb ipilimumab at a dose of 10 mg/kg every 3-weeks followed by 10 mg/kg Q3M, the dosing regimen that was tested in the pivotal first-line melanoma trial (Robert, Thomas et al. 2011). The ipilimumab data suggest that the long-term benefits of anti-CTLA-4 therapy may be sustained with a reduced frequency of dosing in patients who are benefiting from therapy.

Based on these data, tremelimumab will be administered at a dose of 10 mg/kg Q4W for 6 doses. Following the first 6 doses, in the absence of confirmed disease progression, the interval will be increased to Q12W. Dosing will continue as long as the subject is deriving clinical benefit.

### 3.6.5 Benefit-risk and Ethical Assessment

In the nonclinical setting, treatment of tumor-bearing mice with anti-mouse CTLA-4 mAb (9H10) induced antitumor immunity and markedly enhanced T cell-mediated killing of various mouse solid tumors. Clinical trials of tremelimumab, and of the related anti-CTLA-4 antibody ipilimumab, in melanoma suggest activity (improved survival) of these agents in melanoma. Tremelimumab has also shown activity (objective

responses and disease stabilization) in the malignant mesothelioma setting, with preliminary results suggesting that tremelimumab may lead to improved survival with 45.5% of subjects alive at 1 year and 5 subjects were alive at 2 years.

Overall, tremelimumab nonclinical toxicities were consistent with inhibition of CTLA-4, with adverse effects noted for the gastrointestinal tract, skin, lymphoid organs, thyroid tissues, and hematological systems. Dose-limiting toxicities identified in chronic toxicity studies in monkeys included skin rash and gastrointestinal effects. Most toxicities were reversible or showed a trend towards reversibility.

The profile of AEs from > 1000 treated subjects and the spectrum of event severity are consistent with the pharmacologic class and with the signal observed in nonclinical toxicology studies. Adverse events have been observed in every organ system and are mainly due to the inflammation caused by tremelimumab's mechanism of action. The most common AEs involve skin, the gastrointestinal tract, and endocrine system, and are usually mild in nature. Events reported at a frequency of ≥ 5% and assessed by the investigator as related to treatment (listed in descending order of frequency) were diarrhea, rash, pruritus, fatigue, nausea, vomiting, anorexia, headache, abdominal pain, and colitis. Infusion-related AEs were rare.

Overall, the observed benefit-risk profile supports the further investigation of tremelimumab in the patient population chosen for this study.

### 3.7 Combination of anti-CTLA-4 antibody with radiotherapy: Background

A recent phase II study of patients with melanoma brain metastases treated with ipilimumab showed that the primary endpoint of disease control was achieved in a approximately 25% of patients at 12 weeks without unexpected toxicities (Margolin, Ernstoff et al. 2012).These data are corroborated by a retrospective analysis of melanoma patients receiving ipilimumab in the earliest phase II trials (Weber, Amin et al. 2011). In this study, 5/12 identified patients had CNS clinical benefit, with a median survival of 14 months, and 3 patients living longer than 4 years.

Combining an anti-CTLA-4 antibody with radiation therapy (RT), which potentially releases antigenic stimuli and inflammatory cytokines and alters the tumor microenvironment, may allow for synergistic activity (Shiao and Coussens 2010). This could result in improved clinical outcomes and could lead to an entirely new treatment approach for patients with brain metastases in breast and other cancers.

The synergistic effect of RT and immunotherapy has been demonstrated in multiple preclinical studies. The combination of ionizing radiotherapy and anti-CTLA-4 antibody delayed growth of irradiated tumor, inhibited lung metastases, and improved survival in a 4T1 murine carcinoma model (Demaria, Kawashima et al. 2005). These findings were confirmed in a 9H10 model, in which combination therapy enhanced primary tumor regression, and produced abscopal regression of non-irradiated lesions (Dewan, Galloway et al. 2009). Importantly, this study suggested that delays in immunotherapy beyond 2 days may reduce anti -tumor activity; additionally, the fractionated radiotherapy was more effective compared to single-dose. Another murine model demonstrated that the combination of radiotherapy and antibodies against CD137 + PD-1 was curative, and associated with tumor-antigen specific CD8+ T-cell infiltration (Verbrugge, Hagekyriakou et al. 2012)

To date, our clinical experience of combined radiotherapy with CTLA-4 blockade comes from retrospective analyses of melanoma. The historical median survival of melanoma patients requiring brain radiosurgery is 4-6 months. Our colleagues in Radiation Oncology at MSKCC have reported a retrospective experience of 45 melanoma patients receiving concurrent ipilimumab + brain SRS (Kiess, Wolchok et al. 2012). Patients treated with stereotactic radiosurgery (SRS) during ipilimumab administration demonstrated better overall survival, less neurologic deaths and a trend toward fewer local recurrences than those treated with SRS before or after CTLA-4 blockade. A follow-up evaluation demonstrated overall survival of 9 months and 39 months in melanoma subjects receiving non-brain RT during ipilimumab induction and maintenance, respectively (Barker, Postow et al. 2013). The possible synergy between RT and CTLA-4 blockade was also corroborated by retrospective reviews at other institutions (Knisely, Yu et al. 2012). These results indicate that RT and CTLA-4 blockade are well tolerated in patients with brain metastases and that the timing of CTLA-4 blockade to RT administration could be critical. Furthermore, a recent case report indicates that RT combined with CTLA-4 blockade may confer an abscopal effect, whereby regression of metastases is observed distant to the irradiated site (Postow, Callahan et al. 2012).

### 3.7.1 Safety of combination CTLA-4 blockade/RT

In the aforementioned studies, the safety of combination CTLA-4 blockade/RT was evaluated. In a single-institution evaluation of 29 subjects receiving non-brain radiotherapy, grade ≥3 immune related AE's occurred in 22% of patients receiving ipilimumab 3mg/kg, and 43% of patients receiving ipilimumab 10mg/kg. These rates were not significantly different compared to monotherapy historical controls, and included grade III cytokine release (n=2), grade III diarrhea (n=1), grade III transaminase elevation (n=4) , grade III rash/pruritus (n=3), grade 3 radiculitis (n=1), grade 3 thrombocytopenia (n=1), and grade IV uveitis (n=1). Grade ≥3 AE's in irradiated organs was 15%. 77% of patients experienced improvement in symptoms with therapy (Barker, Postow et al. 2013).

In the retrospective evaluation of patients treated with concurrent brain SRS and ipilimumab, patients receiving concurrent SRS and ipilimumab (n=14) experienced grade ≥3 toxicities including rash/pruritus (7%), cardiopulmonary (7%), CNS bleeding of treated brain metastases (14%), and seizure (14%). On MRI, 40% of metastases treated during or before ipilimumab increased in size to greater than 150%, of which only ultimately 7% reflected recurrence. The majority of CNS bleeds or increased tumor size was asymptomatic, but some were associated with seizure or headache. CNS bleeds did not interfere with completion of ipilimumab (Kiess, Wolchok et al. 2012). In a separate retrospective evaluation, melanoma patients who received both SRS and ipilimumab did not experience increases in toxicity or intracerebral disease control, however the timing of SRS compared to ipilimumab in these patients was not reported, and may not have been delivered concurrently (Mathew, Tam et al. 2013). In an additional retrospective series of 13 melanoma patients, combination ipilimumab + WBRT was safe, with only 1 patient experiencing a grade III/IV acute CNS-related toxicity (cognitive change). (Gerber, Young et al. 2014) Finally, the concordant toxicity profiles of tremelimumab and ipilimumab suggest that toxicities are mediated by class-effect (CTLA-4 blockade), and that tremelimumab+RT may have a similar safety profile as ipilimumab+RT.

A related strategy is to combine potential tumor-antigen releasing therapeutic modalities with anti-CTLA-4 therapy. For example, thermal ablation leads to immediate tissue destruction and necrosis secondary to crystallization, osmotic changes, and vascular stasis. This promotes a release of tumor antigen that could activate a specific immune response (Sabel 2009). At MSKCC, we have conducted a pilot study in humans,

evaluating ipilimumab and/or cryoablation in 18 subjects. The prespecified safety endpoint was met, with no subjects experiencing a delay in planned standard-of-care mastectomy. With a median followup of 15 months, no treatment-related grade III/IV toxicities were reported (Diab, Solomon et al. 2013).

In summary, the incidence and prevalence of BCBM continues to increase and these patients need new and effective therapies. We hypothesize, based on the compelling clinical and pre-clinical evidence outlined above, that the combination of tumor-targeted brain RT with systemic CTLA-4 blockade with tremelimumab will induce disease control and ultimately permit a clinically meaningful delay in cytotoxic chemotherapy. We therefore propose a Simon 2-stage study of tremelimumab with brain RT in women with BCBM for whom cytotoxic therapy is planned.

## 3.8 Combination of anti-CTLA-4 therapy with anti-HER2 therapy: background

Trastuzumab is a therapeutic human antibody against human epidermal growth factor 2 (HER2), and is commonly used to treat metastatic breast cancer in patients with HER2-overexpressing tumors (Hudis 2007). The therapeutic mechanism of trastuzumab is multifold, with activity attributed to inhibition of downstream HER2 signaling as well as immune modulation. The immune activity of trastuzumab is pleiotropic, dependent on both antibody-dependent cell-mediated cytotoxicity, antibody production, and T-cell activation (Page, Naidoo et al. 2014).

While trastuzumab has limited efficacy as monotherapy, clinical benefit is maximized when trastuzumab is combined with a cytotoxic backbone (Hudis 2007). Based upon expert opinion and retrospective data, it is now standard practice to continue trastuzumab at the time of progression, when a switch in the cytotoxic backbone is required (von Minckwitz, du Bois et al. 2009, Hamberg, Bos et al. 2011). In patients with newly diagnosed brain metastasis, trastuzumab is often continued during and after brain irradiation, whereas systemic therapy is suspended for several weeks to minimize the risk of exacerbating radiotoxicity.

Trastuzumab is generally well tolerated. However, <5% of patients experience cardiotoxicity, which is generally reversible upon discontinuation of therapy (Hudis 2007). Other potential adverse effects include infusion reaction and rash. The mechanism of cardiotoxicity is thought to be related to inhibition of downstream HER2 signaling, which is integral to growth, repair and survival of cardiac myocytes (Fedele, Riccio et al. 2012). No data suggests an immune-based mechanism of cardiotoxicity.

Because of the immune-mediated mechanism of trastuzumab, combination with anti-CTLA-4 may produce synergistic clinical benefit. In mice, combination anti-CTLA-4 with anti-HER2 and AKT blockade generated synergistic tumor regression (Wang, Li et al. 2012). Additionally, anti-HER2 antibody has been shown to synergize with other immunotherapies, including vaccine therapy and anti-PD-1 (Stagg, Loi et al. 2011), with no reports of unanticipated adverse events. Anti-CTLA-4 has been safely combined with other therapeutic antibodies in humans (Wolchok, Kluger et al. 2013).

## 3.9 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobin G (igG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 T cells and CD80 (B7.1) on immune cells (IC). It 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.) Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ; Stewart et al. 2015).

As of the DCO date (12 July 2016), a total of 2878 patients have been exposed to 1 or more doses of durvalumab in ongoing open-label AstraZeneca- or MedImmune-sponsored Phase I-III monotherapy and combination therapy studies across all indications. Refer to the current duvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy, and pharmacokinetics.

### 3.9.1 Durvalumab in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012) because the mechanisms of action of CTLA-4 and PD-1 are non-redundant; therefore, AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer. Combination CTLA-4 and PD-1 directed therapies have demonstrated synergy compared with either strategy alone in other settings including metastatic melanoma (Wolchok JD NEJM 2013, Postow AACR 2016).

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

### 3.9.2 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 ($5^{th}$, median and $95^{th}$ percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (*N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma*) [Wang et al. 2014]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations ($5^{th}$, median and $95^{th}$ percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

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

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

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

### 3.9.3 Safety of durvalumab

Risks with durvalumab include diarrhea, colitis, pneumonitis /ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, diabetes insipidus, hypophysitis and adrenal insufficiency) hepatitis/hepatotoxicity/increases in transaminases, neurotoxicities, nephritis/increases in creatinine, pancreatitis, rash/pruritus/dermatitis, myocarditis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, and immune complex disease.

Further information on these risks can be found in the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 8% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 5% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see the Dosing Modification and Toxicity Management Guidelines in **Error! Reference source not found.**).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

### 3.9.4 Safety of durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy is being evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and has so far shown a manageable safety and tolerability profile.

The potential risks with the combination of durvalumab + tremelimumab are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006 and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities.

In durvalumab + tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥10% of patients) are fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain hyponatremia and rash.

Approximately 13% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 13% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator.

A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

## 4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

### 4.2 Design

### 4.1.1 Efficacy and safety cohort study (completed as of 3/1/2017)

In this pilot single institution study, breast cancer patients with brain metastasis (BCBM) and measurable systemic disease for whom whole brain radiation treatment or stereotactic radiosurgery is indicated received tremelimumab 10mg/kg q28 days, with the first dose initiated during or in proximity to administration of radiotherapy. The primary objective was to evaluate non-CNS disease control at 12 weeks. Secondary objectives were to characterize safety and to evaluate anti-tumor efficacy using other metrics including overall survival (OS), CNS 24 week objective response, and CNS and non-CNS progression free survival (PFS). Additionally, the safety of tremelimumab and HER2 directed therapy co-administration will be evaluated in a parallel safety cohort.

Eligible patients were ≥18 years with good functional status (ECOG 0-2) and life expectancy ≥12weeks, with pathologically confirmed invasive breast carcinoma (any histologic subtype), radiologically confirmed brain metastases for which standard-of-care brain RT (either SRS or WBRT) was planned, and RECIST1.1 measurable non-CNS metastases with recent progression of disease as determined by the investigator, for which a change in systemic therapy is planned. Alternatively, patients who had stable disease to their current systemic therapy were also eligible if a treatment holiday was planned. Subjects with CNS complications requiring urgent neurosurgical intervention or intrathecal therapy / intravenous methotrexate for leptomeningeal disease were excluded.

A Simon 2-stage single-arm design (n=17) was employed to evaluate for preliminary efficacy. A maximum of 17 subjects will be accrued to the efficacy arm. After the first 3 patients were enrolled in the efficacy arm, a 6 week enrollment hold was conducted in order to ensure safety before additional patients were enrolled. An interim assessment occurred after the first 9 subjects were enrolled, and the accrual to this arm continued,

as it met a pre-specified futility threshold. Patients not requiring continuation of HER2 directed therapy, such as trastuzumab, were enrolled in this arm.

The first dose of tremelimumab was administered at 10mg/kg two days prior to initiation of radiotherapy. If not feasible, tremelimumab was administered any day from 5 days prior to 3 days post the first dose of radiotherapy.

Because brain irradiation is often performed to palliate symptoms, no washout period for cytotoxic therapy was mandated. This will preserve feasibility of enrollment, but may introduce the possibility that some patients may have non-negligible serum chemotherapy levels at the time of tremelimumab administration. Thus, we will exclude enrollment of patients with ongoing reversible ≥CTCAE grade II chemotherapy-related toxicities. We believe the risk of unfavorable drug-drug interactions is acceptably low, as the safety of anti-CTLA-4 therapy combined with various cytotoxic therapies has been demonstrated in humans (Reck, Bondarenko et al. 2013, Weber, Hamid et al. 2013). Concurrent administration of cytotoxic therapy with tremelimumab will not be permitted. Concurrent bone-directed therapies such as denosumab or bisphosphonates will be permitted.

Subsequent tremelimumab doses were administered at 10mg/kg every 28 days +/- 1 week until radiographic progression or until treatment was no longer tolerated.

Patients for whom concurrent HER2 directed therapy is indicated, as determined by the treating investigator, were enrolled in a parallel HER2 directed therapy safety arm. As described in section 3.8, the combination of tremelimumab and HER2 directed therapy with brain irradiation was anticipated to be safe, with possible synergistic benefit. However, because HER2 directed therapy had not yet been evaluated in combination with tremelimumab in humans, additional precautions were taken to monitor for overlapping toxicities. A modified 3+3 design was adopted to minimize exposure in the event of unanticipated toxicities. In a safety run-in, the first 3 subjects each required 6 weeks of follow-up from the first dose of tremelimumab before the subsequent HER2-positive patient could be enrolled. As detailed in section 9, additional subjects will be enrolled if the therapy is tolerated in 2 of more of the first three subjects. If the HER2 directed therapy safety arm completes accrual prior to completion of the Simon 2-stage efficacy arm, an expansion cohort will be considered under a protocol amendment. Similarly, if concurrent HER2 directed therapy /tremelimumab/RT is not tolerated at the specified dose, a dose de-escalation cohort may be considered under a protocol amendment.

Steroids and anti-seizure medications are permitted on study. However, because steroid administration practices vary in clinical practice, and because of the potential impact on immune modulation, recommendations for steroid use will be provided (section 9.1). Serum levels of anti-seizure medications will be monitored at the discretion of the treating neurologist.

As of 3/1/17, the primary endpoint was established for the efficacy arm without HER2-directed therapy and the safety arm with HER2-directed therapy. Specifically, the 12 week disease control rate was 2/20 (10%) in the efficacy arm and 2/6 (33%) in the safety arm. One patient treated with concurrent HER2-directed therapy had a 57% partial response by RECIST v1.1 that was durable at 6 months. Overall, the regimen was well tolerated with 15 grade 3 and no grade 4 attributable toxicity events reported. The most common treatment related AEs were diarrhea (12.9%), fatigue (9.7%), and colitis (6.5%). Thus, an expansion of the HER2 arm is planned in a parallel Simon two-stage design to evaluate efficacy of brain RT with checkpoint blockade and

concurrent HER2-directed therapy. However, because of the diarrhea and colitis associated with tremelimumab mediated CTLA4 blockade when administered at 10mg/kg monthly (a well described class effect), a lower dose of tremelimumab will be co-administered with trastuzumab in the expansion study in combination with durvalumab, a PD-L1 directed antibody that is currently US FDA approved for other indications.

### 4.1.2 Expansion Study (planned as of 3/1/2017)

The expansion cohort for the HER2+ breast cancer patients who are also undergoing concurrent HER2 directed therapy is designed as a Simon's two-stage optimal study with design parameters similar to that used to study patients not requiring continuation of HER2 directed therapy. Specifically, a maximum of 17 HER2+ breast cancer patients will be enrolled in a Simon 2-stage design to evaluate for preliminary efficacy.

As described in section 3.8, the combination of tremelimumab and HER2 directed therapy with brain irradiation was safe, with possible synergistic benefit. However, because HER2 directed therapy has not yet been evaluated in combination with tremelimumab and durvalumab in humans, additional precautions will be taken to monitor for overlapping toxicities. A modified 3+3 design is adopted to minimize exposure in the event of unanticipated toxicities. In the first stage, three patients will be enrolled, and a 6 week enrollment hold will be conducted in order to ensure safety before additional patients are enrolled. An interim assessment will then occur after the first 9 subjects have enrolled, and the accrual to this arm will proceed only if a pre-specified futility threshold is met. Specifically, as detailed in section 9, additional subjects will be enrolled if the therapy is tolerated in 2 of more of the first three subjects. Similarly, if concurrent HER2 directed therapy /tremelimumab/durvalumab/RT is not tolerated at the specified dose, a dose de-escalation cohort may be considered under a protocol amendment.

Patients in this expansion will have two biopsies attempted. The first tissue biopsy will be collected (attempted) at baseline, within 28 days prior to starting study treatment. A second, optional, biopsy will be performed at times such as disease progression, prior to starting a new systemic cancer treatment and if the patient's condition allows it, or at the time of radiographic response, at the investigator's discretion and in discussion with the patient. Tissue biopsy will be taken by core needle or surgical biopsy. For each core needle biopsy, an attempt should be made to collect at least 3 core needle samples; however, if it is not medically feasible to collect 3 samples, the investigator or designee should attempt to collect as much tumor tissue as is deemed medically feasible.

Eligible patients will be ≥18 years with good functional status (ECOG 0-2) and life expectancy ≥12weeks, with pathologically confirmed HER2-positive invasive breast carcinoma (3+ by IHC and/or > 2.0 by FISH), radiologically confirmed brain metastases for which standard-of-care brain RT (either SRS or WBRT) is planned, and RECIST1.1 measurable non-CNS metastases with recent progression of disease as determined by the investigator, for which a change in systemic therapy is planned. Alternatively, patients who have stable disease to their current systemic therapy will also be eligible if a treatment holiday is planned. Subjects with CNS complications requiring urgent neurosurgical intervention or intrathecal therapy / intravenous methotrexate for leptomeningeal disease will be excluded.

The first dose of tremelimumab and durvalumab will be administered at 75mg and 1500mg, respectively, two days prior to initiation of radiotherapy. If not feasible, tremelimumab and durvalumab will be administered any day from 5 days prior to 3 days post the first dose of radiotherapy. Subsequent tremelimumab and durvalumab doses will be administered every 28 days +/- 1 week for 4 cycles. After the 4$^{th}$ cycle patients will receive durvalumab 1500 mg every 28 days +/- 1 week until radiographic progression or treatment is not tolerated.

Because brain irradiation is often performed to palliate symptoms, no washout period for cytotoxic therapy will be mandated. This will preserve feasibility of enrollment, but may introduce the possibility that some patients may have non-negligible serum chemotherapy levels at the time of tremelimumab and durvalumab administration. Thus, we will exclude enrollment of patients with ongoing reversible ≥CTCAE grade II chemotherapy-related toxicities. We believe the risk of unfavorable drug-drug interactions is acceptably low, as the safety of anti-CTLA-4 and PD-1/L1 therapy combined with various cytotoxic therapies has been demonstrated in humans (Reck, Bondarenko et al. 2013, Weber, Hamid et al. 2013). Concurrent administration of cytotoxic therapy on study will not be permitted. Concurrent bone-directed therapies such as denosumab or bisphosphonates will be permitted.

Steroids and anti-seizure medications are permitted on study. However, because steroid administration practices vary in clinical practice, and because of the potential impact on immune modulation, recommendations for steroid use will be provided (section 9.1). Serum levels of anti-seizure medications will be monitored at the discretion of the treating neurologist.

## 4.2 Intervention

### 4.2.1 Tremelimumab and Radiotherapy administration

Dose 1 of tremelimumab (at 10mg/kg) will ideally be administered 2 days prior to initiation of brain radiotherapy (or between 5 days prior and 3 days after initiation of radiotherapy if administration 2 days prior to initiation of brain radiotherapy is not feasible). Subjects will receive either WBRT or SRS, depending on the number and size of their brain metastases, as per the standard of care.

Following dose 1, tremelimumab will be administered q28 days from the date of first tremelimumab administration, plus or minus 1 week. Immune monitoring blood draws will occur as outlined in section 10.

#### 4.2.2 Concurrent trastuzumab and other HER2 directed therapies

The current accepted dosing schedules of maintenance trastuzumab are 2mg/kg IV weekly, or 6mg/kg IV every three weeks. Because both schedules are acceptable and regarded as equivalent, the dose and schedule for trastuzumab will be administered at the discretion of the treating physician. Cardiac monitoring with transthoracic echocardiogram (TTE) or MUGA is recommended every 12 weeks for patients receiving concurrent trastuzumab. Other HER2 directed therapies are also allowed, such as lapatinib and pertuzumab and will be administered as per standard practice at the discretion of the treating physician.

#### 4.2.3 Protocol Expansion: Tremelimumab, durvalumab, and HER2 directed therapies with concurrent RT.

Dose 1 of tremelimumab and durvalumab (75 mg and 1500 mg, respectively) will ideally be administered 2 days prior to initiation of brain radiotherapy (or between 5 days prior and 3 days after initiation of

radiotherapy). Subjects will receive either WBRT or SRS, depending on the number and size of their brain metastases, as per the standard of care.

Following the first dose, tremelimumab and durvalumab will be administered q28 days from the date of first tremelimumab and durvalumab administration, plus or minus 1 week, for 4 cycles. After the fourth cycle, durvalumab will be administered alone until progression of disease or unacceptable toxicity. HER2 directed therapy will be administered per the NCCN-guideline-endorsed dose and schedule, as determined by the investigator.

Immune monitoring blood draws will occur as outlined in section 10.1.

#### 4.2.4 Duration of treatment and criteria for retreatment

For patients receiving durvalumab + tremelimumab, retreatment is allowed (once only) for patients meeting the retreatment criteria below. The same treatment guidelines followed during the initial treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Patients receiving the combination of durvalumab and tremelimumab may undergo retreatment in the clinical scenario, described below:

1. Patients who complete the 4 dosing cycles of the combination of durvalumab and tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab monotherapy portion of the combination regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

For the durvalumab + tremelimumab treatment group, before restarting their assigned treatment, the Investigator should ensure that the patient:

1. Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient

2. Still fulfils the eligibility criteria for this study, including re-consenting to restart durvalumab and tremelimumab

3. Has not received an intervening systemic anticancer therapy after their assigned treatment discontinuation.

4. Has had a baseline tumor assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial treatment period until study treatment is stopped.

During the retreatment period, patients receiving durvalumab + tremelimumab may resume durvalumab dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for 4 doses each. After the 4$^{th}$ dose, the treating investigator and site PI will review the patient's clinical and radiographic status to confirm if the patient should continue on the tremelimumab + durvalumab combination, or if they should continue with durvalumab monotherapy at 1500 mg q4w.

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicity that indicate that continuing treatment will not further benefit the patient. A patient with a confirmed progression receiving durvalumab + tremelimumab cannot continue therapy or obtain retreatment if dosing is ongoing in the combination portion of therapy (q4w dosing) and progression occurs in a target lesion that has previously shown a confirmed response.

#### 4.2.5 Toxicity Monitoring

Subjects will be followed with regular physical examination and toxicity assessment using the NCI CTCAE 4.0, as outlined in sections 10-11. They will follow with regular radiation oncology assessments as per the standard of care.

## 5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

## 5.2 Brain radiotherapy

Subjects will receive either WBRT or SRS, at the discretion of the treating radiation oncologist.

### 5.2.1 Whole Brain Radiotherapy

As determined by the radiation oncologist, subjects will receive multiple fractions of WBRT, most commonly 10 days in fractions of 3Gy. Treatment will be delivered with right and left lateral equally weighted fields with the dose calculated on the central ray at mid-separation of the beams. Megavoltage LINAC with 6 MV or higher should be used.

### 5.2.2 Stereotactic Radiosurgery

Eligibility for SRS will be determined by the treating radiation oncologist. At MSKCC, SRS is generally administered in cases of oligometastatic disease, with ≤3 foci of disease measuring less than 4cm each. Dosing is dependent on a number of factors including lesion size and location, but is usually delivered in one fraction.

### 5.2.3 Rationale for including both SRS and WBRT study populations

The dose and fractionation of radiotherapy may be relevant in determining response to therapy. One murine mammary carcinoma model demonstrated that only fractionated dosing was capable of producing an abscopal effect with combined RT+ anti-CTLA-4 (Dewan, Galloway et al. 2009). This was corroborated by a murine melanoma study which demonstrated optimal tumor control with 7.5Gy/fraction dosing, which generated the highest interferon production, and a favorable ratio of effector to regulatory T-cell proliferation (Schaue, Ratikan et al. 2012). The translatability of these findings to humans is unknown, and the relative immunogenicity of alternative radiotherapy regimens such as SRS and WBRT should be explored in a clinical trial.

## 5.2 Tremelimumab

### 5.2.1 Investigational Product

MedImmune will provide the investigator(s) with investigational product (Table 5.2.1) using designated distribution centers.

**Table 5.2.1 Identification of Investigational Product**

| Investigational Product | Manufacturer | Concentration and Formulation as Supplied |
|---|---|---|
| Tremelimumab | MedImmune | Formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.2% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA), pH 5.5. |

Tremelimumab vials should be stored at refrigerated temperatures (2°C to 8°C), and should not be frozen.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines (such as GMP Annex 13 requirements for labeling). Label text will be translated into local languages, as required.

Investigational product will be supplied to the site in containers in coded kits. Each kit has a unique number that is printed on all labels within the kit (i.e., the outer carton label and the label of each vial within the carton).

### 5.2.2 Other Study Medications

In the parallel concurrent safety arm and in the protocol expansion, subjects will continue to receive HER2 directed therapy such as trastuzumab. No other study medications were specified for use in the first part of this clinical protocol. In the protocol expansion, subjects will receive tremelimumab, durvalumab, and concurrent HER2 directed therapy for the first 4 cycles. After the 4$^{th}$ cycle, subjects will continue on durvalumab and HER2 directed therapy. Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management [including palliative radiotherapy on non-target lesions, etc]) should be used when necessary for all subjects with the exception of prohibited concomitant medications.

### 5.2.3 Treatment Regimen

In the first part of this clinical protocol, tremelimumab was administered as an IV solution of 10 mg/kg at a rate of 250 mL/hr, followed by observation. Subjects received one dose of investigational product Q4W until disease progression.

### 5.2.4 Investigational Product Dose Preparation

Tremelimumab is supplied as a sterile IV solution, filled in 20 mL clear glass vials with a rubber stopper and aluminium seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL accounting to 400 mg/vial) of tremelimumab, in an isotonic solution at pH 5.5. Vials containing tremelimumab must be stored in the

refrigerator at 2-8°C. The 20 mg/mL solution will be diluted into a saline bag for IV infusion. Vials containing tremelimumab may be gently inverted for mixing, but should not be shaken.

For dose preparation steps, the following ancillary items are required:

- IV infusion bags of 0.9% sodium chloride injection (250 mL size). Saline bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefin (e.g., polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP-free.
- IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate (TOTM) or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. Lines should contain a 0.22 or 0.2 µm in-line filter. The in-line filter can be made of polyethersulfone (PES) or polyvinylidine fluoride DRF (PVDF). Lines containing cellulose -based filters should not be used with tremelimumab.
- Catheters/infusion sets made of polyurethane or fluoropolymer with silicone and stainless steel and/or PVC components.
- Syringes made of polypropylene and latex-free. Polycarbonate syringes should not be used with tremelimumab.
- Needles made of stainless steel.

#### 5.2.4.1 Dose Calculation

Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight.

The dose will be calculated using the following formula:

$$\text{Dose (mL)} = \frac{[\text{subject weight (kg)} \times \text{dose level (10 mg/kg)}]}{\text{drug concentration (20 mg/mL)}}$$

The corresponding volume of investigational product should be rounded to the nearest tenth mL (0.1 mL). Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

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

$$\text{Number of vials} = \text{Dose (mL)} \div 20\ \text{(mL/vial)}$$

#### 5.2.4.2 Dose Preparation Steps

Tremelimumab does not contain preservatives and any unused portion must be discarded. Preparation of tremelimumab and preparation of the IV bag are to be performed aseptically. Total in-use storage time for the prepared final IV bag should not exceed 24 hours at 2-8°C or 4 hours at room temperature (25°C). However, it is recommended that the prepared final IV bag be stored in the dark at 2-8°C until needed. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. If storage time exceeds these limits, a new dose must be prepared from new vials.

The investigational product manager or qualified personnel will be responsible for preparing the IV doses using the following steps:

1) All investigational product vials should be equilibrated to room temperature for 30 minutes prior to dose preparation.
2) To prepare the IV bag, first, calculate the dose volume of investigational product required. Second, remove the volume of 0.9% sodium chloride IV solution equivalent to the calculated dose volume of investigational product from the IV bag. Lastly, add the calculated dose volume of investigational product to the IV bag. Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.

Example: A subject weighing 85 kg will require 42.5 mL (3 vials) of investigational product. Remove 42.5 mL of saline from the commercial IV bag. Add the 42.5 mL of investigational product to the IV bag and gently mix by inverting up and down.

**5.2.5 Treatment Administration**

The first day of dosing is considered Day 1. Each dose of investigational product should be administered using the following guidelines:

1) Investigational product must be administered at room temperature (25°C) by controlled infusion via an infusion pump into a peripheral vein. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion 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.
3) 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.
4) 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.
5) If there are no requirements to slow, interrupt, or permanently stop the infusion, the anticipated infusion time to deliver each dose (250 mL) is anticipated to be at least 60 minutes.
6) Some investigational product may remain in the IV line after the infusion has completed. Fifteen to 30 mL of 0.9% sodium chloride IV solution should be added to the infusion bag after the investigational product has been administered to flush the line. The infusion rate should not be changed.

The duration of the investigational product administration will be recorded.

**5.2.6 Monitoring of Dose Administration**

Vital signs (blood pressure, temperature, pulse, and respiration rate) will be collected before investigational product infusion, every 30 minutes +/- 10 minutes during infusion, at completion of infusion, and 30 and 60 minutes +/- 10 minutes post infusion.

As with any antibody, allergic reactions to dose administration are possible. Therefore, 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, as per local institutional guidelines.

## 5.3 Durvalumab + tremelimumab combination therapy

### 5.3.1 Investigational Product

MedImmune will provide the investigator(s) with investigational product (Table 5.3.1) using designated distribution centers.

**Table 5.3.1 Identification of Investigational Product**

| Investigational Product | Manufacturer | Concentration and Formulation as Supplied |
|---|---|---|
| Durvalumab | MedImmune | Formulated at a minimal concentration of 50 mg/mL in 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, pH 6.0. |
| Tremelimumab | MedImmune | Formulated at a nominal concentration of 20 mg/mL in 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.2% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate (EDTA), pH 5.5. |

Durvalumab vials should be stored at refrigerated temperatures (2°C to 8°C), and should not be frozen.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines (such as GMP Annex 13 requirements for labeling). Label text will be translated into local languages, as required.

### 5.3.2 Durvalumab + Tremelimumab Combination Therapy Treatment Regimen

Patients in the protocol expansion will receive 1500 mg durvalumab via IV infusion and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles. Patients will then continue 1500 mg durvalumab q4w, starting on Week 17, until disease progression or unacceptable toxicity. The first durvalumab monotherapy dose at 1500mg Q4W will be 4 weeks after the final dose of durvalumab in combination with tremelimumab. Dosing outside the window should be discussed with the Study Physician. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour (maximum 2 hours) after the end of tremelimumab infusion. The duration of each infusion should be 60 minutes (+/- 5 minutes). Less than 55 minutes is considered a deviation. In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 1mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which

point the patient should start receiving the fixed dosing of durvalumab 1500mg plus tremelimumab 75 mg Q4W.

#### 5.3.3 Dose Calculation

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

#### 5.3.4 Dose Preparation Steps – Durvalumab

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

24 hours at 2°C to 8°C (36°F to 46°F)

4 hours at room temperature

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

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL of durvalumab (ie, 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that final concentration is within 1 to 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Weight-based dosing (for patients <30kg) will be administered using an IV bag containing 0.9% (w/v) saline of 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1-20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

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

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. Durvalumab does not contain preservatives, and any unused portion must be discarded

#### 5.3.5 Dose Preparation Steps – Tremelimumab

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

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

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 (i.e.,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.

Weight-based dosing (for patients ≤30 kg) 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.

It is recommended that the prepared final IV bag be stored in the dark at 2ºC-8°C (36°F-46°F) until needed. If storage time exceeds these limits, a new dose must be prepared from new vials. The refrigerated infusion solutions in the prepared final IV bag should be equilibrated at room temperature for about 2 hours prior to administration. Tremelimumab does not contain preservatives and any unused portion must be discarded.

The IV line will be flushed with a volume of IV diluents 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.

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 IV bags have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab.

#### 5.3.6 Durvalumab and Tremelimumab Administration

The first day of dosing is considered Day 1. Each dose of investigational product should be administered using the following guidelines:

1) Investigational product must be administered at room temperature (25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion 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.
3) 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.
4) 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.
5) If there are no requirements to slow, interrupt, or permanently stop the infusion, the anticipated infusion time to deliver each dose is approximately 60 minutes (±5 minutes). Less than 55

minutes is considered a deviation. If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

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

The duration of the investigational product administration will be recorded.

#### 5.3.7 Monitoring of Dose Administration

Vital signs (blood pressure, temperature, pulse, and respiration rate) will be collected before investigational product infusion, every 30 minutes +/- 10 minutes during infusion, at completion of infusion, and 30 and 60 minutes +/- 10 minutes post infusion.

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

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

As with any antibody, allergic reactions to dose administration are possible. Therefore, 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, as per local institutional guidelines.

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

## 6.1 CRITERIA FOR SUBJECT ELIGIBILITY

### 6.2 Subject Inclusion Criteria

Eligible subjects must fulfill all of the following criteria:

| | |
|---|---|
| 1 | Diagnosis of CNS metastases for whom SRS or WBRT is indicated, as determined by radiation oncologist assessment; |
| 2 | Age 18 and older at the time of consent; |
| 3 | Written informed consent and authorization obtained from the subject/HIPAA-appointed legal |

| | |
|---|---|
| | representative prior to performing any protocol-related procedures including screening evaluations; |
| 4 | ECOG performance of 0-2 with anticipated life expectancy of ≥12 weeks; |
| 5 | Histologically or cytologically confirmed invasive breast cancer that is HER2-positive (3+ by IHC and/or >2.0 by FISH) if concurrent HER2-directed therapy is planned; |
| 6 | Non-CNS progression of disease as assessed by the investigator/treating physician, for which a change in systemic therapy is planned OR achievement of stable or responsive non-CNS disease for which a holiday from the current systemic therapy is planned, as assessed by the investigator/treating physician. |
| 7 | Measurable non-CNS disease, defined by RECIST1.1 criteria (see section 12) |
| 8 | Recovered from all toxicities associated with prior treatment, to acceptable baseline status or grade 1 or less (for lab toxicities see below limits for inclusion, as per criterion 9), except for toxicities not considered a safety risk, such as alopecia or vitiligo. Peripheral neuropathy must be grade 2 or less. |
| 9 | Adequate organ and marrow function, as defined below:<br>• platelets ≥ 75x $10^3$/µL;<br>• absolute neutrophil count (ANC) ≥ 1,000/µL;<br>• hemoglobin ≥ 9.0 g/dL;<br>• total bilirubin ≤1.5 x ULN (upper limit of normal) except subject with documented Gilbert's syndrome (≤5 x ULN) or liver metastasis, who must have a baseline total bilirubin ≤3.0 mg/dL;<br>• AST and ALT ≤ 3 x ULN, unless associated with hepatobiliary metastases, in that case ≤5 x ULN<br>• serum creatinine ≤ 2 mg/dL (or glomerular filtration rate ≥ 50 ml/min as determined by the Cockcroft-Gault equation); |
| 10 | Negative hepatitis B serologic tests. If positive results are not indicative of active or chronic infection, the subjects can enter the study at the investigator's discretion. |
| 11 | Females of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception prior to the first dose of investigational product (as per appendix 20.1), and must agree to continue using such precautions for 6 months after the final dose of investigational product; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. They must also refrain from egg cell donation for 6 months after the final dose of investigational product;<br>• Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause);<br>• A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in appendix table 20.1; |
| 12 | Non-sterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (as per appendix 20.1) from Days 1 through 90 post last dose. In addition, they must refrain from sperm donation for 90 days after the final dose of investigational product |
| 13 | LVEF ≥50% for patients enrolling in the HER2 directed therapy arm |
| 14 | Willing to attempt a baseline tumor biopsy procedure |

## 6.3 Subject Exclusion Criteria

Patients may not enter the study if they fulfill any of the following criteria:

| | |
|---|---|
| 1 | CNS complications for whom urgent neurosurgical intervention is indicated (e.g., resection, shunt placement); |
| 2 | Known leptomeningeal metastases not amenable to radiotherapy. Patients receiving radiotherapy for leptomeningeal metastases are eligible; |
| 3 | Received any prior monoclonal antibody against CTLA-4, programmed cell death 1 (PD1) or programmed cell death 1 ligand 1 (PD-L1); |
| 4 | Subjects with a history of hypersensitivity to compounds of similar biologic composition to tremelimumab or any constituent of the product; |
| 5 | Subjects with a history of hypersensitivity to compounds of similar biologic composition to durvalumab or any constituent of the product; |
| 6 | Patients unable to obtain MRI for any reason (e.g., due to pacemaker, ferromagnetic implants, claustrophobia, extreme obesity); |
| 7 | Concurrent enrollment in another therapeutic clinical study or receipt of an investigational product within the last 4 weeks (participation in the survival follow-up period of a study is not an exclusion criterion); |
| 8 | Medical conditions (aside from newly-diagnosed brain metastases) for which the chronic use of corticosteroids or other immunosuppressive medications are indicated. Note: inhaled and topical steroids are permitted; |
| 9 | Use of immunosuppressive medications within 14 days before the first dose of study drug. The following are exceptions to this criterion: Intranasal, inhaled, topical steroids, or local steroid injections (e.g. intra articular injection); systemic corticosteroids at physiological doses not to exceed 10mg/day of prednisone or its equivalent; steroids as premedication for hypersensitivity reactions (e.g. CT scan premedication). |
| 10 | Subjects should not be vaccinated with live attenuated vaccines within one month prior to starting tremelimumab treatment; |
| 11 | Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results; |
| 12 | Any serious uncontrolled medical disorder or active infection that would impair the subject's ability to receive investigational product, such as conditions associated with frequent diarrhea; |
| 13 | Active or history of autoimmune or inflammatory disorders, including inflammatory bowel disease (e.g., colitis, Crohn's), diverticulitis (with the exception of diverticulosis), irritable bowel disease, celiac disease or other serious gastrointestinal chronic conditions associated with diarrhea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis, Sarcoidosis syndrome, Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, hypophysitis, uveitis, etc. Patients without active disease in the last 5 years may be included but only after consultation with the study physician. Note: the following are exceptions to this criterion: Vitiligo or alopecia; patients with hypothyroidism (i.e. following Hashimoto syndrome) stable on hormone replacement; any chronic skin condition that does not require systemic therapy; patients with celiac disease controlled by diet alone; |
| 14 | Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms |

| | |
|---|---|
| | (ECGs) using Frederica's Correction; |
| 15 | Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, intersti tial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, active peptic ulcer disease or gastritis, and active bleeding diatheses; |
| 16 | Known history of previous clinical diagnosis of tuberculosis; |
| 17 | History of allogeneic organ transplant; |
| 18 | History of leptomeningeal carcinomatosis; |
| 19 | No active, second potentially life-threatening cancer. No history of another primary malignancy excœpt for; malignancy treated with curative intent and no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence; adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease; adequately treated carcinoma in situ without evidence of disease; |
| 20 | Pregnant or breast feeding at time of consent; |
| 21 | Any condition that would prohibit the understanding or rendering of information and consent and compliance with the requirements of this protocol; |
| 22 | Known positive for HIV, chronic or active hepatitis B or C. |
| 23 | Patient is unable to receive IV contrast. |
| 24 | Neuroimaging evidence of midline shift |
| 25 | Major surgical procedure, as defined by the investigator, within 28 days prior to the first dose of IP. Note: Local surgery or isolated lesions for palliative intent is acceptable. |

### 6.3 Restrictions on Concomitant Therapies

#### 6.3.1 Non-Permitted Concomitant Therapies

The following medications are to be considered exclusionary by the investigator and are not permitted from signing of the informed consent form through the periods indicated. The investigator must be notified if a subject receives any of the following during the study:

| | |
|---|---|
| 1 | Immunosuppressive doses of steroids or other immunosuppressive medication, Exceptions include : 1) inhaled and topical steroids when medically indicated as treatment for an acute illness or as a pretreatments before CT scans (for contrast allergies); 2) corticosteroids as treatment for infusion reactions and treatment-related adverse events as described in section 11; and 3) corticosteroids for the treatment of symptomatic brain metastases are permitted (refer to section 9 for guidelines); |
| 2 | Other cancer therapy (chemotherapy or immunotherapy), with the exception of HER2 directed therapies, which may be continued in subjects enrolled on the concurrent therapy arm. Surgery and radiation therapy with palliative intent are permitted at any time; |
| 3 | Live/attenuated vaccines 28 days prior to day 1 and for at least 6 months after the last dose of study therapy; |
| 4 | Sunitinib within 3 months after the last dose of study therapy; |
| 5 | Drugs with laxative properties and herbal or natural remedies for constipation should be avoided |

| | |
|---|---|
| | if possible through 90 days post last dose during the study because of the potential for exacerbation of diarrhea which is an identified risk for study therapy; |
| 6 | Inactivated vaccinations +/- 30 days around any dose of study therapy; |
| 7 | EGFR TKIs within 90 days post last dose; |
| 8 | mAbs against CTLA-4, PD-1, or PD-L1, and any investigational anticancer therapy, other than those under investigation, should not be given while the patient is on study therapy; |
| 9 | Herbal and natural remedies which may have immune-modulating effects. |

#### 6.3.2 Permitted Concomitant Therapies

Patients may receive the following concomitant therapies during the study:

| | |
|---|---|
| 1 | Inhaled or oral steroids for treating mild to moderate asthma or allergies, or topical steroids for localized (<5% of body surface area) dermatitis |
| 2 | NSAIDS, acetylsalicylic acid, and COX-2 inhibitors |
| 3 | Antihistamines and other non-steroidal anti-allergy medication |
| 4 | Previously-initiated bone metastases-directed therapies, including bisphosphonate therapy or denosumab. |
| 5 | At the discretion of the investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high dose corticosteroids and TNF-α inhibitors to treat adverse reactions. |
| 6 | All prescription and nonprescription drugs must be recorded in the concomitant medications section of the case report form, listing generic or brand name, indication, dose, route, and dates of administration. All non-drug therapies must be recorded in the respective sections of the case report form or as adverse events. |
| 7 | HER2 directed therapies, such as trastuzumab is permitted in subjects enrolled on the concurrent therapy arm who have progressed on a trastuzumab or other HER2 directed-containing chemotherapy combination. |

## 7.0 RECRUITMENT PLAN

### 7.1 Expansion recruitment plan

The study will enroll at two locations, MSKCC and Cedars-Sinai Medical Center (CSMC) in Los Angeles. MSKCC and CSMC provide large referral bases, with approximately 25 women with HER2-positive breast cancer treated with WBRT or SRS across both sites each year (15 at MSKCC and 10 at CSMC). Notably, the completed efficacy and safety arms for this study enrolled briskly. Given that there are no competing trials at MSKCC or CSMC and given that this patient population is typically highly motivated, we anticipate an average accrual rate of 1-2 patients per month with accrual of 17 patients within 1 year (approx 10 at MSKCC and 7 at CSMC).

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at both sites. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The site principal investigator (PI) may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these numbers and patients regarding the possibility of enrolling in the study.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team, specifically the radiation oncology, medical oncology, or urgent care / inpatient departments. Potential patients may also be identified by the radiology department, who can identify breast cancer patients who demonstrate new/progressive CNS disease on MRI imaging.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

Once patients are identified, an expedited consultation will be facilitated by the site PI or another consenting clinician, in order to obtain consent and assess for eligibility. Additionally, an expedited radiation oncology evaluation will be facilitated to evaluate for WBRT/SRS. Radiation therapy will then be administered as per standard of care, and tremelimumab/durvalumab will be administered at a scheduled primary investigator appointment or as an inpatient if the subject is hospitalized.

The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for MSK patients for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable). Cedars Sinai will obtain a limited waiver from their IRB/privacy board separately.

## 8.1 PRETREATMENT EVALUATION

A signed written, informed consent form must be obtained prior to screening assessments and before any study-specific assessments are initiated.

The following will be obtained prior to enrollment:

<u>Within 4 weeks (28 days) of enrollment:</u>

- Patients must undergo MRI of the brain as well as either contrast-enhanced PET/CT or contrast-enhanced CT of the chest, abdomen, and pelvis with bone scan for baseline assessment
- For subjects continuing trastuzumab or other HER2 directed therapies, a baseline TTE or MUGA must be obtained

- A baseline biopsy will be performed (attempted) for all patients

Within 2 weeks (14 days) of enrollment:

- Medical History
- Height, body weight, ECOG PS, and vital signs including blood pressure, pulse, temperature, and respiration rate.
- Physical exam will be completed. Any changes in the patients' mental or physical condition since screening that would make him/her ineligible for the study should be considered
- Clinical safety labs (CBC with differential, CMP, magnesium, phosphorus, INR/PT, amylase/lipase, LDH, TSH with reflexive free T3/free T4, gamma glutamyltransferase)
- A serum HCG test will be obtained for all women of childbearing potential
- Urinalysis
- A baseline electrocardiogram (ECG) in triplicate, 2-5 minutes apart
- A baseline CA15-3 and CEA
- Baseline peripheral blood for immune monitoring (for flow cytometric analysis, circulating soluble factors, baseline serologic evaluation, and T-cell repertoire analysis)
- Screening HIV, Hepatitis B and C studies

## 9.1 TREATMENT/INTERVENTION PLAN

Tremelimumab +/- durvalumab + WBRT/SRS will be administered as per the schedule delineated in section 4.0.

### 9.1 Concomitant Steroid Administration for symptomatic CNS disease

Subjects with newly-diagnosed CNS metastases frequently benefit from steroids for symptomatic relief. Current practices are founded on level 3 evidence alone, with no randomized studies demonstrating superior benefit of higher steroid dose over lower steroid dose. (Ryken, McDermott et al. 2010) Therefore, it is reasonable to treat patients with lower-dose steroids at the onset of radiation therapy and titrate up if needed, in order to minimize the immunosuppression associated with steroids.

We defer to the discretion of the treating physician; however, in an effort to standardize steroid use as much as possible, we offer the following recommendations, which were developed in collaboration with radiation oncology and neurology co-investigators.

**Table 9.1-1: Standardized Recommendations for Steroid Use for CNS Mets**

| Scenario | Dexamethasone Induction | Dexamethasone Taper |
|---|---|---|
| **SRS** | | |
| Asymptomatic | None | None |
| Mild-Moderate Symptoms | Conservative management with analgesics.<br><br>If needed, 2mg PO BID x 7d | 1.5mg PO BID x 2d<br>1.0mg PO BID x 2d<br>0.5mg PO BID x 2d<br>0.5mg PO daily x 2d |

| | | |
|---|---|---|
| Severe Symptoms (or) Insufficient response to 2mg regimen | 4mg PO BID x 7d | 2mg PO BID x 7d<br>1.5mg PO BID x 3d<br>1.0mg PO BID x 3d<br>0.5mg PO BID x 3d<br>0.5mg PO daily x 3d |
| Adverse effect to SRS | 2mg PO BID x 7d | 1.5mg PO BID x 2d<br>1.0mg PO BID x 2d<br>0.5mg PO BID x 2d<br>0.5mg PO daily x 2d |
| **WBRT** | | |
| Asymptomatic | None | None |
| Mild-Moderate Symptoms | Conservative management with analgesics.<br><br>If needed, 2mg PO BID x 7d | 1.5mg PO BID x 2d<br>1.0mg PO BID x 2d<br>0.5mg PO BID x 2d<br>0.5mg PO daily x 2d |
| Severe Symptoms (or) Insufficient response to 2mg regimen | 4mg PO BID x 7d | 2mg PO BID x 7d<br>1.5mg PO BID x 3d<br>1.0mg PO BID x 3d<br>0.5mg PO BID x 3d<br>0.5mg PO daily x 3d |
| Adverse effect to WRBT | 2mg PO BID x 10d | 1.5mg PO BID x 2d<br>1.0mg PO BID x 2d<br>0.5mg PO BID x 2d<br>0.5mg PO daily x 2d |

## 9.2 Efficacy arm safety analysis (completed as of 3.1.17)

A maximum of 17 subjects were accrued to the efficacy arm. After the first 3 patients were enrolled in the efficacy arm, a 6 week enrollment hold was conducted in order to ensure safety before additional patients were enrolled. Thereafter, stopping rules (based on a repeated significance testing method) were employed to continuously assess safety. (Ivanova, Qaqish et al. 2005) These criteria were based on assumptions that a toxicity rate of 50% is deemed unacceptable, and a rate of 20% is deemed acceptable. The boundaries to stop the study were given as follows:

- If 3 of the first 5 patients have a SAE attributable to the experimental intervention, stop the study.
- If 5 of the first 10 patients have a SAE attributable to the experimental intervention, stop the study.
- If 6 of the first 17 patients have a SAE attributable to the experimental intervention, stop the study.

With these parameters, there is a 0.94 probability of crossing the boundary if the true toxicity rate is .50, and there is a 0.14 probability of .14 probability of crossing the boundary if the true toxicity rate is .20."

## 9.3 HER2 directed therapy co-administration arm safety run-in and expansion schedule

In the HER2 directed therapy safety arm, each of the first 3 HER2-positive subjects treated with both HER2 directed therapy and tremelimumab required 6 weeks of follow-up from the first dose of tremelimumab before additional HER2-positive patients were enrolled.

During the safety run-in, the following were criteria that would prompt discontinuation of enrollment of subsequent patients in the HER2 directed therapy safety arm:

- Any subject experiencing symptomatic CHF requiring therapeutic intervention. The CHF must be attributable to the experimental intervention. The diagnosis should be confirmed by a TTE demonstrating evidence of heart failure. A cardiology consultation should be obtained in cases of diagnostic uncertainty.
- Any subject with a cardiac event requiring therapy, including myocardial infarction or myocarditis/pericarditis, if the cardiac event is attributable to the experimental intervention.
- SAE's attributable to the experimental intervention, requiring treatment discontinuation, occurring in two of three subjects. If a serious adverse event (SAE) attributable to the experimental intervention occurs in 1/3 subjects a discussion and consensus will be required amongst the principal investigator before enrollment continues.
- Closure of the tremelimumab/RT efficacy arm related to toxicity concerns.

If cardiac toxicity or additional SAEs occur in patients following the safety run-in, the decision to continue enrollment of additional patients requiring concurrent therapy will be made by the principal investigator. If enrollment is discontinued for safety concerns, the decision of whether to halt therapy in previously enrolled patients will be made on a case-by-case basis by the principle investigator in discussion with the sponsor.

Patients who tolerate therapy are defined as patients who do not discontinue tremelimumab for safety-related reasons within 6 weeks of initiating tremelimumab.

Following the safety run-in, additional subjects were enrolled according to table 9.2.1. During the safety run-in, if none or one subject out of the three subjects enrolled experience unacceptable toxicity; we will expand to enroll 3 more patients. If either 0/6 or 1/6 subjects tolerate therapy, the combination will be deemed safe. Depending on availability of resources, if the combination is deemed safe, we may consider enrollment of additional subjects in an expansion cohort, to be defined under a protocol amendment. Similarly, if the combination is deemed not tolerable, we may consider enrollment of additional subjects in a dose de-escalation cohort.

Cardiac monitoring with TTE or MUGA is recommended at baseline and every 12 weeks (+/- 1 week ) for patients receiving concurrent HER2 directed therapy while on study. Left ventricular dysfunction, symptomatic or not, should be treated and followed according to standard medical practice.

**Table 9.2.1: Concurrent arm enrollment schema**

| # pts with safety-related | Next step |
|---|---|

| | | |
|---|---|---|
| | **treatment discontinuation** | |
| Safety run-in | ≤1/3 | Expand to 6 subjects |
| | ≥2/3 | **Therapy not tolerable; consider dose de-escalation cohort** |
| Expansion | ≤1/6 | **Therapy tolerable, consider expansion cohort** |
| | ≥2/6 | **Therapy not tolerable; consider dose de-escalation cohort** |

## 9.4 Expansion of the HER2+ safety cohort

As of 3/1/2017, the safety arm of patients with HER2-positive disease requiring continuation of HER2 directed therapy met the criteria for treatment expansion per the above enrollment schema. As a result, this cohort of patients will be expanded in order to evaluate efficacy in a Simon two-stage design. In this expansion, we will evaluate the combination of tremelimumab (treme), durvalumab (durva), and HER2 directed therapy plus brain irradiation in breast cancer patients with brain metastases (BCBM) for whom post-brain irradiation cytotoxic chemotherapy is planned. Subjects will receive either whole brain radiation treatment (WBRT) or stereotactic radiosurgery (SRS), as per standard of care, with tremelimumab administered at 75 mg and durvalumab administered at 1500 mg every 28 days for 4 cycles. After the 4$^{th}$ cycle, patients will continue to receive 1500 mg durvalumab every 28 days until disease progression or unacceptable toxicity. Patients will continue to receive HER2 directed therapy at a NCCN -guideline-endorsed dose and schedule, as determined by the investigator. Study design parameters and safety rules are consistent with those that were used to study subjects not requiring concurrent HER2 directed therapy.

### 9.5 Determining when to reinitiate systemic therapy

Subjects will be eligible to reinitiate cytotoxic therapy when any of the following criteria are met:

- Subject is experiencing symptomatic progression of disease as determined by either the medical oncologist, radiation oncologist, or neurologist
- Subject has confirmed progression of disease by irRC per section 12
- At the discretion of the investigator

Subjects requiring reinitiation of therapy before adjudication of the primary endpoint will be designated progressors, and will be included in calculating disease control rate, as per the intention to treat principle.

## 10.0 EVALUATION DURING TREATMENT/INTERVENTION

Subjects will require frequent monitoring which includes history and physical exam, toxicity grading, laboratory analyses, response assessment imaging (including body imaging), and ECG. Detailed monitoring schedules are provided in tables 10.0-1, 10.0-2, 10.1-1, and 10.1-2.

**Table 10.0-1 Study Flowsheet for q4wk Treatment Period**

| *Study Flowchart* | Screening | Q4wk Treatment Period | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Dose 1 (4 weeks) | | Dose 2 (4 weeks) | Dose 3 (4 weeks) | Dose 4 (4 weeks) | Dose 5 (4 weeks) | Dose 6 (4 weeks) | Dose 7 (4 weeks) |
| Treatment week | -2 to 0 | 1 | 3 | 5 | 9 | 13 | 17 | 21 | 25 |
| Treatment day | -14 to 0 | 1 | 15 +/- 1 week | 29 +/- 1 week | 57 +/- 1 week | 85 +/- 1 week | 113 +/- 1 week | 141 +/- 1 week | 169 +/- 1 week |
| **Treatment Administration** | | | | | | | | | |
| Tremelimumab 10mg/kg | | x[3] | | x | x | x | x | x | x |
| Radiotherapy | | x | | | | | | | |
| **Tumor assessment** | | | | | | | | | |
| MRI brain w/& w/o Gd | x[4] | | | | | X | x[2] | | X |
| CT CAP with PET or bone scan | x[4] | | | | | X | x[2] | | X |
| **Study procedures** | | | | | | | | | |
| Eligibility + Informed Consent | x | | | | | | | | |
| Demographics | x | | | | | | | | |
| Physical Exam | x | x | x | x | x | x | x | x | x |
| Medical History | x | x | x | x | x | x | x | x | x |
| ECOG PS | x | x | x | x | x | x | x | x | x |
| Vital signs, including height(screening only) | x | x | x | x | x | x | x | x | x |
| ECG | x | | | | | | | | |
| TTE or MUGA (in concurrent HER2 directed therapy) | x[4] | | | | | X | | | X |
| Medication reconciliation | x | x | x | x | x | X | x | x | X |
| CTCAE Adverse Events | x | x | x | x | x | x | x | x | x |
| **Labs** | | | | | | | | | |
| Blood Hematology (CBC, diff) | x | x | x | x | x | x | x | x | x |
| Chemistry (CMP) | x | x | x | x | x | x | x | x | x |
| Tumor markers (CA15-3, CEA) | x | x | x | x | x | x | x | x | x |
| Magnesium, Amylase/Lipase, LDH | x | | x | x | x | x | x | x | x |
| Phosphorus | x | | | | | | | | |
| INR/PT | x | | | | | | | | |
| TSH ( with reflexive FT3, FT4) | x | x | | x | x | x | x | x | x |
| Serum Pregnancy test | x | | | | | | | | |
| HIV and Hepatitis B,C virologies | x | | | | | | | | |
| **Immune monitoring studies** | | | | | | | | | |
| Circulating soluble factors (cytokines, chemokines) | x | x[1] | x | x | | x | x | | x |
| PBMC collection (flow, functional assay, immune repertoire) | x | x[1] | x | x | | x | x | | x |

1 – Immune monitoring studies will be drawn on the day of tremelimumab administration

2- Response assessment will occur at week 13 +/- 1 week, with a confirmatory scan at week 17 +/- 1 week in patients with evidence of radiographic progression
3- The first dose of tremelimumab will ideally be administered 2 days prior to initiation of radiotherapy (but if not feasible, the first dose can be administered from 5 days preceding to 3 days following initiation of radiotherapy).
4 – Can be within 4 weeks (28 days) of enrollment

**Table 10.0-2: Study Flowsheet for q4week treatment period, end of treatment, and follow-up**

| ***Study Flowchart*** | Q4wk Treatment Period | | End of Treatment[2] (Within 30 days post last dose) | Short Term Follow up Visits[2] | | |
|---|---|---|---|---|---|---|
| | Dosing visits (dose 8, 9, 10) | (Dose 10, | | 4wk +/- 1 week after last dose[3] | 8wk +/- 1 week after last dose | 12wk +/- 1 week after last dose |
| Treatment week | 29, 33, 37… | | | | | |
| Treatment day | 197, 225,253+/- 1 week… | | | | | |
| **Treatment Administration** | | | | | | |
| Tremelimumab 10mg/kg | x | | | | | |
| Radiotherapy | | | | | | |
| **Tumor Assessment** | | | | | | |
| MRI brain w/ & w/o Gd | x[4] | | X | | | |
| CT CAP with PET or bone scan | x[4] | | x | | | |
| **Study Procedures** | | | | | | |
| Eligibility + Informed Consent | | | | | | |
| Demographics | | | | | | |
| Physical Exam | x | | x | x | x | x |
| Medical History | x | | x | x | x | x |
| ECOG | x | | x | x | x | x |
| Vital signs | x | | x | x | x | x |
| Medication reconciliation | x | | x | x | x | x |
| TTE or MUGA (in concurrent HER2 directed therapy) | x[1] | | X | | | X |
| CTCAE Adverse Events | x | | x | x | x | x |
| **Labs** | | | | | | |
| Blood Hematology (CBC, diff) | x | | x | x | x | x |
| Chemistry (CMP, LDH, TSH with reflexive FT3, FT4) | x | | x | x | x | x |
| Tumor markers (CA15-3, CEA) | x | | x | x | x | x |
| **Immune monitoring studies** | | | | | | |
| Circulating soluble factors (cytokines, chemokines) | | | x | | | |
| PBMC collection (flow, functional assay, immune repertoire) | | | x | | | |

1- TTE or MUGA every 12 weeks (+/- 1 week ) while on concurrent HER2 directed therapy
2 – End of treatment and short term follow up visit assessments are to be performed only if clinically appropriate.
3 – If the End of Treatment visit occurs within the 4 week Short Term Follow up visit window, the assessments performed can be used to satisfy both visits.
4 – Imaging assessments are to be performed every 12 weeks (+/- 1 week) (e.g. Dose 10, Dose 13, Dose 16, ect)

**Table 10.1-1 Study Flowsheet for the HER2 Expansion Treatment Period**

| ***Study Flowchart*** | Screening | Q4wk Treatment Period | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Dose 1 (4 weeks) | | Dose 2 (4 weeks) | Dose 3 (4 weeks) | Dose 4 (4 weeks) | Dose 5 (4 weeks) | Dose 6 (4 weeks) | Dose 7 (4 weeks) |
| Treatment week | -2 to 0 | 1 | 3 | 5 | 9 | 13 | 17 | 21 | 25 |
| Treatment day | -14 to 0 | 1 | 15 +/- 1 week | 29 +/- 1 week | 57 +/- 1 week | 85 +/- 1 week | 113 +/- 1 week | 141 +/- 1 week | 169 +/- 1 week |
| **Treatment Administration** | | | | | | | | | |
| Durvalumab 1500 mg | | x[3] | | x | x | x | x | x | x |
| Tremelimumab 75 mg | | x[3] | | x | x | x | | | |
| Radiotherapy | | x | | | | | | | |
| **Tumor assessment** | | | | | | | | | |
| MRI brain w/& w/o Gd | x[4] | | | | | x | x[2] | | x |
| CT CAP with PET or bone scan | x[4] | | | | | x | x[2] | | x |
| Tumor core needle or surgical biopsy[8] | x | | | | | | | | |
| **Study procedures** | | | | | | | | | |
| Eligibility + Informed Consent | x | | | | | | | | |
| Demographics | x | | | | | | | | |
| Physical Exam | x | x | x | x | x | x | x | x | x |
| Medical History | x | x | x | x | x | x | x | x | x |
| ECOG PS | x | x | x | x | x | x | x | x | x |
| Vitalsigns[5] | x | x | x | x | x | x | x | x | x |
| Weight (height at screening only) | x | x | | x | x | x | x | x | x |
| ECG | x | x[6] | | | | | | | |
| TTE or MUGA (in concurrent HER2 directed therapy) | x[4] | | | | | x | | | x |
| Medication reconciliation | x | x | x | x | x | x | x | x | x |
| CTCAE Adverse Events | x | x | x | x | x | x | x | x | x |
| **Labs** | | | | | | | | | |
| Blood Hematology (CBC, diff) | x | x | x | x | x | x | x | x | x |
| Chemistry (CMP) | x | x | x | x | x | x | x | x | x |
| Tumor markers (CA15-3, CEA) | x | x | x | x | x | x | x | x | x |
| Amylase/Lipase | x | x | x | x | x | x | x | x | x |
| Phosphorus | x | | | | | | | | |
| Gamma GTP, Magnesium[7] | x | x | | | | | | | |
| Lactate Dehydrogenase | x | x | | x | x | x | x | x | x |
| Uric Acid | x | x | | x | x | x | x | x | x |
| INR/PT | x | | | | | | | | |
| TSH ( with reflexive FT3, FT4) | x | x | | x | x | x | x | x | x |
| Serum Pregnancy test | x | | | | | | | | |
| Urinalysis | x | | | x | x | x | x | x | x |
| HIV and Hepatitis B,C virologies | x | | | | | | | | |
| **Immune monitoring studies** | | | | | | | | | |
| Circulating soluble factors (cytokines, chemokines) | x | x[1] | x | x | | x | x | | x |
| PBMC collection (flow, functional assay, immune repertoire) | x | x[1] | x | x | | x | x | | x |

1 – Immune monitoring studies will be drawn on the day of tremelimumab administration

2- Response assessment will occur at week 13 +/- 1 week, with a confirmatory scan at week 17 +/- 1 week in patients with evidence of radiographic progression
3- The first dose of tremelimumab will ideally be administered 2 days prior to initiation of radiotherapy (but if not feasible, the first dose can be administered from 5 days proceeding to 3 days following initiation of radiotherapy). Concurrent HER2-directed therapy will be administeredat a dose and schedule consistent with NCCN guidelines at the treating physicians' discretion
4 – Can be within 4 weeks (28 days) of enrollment
5 – Subjects will have their vital signs (BP, HR, RR, Temp) taken before, during, and after each infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±10 minutes)
- At the end of the infusion (at 60 minutes ±10 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±10 minutes). A 1-hour observation period is required after the first infusion. If no clinically significant infusion reactions are observed during orafter 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 blood pressure and pulse measurements should follow the principles as described above or more frequentlyif clinically indicated

6 – During Screening, ECGs should be taken in triplicate 2-5 minutes apart. On Cycle 1 Day 1, ECGs should be taken withinan hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion. Baseline and abnormal ECGs should be performed in triplicate. At all other times, single. After C1D1, ECGs should be performedas clinically indicated.
7 – To be performedas clinically indicated after C1D1
8 – The first tumor biopsy will be taken (attempted) at baseline, within 28 days prior to dosing or initiation of radiotherapy, whichever is first. An optional tumor biopsy will be performed at times such as disease progression, if the patient's condition allows it, or at the time of radiographic response, at the investigator's discretion and in discussion with the patient.

**Table 10.1-2: Study Flowsheet for the HER2 Expansion Treatment Period, End of Treatment, and Follow-up**

| ***Study Flowchart*** | Q4wk Treatment Period<br>Dosing visits (dose 8, 9, 10…) | End of Treatment[2] (Within 30 days post last dose) | Short Term Follow up Visits[2]<br>4wk +/- 1 week after last dose[3] | 8wk +/- 1 week after last dose | 12wk +/- 1 week after last dose |
|---|---|---|---|---|---|
| Treatment week | 29, 33, 37… | | | | |
| Treatment day | 197, 225,253+/- 1 week … | | | | |
| **Treatment Administration** | | | | | |
| Durvalumab 1500mg | x | | | | |
| **Tumor Assessment** | | | | | |
| MRI brain w/& w/o Gd<br>CT CAP with PET or bone scan | x[4] | x | | | |
| Tumor core needle or surgical biopsy | | X[6] | | | |
| **Study Procedures** | | | | | |
| Physical Exam | x | x | x | x | x |
| Medical History | x | x | x | x | x |
| ECOG | x | x | x | x | x |
| Weight, Vital signs[5] | x | x | x | x | x |
| Medication reconciliation | x | x | x | x | x |
| TTE or MUGA (in concurrent HER2 directed therapy) | x[1] | x | | | |
| CTCAE Adverse Events | x | x | x | x | x |
| **Labs** | | | | | |
| Blood Hematology (CBC, diff) | x | x | x | x | x |
| Chemistry (CMP) | x | x | x | x | x |
| Amylase/Lipase | x | | | | |
| Lactate Dehydrogenase | x | | | | |
| Uric Acid | x | | | | |
| TSH with reflexive FT3, FT4 | x | x | x | x | x |
| Tumor markers (CA15-3, CEA) | x | x | x | x | x |
| Urinalysis | x | | | | |
| **Immune monitoring studies** | | | | | |
| Circulating soluble factors (cytokines, chemokines) | | x | | | |
| PBMC collection (flow, functional assay, immune repertoire) | | x | | | |

1- TTE or MUGA every 12 weeks (+/- 1 week ) while on concurrent HER2 directed therapy
2 – End of treatment and short term follow up visit assessments are to be performed only if clinically appropriate.
3 – If the End of Treatment visit occurs within the 4 week Short Term Follow up visit window, the assessments performed can be used to satisfy both visits.
4 – Imaging assessments are to be performed every 12 weeks (+/- 1 week) (e.g. Dose 10, Dose 13, Dose 16, ect)
5 - Subjects will have their vital signs taken before, during, and after each infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±10 minutes)
- At the end of the infusion (at 60 minutes ±10 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±10 minutes). A 1-hour observation period is required after the first infusion. 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 blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated

6 – A second, optional tumor biopsy will be performed at times such as disease progression, prior to starting a new anti-cancer regimen and if the patient's condition allows it, or at the time of radiographic response, at the investigator's discretion and in discussion with the patient.

## 11.1 TOXICITIES/SIDE EFFECTS

### 11.1 Overview of Tremelimumab Toxicity Profile

In the nonclinical setting, treatment of tumor-bearing mice with anti-mouse CTLA-4 mAb (9H10) induced antitumor immunity and markedly enhanced T cell-mediated killing of various mouse solid tumors. Clinical trials of tremelimumab, and of the related anti-CTLA-4 antibody ipilimumab, in melanoma suggest activity (improved survival) of these agents in melanoma. Tremelimumab has also shown activity (objective responses and disease stabilization) in the malignant mesothelioma setting, with preliminary results suggesting that tremelimumab may lead to improved survival with 45.5% of subjects alive at 1 year and 5 subjects were alive at 2 years.

Overall, tremelimumab nonclinical toxicities were consistent with inhibition of CTLA-4, with adverse effects noted for the gastrointestinal tract, skin, lymphoid organs, thyroid tissues, and hematological systems. Dose-limiting toxicities identified in chronic toxicity studies in monkeys included skin rash and gastrointestinal effects. Most toxicities were reversible or showed a trend towards reversibility.

The profile of AEs from > 1000 treated subjects and the spectrum of event severity are consistent with the pharmacologic class and with the signal observed in nonclinical toxicology studies. Adverse events have been observed in every organ system and are mainly due to the inflammation caused by tremelimumab's mechanism of action. The most common AEs involve skin, the gastrointestinal tract, and endocrine system, and are usually mild in nature. Events reported at a frequency of ≥ 5% and assessed by the investigator as related to treatment (listed in descending order of frequency) were diarrhea, rash, pruritus, fatigue, nausea, vomiting, anorexia, headache, abdominal pain, and colitis. Infusion-related AEs were rare.

## 11.2 Adverse event management

### 11.2.1 Dose modification and universal management guidelines for drug-related adverse events.

No dose reduction is allowed. Dosing may be delayed up to + 3 days during the treatment phase to allow recovery from treatment-related toxicity. Toxicity management guidelines for anti-CTLA-4 monoclonal antibodies have been developed and published in the past 5 years (Weber, Kahler et al. 2012). Detailed management guidelines have been created for diarrhea and/or colitis-related events (Appendix 20.1). However, for management of most other toxicities follow the guideline in table 11.2.

Specific detailed management guidelines have been created for diarrhea and colitis-related events. However, for management of most other toxicities follow the guideline in Table 11.2 below.

**Table 11.2 General Toxicity Management Guideline**

| Condition | Management |
|---|---|
| Onset of any toxicity | • Rule out alternative etiology |
| CTCAE Grade 1 | • Provide symptomatic treatment.<br>• Possible topical steroids if applicable.<br>• If symptoms resolve, continue tremelimumab dosing.<br>• If symptoms persist >10 days, treat as CTCAE Grade 2. |
| CTCAE Grade 2 | • Provide symptomatic treatment<br>• Do not give scheduled dose; dosing may be resumed at next scheduled dose if symptoms are resolved.<br>• Dosing delays are not permitted (except per protocol specified window of +3 days in treatment phase).<br>• Consider oral or intravenous (IV) steroids at the onset of symptoms. Taper steroid over 4 weeks if symptoms improve<br>• For persistent Grade 2 CTCAE events: treat as CTCAE grade 3 event, start high-dose IV steroids |
| CTCAE Grade 3 | • Start high-dose IV steroids at the onset of the symptoms<br>• Provide symptomatic treatment<br>• Permanent discontinuation* of tremelimumab for CTCAE Grade 3 events thought to be drug-related.<br>• Exception are endocrinopathies that are asymptomatic and controlled with hormone replacement therapy, and rash or other skin disorders |

**Table 11.2 General Toxicity Management Guideline**

| Condition | Management |
|---|---|
| CTCAE Grade 4 | • Start high dose IV steroids at the onset of the symptoms<br>• Provide symptomatic treatment<br>• Permanent discontinuation* of tremelimumab for all Grade 4 events |
| Steroid refractory toxicity (no improvement after 5 days on high dose IV steroids) or relapse after reducing high dose steroids | • Continue symptomatic treatment and steroids<br>• Possible infliximab 5 mg/kg IV for gastro-intestinal toxicities unless contraindicated [consult with GI specialist]. Caution: rule out bowel perforation and refer to label before using infliximab.<br>• For patients with increased AST/ ALT, or Total Bilirubin levels, consider Mycophenolate mofetil |

*Patients will not receive any subsequent dose, but will remain on study and follow the other procedures required from the study (e.g. follow up procedures, imaging follow-up, blood sample collections).

#### *11.2.1.1 Guidelines for hypersensitivity reactions*

In case of hypersensitivity reactions, the investigator should institute treatment measures deemed medically appropriate per institutional guidelines.

- Grade 1 = Transient flushing or rash; drug fever < 38°C
- Grade 2 = Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C
- Grade 3 = Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension; anaphylaxis
- Grade 4 = Anaphylaxis
- Grade 5 = Death

11.2.1.1.1 Dose modification and delay for non-related adverse events

Dosing delays for toxicities not related to treatment are at the discretion of the treating investigator. Any patient who has a treatment delay due to an unrelated toxicity will reinitiate treatment at the discretion of the treating investigator.

### 11.2.2 Guidelines for skipping the next scheduled dose for drug-related adverse events.

The following guidance (see Table 11.2.2.1 below) is for consideration when determining when to skip/hold the next scheduled dose of tremelimumab during management of drug-related toxicities. When a scheduled dose of tremelimumab is skipped; the dosing may be resumed at the next scheduled dose if the symptoms have resolved to CTCAE Grade ≤ 1. Dose delays are not allowed (except per protocol specified window of 2 days in induction and 5 days in maintenance phase). No dose reductions are permitted for tremelimumab.

**Table 11.2.2.1 Guidelines for skipping a tremelimumab dose**

| Condition | Action |
|---|---|
| For persistent NCI CTCAE Grade 1 treatment-related toxicities (> 10 days). | **Manage** as a NCI CTCAE Grade 2 |
| Subjects with AST/ALT 5-8 × ULN or total bilirubin 3-5 × ULN.<br><br>Subjects with any NCI CTCAE Grade 2 treatment-related laboratory abnormalities.<br><br>For ongoing NCI CTCAE Grade 2 related toxicities, dosing may be resumed at next scheduled dose if the event is resolving and at Grade ≤ 1.<br><br>Exceptions to this are:<br>• Investigational product may be dosed for NCI CTCAE Grade ≤ 3 endocrine disorders, if asymptomatic and controlled with hormone replacement therapy. Skip investigational product dose for Grade ≥ 2 endocrinopathies that are under treatment and remain symptomatic.<br>• For hypersensitivity reactions and infusion reactions NCI CTCAE Grade ≤ 2: slow the infusion rate or temporarily pause the infusion, medicate the subject with symptomatic therapies (i.e. anti-histaminic drugs), and consider premedication per institutional guidelines.<br>• Investigational product may be dosed for NCI CTCAE Grade 2 rash or other skin disorders; skip dose for Grade 3 skin disorders, with the exception of vitiligo, for which tremelimumab may be continued. | **Skip** scheduled tremelimumab dose |

ALT = alanine transaminase; AST = aspartate transaminase; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

During the study, patients may immunosuppressive medications such as steroids may be indicated for management of underlying disease, treatment-related toxicity, or unrelated conditions. If symptoms resolved to CTCAE Grade ≤1, tremelimumab dosing may be resumed during steroid taper. Patients with adrenal insufficiency may take daily prednisone or equivalent therapy for their endocrinopathy while receiving tremelimumab treatment. Topical and inhaled steroids in standard doses are allowed.

### 11.2.3 Guidelines for permanent dosing discontinuation (safety related)

Table 11.2.3.1 below lists the safety related conditions when patients must be permanently discontinued from tremelimumab treatment. Additionally, tremelimumab should be permanently discontinued for any adverse event, which in the opinion of the investigator, contraindicate further dosing. When tremelimumab dosing is permanently discontinued, continue to follow the patient (e.g. they will follow the other procedures required from the study; follow up procedures, imaging follow-up, blood samples collection etc.).

**Table 11.2.3.1 Guideline for Permanent Discontinuation of tremelimumab**

| Action | Condition |
|---|---|
| **Permanent Discontinuation of tremelimumab** | CTCAE Grade ≥3 treatment-related diarrhea or colitis |
| | AST or ALT > 8 x ULN or total bilirubin > 5x ULN |
| | CTCAE Grade ≥3 hypersensitivity reaction or infusion reaction;<br>Recurrent/persistent CTCAE Grade 2 hypersensitivity despite optimal premedication |
| | CTCAE Grade ≥ 3 related endocrine disorders, if symptomatic and not controlled with hormone replacement therapy. [Tremelimumab may de dosed for CTCAE Grade ≤ 3 endocrine disorders, if asymptomatic and controlled with hormone replacement therapy] |
| | CTCAE Grade 4 rash or other skin disorders [with the exception of vitiligo, which may be dosed regardless of severity] |
| | Any CTCAE Grade 4 event thought to be drug related |
| | Any patient who receives infliximab or any other TNF alfa inhibitor |
| | If 2 consecutive doses are missed due to on-going related toxicities |
| | Begins new investigational therapy, chemotherapy, cytokine therapy, or immunotherapy (including vaccines) must withdraw from treatment |
| | Patient becomes pregnant |

## 11.3 Toxicities/Side effects of durvalumab + tremelimumab combination therapy

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines in section 20.3. Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see the Dosing Modification and Toxicity Management Guidelines in section 20.3).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in section 20.3. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting investigator.

If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible. Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) assessments. Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab and tremelimumab (see current Investigator Brochures for durvalumab and tremelimumab.

**Dose reductions are not permitted.**

### 11.3.1 Durvalumab + tremelimumab adverse events of special interest

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

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

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

AESIs observed with durvalumab and tremelimumab include:

- Diarrhea/Colitis
- Pneumonitis/ILD
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)

- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, diabetes insipidus, type I diabetes mellitus, and hyper- and hypothyroidism)
- Rash/Dermatitis
- Nephritis/Blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Cardiac disorders (myocarditis)
- Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.

- In addition, infusion related reactions and hypersensitivity, anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs

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

### Pneumonitis

AEs of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Gui delines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Table 20.3.

### 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 11.2.1.1.

### Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (**Error! Reference source not found.**). 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 Section 11.2.1.1.

### Hepatic function abnormalities (hepatotoxicity)

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single

blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the IP. Guidelines for management of patients with hepatic function abnormality are provided in Table 20.3.

**Gastrointestinal disorders**

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving tremelimumab are provided in Table 20.3.

**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 20.3.

**Pancreatic disorders**

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Table 20.3.

**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 20.3.

**Nephritis**

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

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2) , in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Table 20.3.

### 11.3.2 Immune-related adverse events

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis,

and endocrinopathies (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**). 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 20.3, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (**Error! Reference source not found.**). These guidelines recommend the following:

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

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should immediately contact the Study Physician.

## 12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

### 12.2 Evaluation of Primary Endpoint

#### 12.2.1 Response Assessments

Imaging assessments will be performed at baseline (within 28 days before randomization) and every 3 months +/- 1 week during the q28d treatment period until confirmed objective disease progression irrespective of whether the subject has discontinued investigational product. In the absence of progression, the next assessment should be performed at the next scheduled visit. In addition, when available, scans done

after disease progression in subjects who permanently discontinue investigational product will be obtained when possible to determine if there was any delayed tremelimumab +/- durvalumab activity unless consent is withdrawn or the subject is lost to follow-up or starts receiving another anticancer therapy. Additional scans can also be done at any time based on investigator discretion.

An initial increase in tumor burden or the appearance of new lesions could precede immunotherapy-induced tumor regression (Wolchok, Hoos et al. 2009). According to this model of response, subjects initially assessed as PD by RECIST1.1 criteria, in the absence of significant clinical deterioration warranting discontinuation of study treatment will continue treatment and receive a confirmatory scan at least 4 weeks later. The following criteria will be used to determine if study treatment is continued:

- If the tumor burden at the confirmatory scan is more than 20% larger than the tumor burden at the initial PD scan, the subject will be considered to have confirmed PD and will be discontinued from study treatment
- If the tumor burden at the confirmatory scan is within 20% of the tumor burden at the initial PD scan, the subject will be considered to have SD and will continue treatment until the next scheduled scan 3 months after the initial PD. Any subsequent scheduled tumor assessment visit showing that the tumor burden is more than 20% larger than the tumor burden at the initial PD scan will be considered as confirmed PD, and the subject will be discontinued from study treatment
- In subjects with new lesions in the setting of overall response, the decision to continue treatment will be discussed on a case by case basis between the principal investigator and study monitor
- It is important to maintain the schedule of assessments every 3 months and subjects having confirmatory scans for PD must return for the next scheduled visit per protocol.

### 12.2.2 RECIST1.1 Criteria

Tumor burden will be assessed using RECIST criteria v1.1 (Eisenhauer, Therasse et al. 2009). To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion (10mm by CT scan [CT scan slice thickness no greater than 5mm], 10mm caliper measurement by clinical exam, or 20mm by chest x-ray). A lymph node must be at least 15mm in short axis when measured by CT scan. When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Remaining lesions will be considered non-target lesions. For full details of the RECIST1.1 criteria, refer to the Eisenhauer reference.(Eisenhauer, Therasse et al. 2009)

The RECIST1.1 criteria response definitions are summarized as follows:

- Complete response: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10mm.
- Partial response: At least a 30% decrease in the sum of 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 5mm.

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

## 12.3 Evaluation of Secondary Endpoints

### 12.3.1 Objective response and disease control rate by irRC

We will assess disease control at 12 weeks using immune-related response criteria (irRC) (Wolchok, Hoos et al. 2009). Response is defined as irCR, irPR or irSD over a period of at least 4 weeks. Imaging before the week 12 time point will not be specified, to account for the possibility that a subset of patients will experience an immune-related response, by which responses are preceded by radiographic progression, related to delayed response kinetics and/or T-cell tumoral infiltration.

### 12.2.2 CNS Response Determination

CNS response will not be included in the primary endpoint. Investigators may plan more frequent imaging as clinically indicated, including MRI imaging.

Subjects who experience systemic disease control and CNS progression may continue receiving study medication at the discretion of the investigator. These subjects may receive additional brain-directed SRS if clinically warranted.

**Table 12.2.2.1: RANO Criteria for CNS response (Wen, Macdonald et al. 2010)**

| Response | Criteria |
|---|---|
| Complete Response | Requires all of the following: complete disappearance of all enhancing measurable and non measurable disease sustained for at least 4 weeks; no new lesions; stable or improved non enhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with non measurable disease only cannot have a complete response; the best response possible is stable disease. |
| Partial Response | Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of non measurable disease; no new lesions; stable or improved non enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with non measurable disease only cannot have a partial response; the best response possible is stable disease. |
| Stable Disease | Requires all of the following: does not qualify for complete response, partial response, or progression; stable non enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose. |
| Progression | Defined by any of the following: ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR non enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of non measurable disease. |

## 12.3 Exploratory assessments

### 12.3.1 Immunologic correlatives

Exploratory correlative studies will be performed to evaluate anti-tumor and immunological response pre- and post-treatment on individuals. Peripheral blood samples will be studied, and these tests will be done at the IMF (currently located in the Zuckerman building). The following exploratory endpoints are proposed:

1) To evaluate the effect of tremelimumab +/- durvalumab + RT on: lymphocyte phenotype and serum cytokines, disease related biomarkers, and humoral and cellular responses to tumor antigens and recall non-tumor antigens;

2) To evaluate serological and cellular immune correlates of toxicity and/or clinical activity;

To this end, the specimens to be collected for IMF evaluation include research blood samples at time points as delineated in table 10.1-1 and 10.1-2. For each blood draw, 4 CPT tubes will be collected for:

- Flow cytometric analysis:
  - T-cells: activation and memory markers
  - Dendritic cells: activation and maturation markers and markers of inhibitor/tolerogenic DCs
- Intracellular cytokine assay (ICCA) and ELISPOT: to detect responses to specific tumor antigens (for example, HER2 or MUC1) which are expressed in breast cancers
- Serum cytokines: Soluble factors, such as interferon gamma, are detectable at increased levels following administration of anti-CTLA-4 plus cryotherapy in breast cancer patients (Page, Yuan et al. 2014), and may serve as a pharmacodynamic marker of immune activation and biomarker of response
- Serology assays: Antibody levels to cancer testis antigens and breast tumor specific antigens will be assessed by multiplex assays and enzyme-linked immunosorbent assay (ELISA).
- DNA deep sequencing T-cell repertoire analysis: Maintenance of peripheral T-cell clonal diversity has been described as a predictor of clinical benefit to anti-CTLA4. (Cha, Klinger et al. 2014)
- CBC: to quantify absolute lymphocyte count (ALC)

### 12.3.2 Imaging

In subjects receiving PET/CT, radiographic response by PET will be compared to standard assessment with CT CAP. This comparison will help to evaluate whether metabolic uptake might be useful in distinguishing clinical response to immunotherapy in breast cancer patients, who frequently are evaluated off-protocol with PET/CT.

PET/CT is commonly used as a standard-of-care modality for evaluating response to palliative therapy in metastatic breast cancer off-study. However, on study, response to treatments is often measured anatomically using the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines version 1.1. However, there are limitations in using anatomic response criteria alone, particularly when evaluating bone metastases without an extra-osseous component, which is common in breast cancer patients. Furthermore, while RECIST

criteria may be appropriate for evaluating response to conventional cytotoxic therapies, they may not be ideal for evaluating response in the setting of dynamic infiltration with immunotherapy.

#### *12.3.2.1 PERCIST Criteria*

PERCIST (PET response criteria in solid tumors) is a commonly proposed method for measuring treatment response based on metabolic response criteria with PET. A limitation of PERCIST is that it only takes into account the single hottest lesion and it relies upon SUV peak measurements, which are not easily reproducible in lesions with low FDG-avidity, as are often found in breast cancer. Since there are no standardized methods for quantifying FD G-tracer avidity in individual tumor lesions, we will use a modification of PERCIST criteria called "PET Response Criteria" (PRC) that is currently being utilized in other cancer protocols at MSK requiring metabolic assessment. In brief, up to 5 FDG-avid target lesions will be selected, SUVmax measured for each lesion, and the sum of all lesions (Sum SUVmax) recorded. On subsequent studies, the same target lesions will be measured and Sum SUVmax recorded. Lesions where SUVmax is no greater than background will be recorded as zero. Response or progression will be graded as follows:

- Complete Response: All lesions no greater than background SUVmax
- Partial Response: Sum SUVmax decreased by >30% but still greater than background SUVmax
- Stable Disease: Lesions that do not fit criteria for response or progression
- Progressive Disease: Sum SUVmax increased by > 30% or development of a new lesion

Thus, PET will be performed in conjunction with dedicated CT in this study in order to explore similarities and differences in the information conferred, ultimately in order to inform future studies.

### 12.3.3 Tumor Biopsies

Patients in the expansion will have two biopsies collected (attempted). The first tissue biopsy will be attempted at baseline, within 28 days prior to starting treatment. A second, optional, tumor biopsy will be performed at times such as disease progression, prior to starting a new systemic cancer treatment and if the patient's condition allows it, or at the time of radiographic response, at the investigator's discretion and in discussion with the patient. For each core needle biopsy, an attempt should be made to collect at least 3 core needle samples; however, if it is not medically feasible to collect 3 samples, the investigator or designee should attempt to collect as much tumor tissue as is deemed medically feasible.

Biopsy samples will be collected for exploratory biomarker research, to be used in understanding the effects of tremelimumab and durvalumab.

## 12.4 Evaluable patients

All patients who receive at least one dose of tremelimumab +/- durvalumab will be evaluable for toxicity and will be included in the intent to treat analysis.

Patients who complete 12 weeks on study and undergo protocol imaging will be evaluable for response. Subjects who clinically progress or die prior to the 12 week assessment will be included in the analysis as failures.

## 13.1 CRITERIA FOR REMOVAL FROM STUDY

Permanent discontinuation of the drug: An individual subject will not receive any further Tremelimumab/durvalumab if any of the following occur in the subject in question:

a) Withdrawal of consent from further treatment with investigational product
b) Lost to follow-up
c) An AE that, in the opinion of the investigator, contraindicates further dosing
d) Adverse event related to Tremelimumab/durvalumab that met criteria for discontinuation as defined in Section 11
e) Subject who skips 2 consecutive doses because of ongoing treatment-related toxicity;
f) Subject who has received any amount of infliximab or other tumor necrosis factor alpha (TNF-α) inhibitor.
g) Subject is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
h) Pregnancy or intent to become pregnant
i) Subject noncompliance that, in the opinion of the investigator, warrants withdrawal; e.g., refusal to adhere to scheduled visits
j) Initiation of alternative anticancer therapy including another investigational agent
k) Confirmation of progressive disease and investigator determination that the patient is no longer benefitting from treatment
l) Grade ≥ 3 infusion reaction

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study.

Subjects, who are permanently discontinued because of toxicity and in the absence of disease progression, will be asked to come in for every protocol-specified visit and will follow all protocol procedures with the exception of dosing. For subjects refusing to return to the site, they should be contacted by phone unless consent is withdrawn.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety, including the collection of any protocol-specified blood, or urine specimens, as specified in section 10, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. Subjects who decline to return to the site for evaluations will be offered follow-up by phone as an alternative.

**Withdrawal of consent:** If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely.

**Withdrawal of treatment:** at any time the subject may withdrawal the consent to further treatment, without withdrawing the consent to the study; in this case the subject will not receive any further investigational product, but he/she will continue to follow the study procedures.

**Lost to follow-up:** Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at that time.

Note: For subjects refusing to continue participation in the study, they should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

### 13.1 Premature Patient Withdrawal

A patient may withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator has the right to withdraw patients from the study. Should a patient (or a patient's legally authorized representative) decide to withdraw, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

A complete final evaluation should be made at the time of the patient's withdrawal, the Study Status Outcome form in the case report form should be completed with an explanation of why the patient is withdrawing, and an attempt should be made to perform a follow-up evaluation.

Reasons for a premature withdrawal of a patient include, but are not limited to, the following:

- Significant protocol violation or noncompliance on the part of the patient or Investigator
- Refusal of the patient to continue treatment or observations
- Best medical interest of the patient (at the discretion of the Investigator)
- Unrelated medical illness or complication
- Lost to follow-up

### 13.2 Very Premature Patient Withdrawal

Patients who withdraw consent prior to the first dose of tremelimumab will be replaced, and will not be included in subsequent analysis.

## 14.1 BIOSTATISTICS

## 14.2 Sample Size Determination

The overarching goal of this pilot study is to evaluate preliminary efficacy of the combination of tremelimumab with brain irradiation, and to confirm safety of concurrent HER2 directed therapy + tremelimumab at the previously-defined recommended doses for these two agents. The total maximum accrual will be 23 patients, 17 in the efficacy cohort and 6 in the HER2 directed therapy co-administration safety cohort. If preliminary efficacy is ascertained, this will prompt a multi-institutional randomized trial which will more definitively evaluate efficacy.

### 14.2.1 Primary Endpoint: Efficacy Cohort

Because clinically there can be a discord between the response of brain metastases and non-CNS metastases to any given therapy, because there are no uniformly accepted criteria for evaluating brain metastases responses to immunotherapy, and because criteria for evaluating CNS and non-CNS responses differ, we have chosen to evaluate non-CNS disease control rate as the primary endpoint.

In the efficacy cohort, a Simon two-stage design will test whether tremelimumab and brain irradiation yields a 12 week non-CNS disease control rate (CR + PR + SD per RECIST 1.1) that is of clinical interest. This design limits the expected number of subjects who receive treatment when the true 12 week non-CNS disease control rate is not of clinical value.

The Simon design will test the null hypothesis that the true non-CNS disease control rate is ≤ 5% versus the alternative hypothesis that the true non-CNS disease control rate is > 25%. The 2-stage testing will target a Type I error rate of 5 % and will have 80 % power to reject the null hypothesis if the true non-CNS disease control rate is 25%.

The Simon design requires 9 treated subjects assigned to treatment for the first stage and calls for termination of a cohort at stage 1 if there are 0 subjects with non-CNS disease control amongst the 9 assigned subjects within the cohort. Otherwise, if 1 subjects with non-CNS disease control are identified in up to 9 subjects in a cohort, additional subjects will be assigned to a total of 17 subjects. The treatment will be considered of clinical interest if, at the end of the second stage, there are ≥ 3 subjects with non-CNS disease control amongst 17 assigned subjects. Subjects who withdraw consent prior to receiving the first dose of tremelimumab will be replaced, and will not be included in analysis, but will be documented and reported with the results of the study.

#### *14.2.1.1 Rationale of Alternative Hypothesis*

Tremelimumab + RT is a novel treatment modality—unique from cytotoxic chemotherapy—which could potentially provide clinical benefit in a heavily pre-treated patients for whom relatively few effective cytotoxic therapies remain. Another potential advantage of tremelimumab/RT is that patients may benefit from a "respite period" during which they may recover from the cumulative toxicities of cytotoxic chemotherapy, while still receiving active therapy. Because of these unique attributes, and because of the durability of clinical benefit observed in melanoma patients treated with anti-CTLA-4, we have selected an alternative hypothesis of 25% non-CNS disease control rate, which we believe would be of sufficient clinical value to consider further study.

#### *14.2.1.2 Rationale of Null Hypothesis*

By study criteria, women are eligible for study participation if, as determined by the investigator, they experienced a non-CNS progression of disease for which a change is systemic therapy cytotoxic chemotherapy is planned after brain irradiation. The null hypothesis, therefore, is based upon the expectation of a 12-week non-CNS disease control rate of 5% or less off systemic therapy.

In light of the potential intangible benefits of a "chemotherapy holiday," the 5% null hypothesis establishes a conservative lower threshold by which the therapy should be abandoned from further study. In other words, should this strategy confer a 25% non-CNS disease control rate, a rate which is comparable to the expected benefits of chemotherapy in this setting, and also permit a "chemotherapy holiday," then the strategy would warrant further study.

#### *14.2.1.3 Efficacy Cohort Continuous Safety Assessment*

In the tremelimumab efficacy arm, stopping rules (based on a repeated significance testing method) will be employed to continuously assess safety. (Ivanova, Qaqish et al. 2005) These criteria were based on assumptions that a toxicity rate of 50% is deemed unacceptable, and a rate of 20% is deemed acceptable. The boundaries to stop the study are given as follows:

- If 3 of the first 5 patients have a SAE attributable to the experimental intervention, stop the study.
- If 5 of the first 10 patients have a SAE attributable to the experimental intervention, stop the study.
- If 6 of the first 17 patients have a SAE attributable to the experimental intervention, stop the study.

With these parameters, there is a 0.94 probability of crossing the boundary if the true toxicity rate is .50, and there is a 0.14 probability of .14 probability of crossing the boundary if the true toxicity rate is .20."

### 14.1.2 HER2 directed therapy Co-administration Safety cohort

In the HER2 directed therapy co-administration cohort, the safety of HER2 directed therapy and tremelimumab co-administration will be evaluated in a minimum of 3 subjects. The sample sizes and dose expansion algorithm is based upon a classical 3+3 dose escalation design, whereby the recommended dose is the dose at which treatment-limiting toxicity occurs in ≤1/6 subjects within the first 6 weeks of therapy.

If the combination of HER2 directed therapy + tremelimumab + RT is deemed tolerable, a dose expansion cohort will be considered, to further evaluate overall safety and toxicity profile of the combination. This cohort will accrue following a protocol amendment. Similarly, if time permits and the treatment is deemed too toxic, a dose de-escalation cohort may be considered under a separately filed protocol amendment.

This cohort is not statistically powered to evaluate for preliminary efficacy of the combination of tremelimumab + HER2 directed therapy + RT, however if data permit, we will conduct preliminary analyses to evaluate for differential clinical activity across the two cohorts.

In the event that accrual of the efficacy arm completes prior to completion of the HER2 directed therapy safety arm, the primary endpoint may be reported independently of the secondary and exploratory endpoints.

### 14.1.3 The HER2+ Protocol Expansion

As of 3/1/17, the 12 week disease control rate was 2/20 (10%) in the efficacy arm and 2/6 (33%) in the safety arm. One patient treated with concurrent HER2-directed therapy had a 57% partial response by RECIST v1.1 that was durable at 6 months. Overall, the regimen was well tolerated with 15 grade 3 and no grade 4 attributable toxicity events reported. The most common treatment related AEs were diarrhea (12.9%), fatigue (9.7%), and colitis (6.5%). Thus, an expansion of the HER2 arm is planned in a parallel Simon two-stage design to evaluate efficacy of brain RT with checkpoint blockade and concurrent HER2-directed therapy. In this expansion, we will evaluate the combination of tremelimumab (treme), durvalumab (durva), and HER2 directed therapy plus brain irradiation in breast cancer patients with brain metastases (BCBM) for whom post-brain irradiation cytotoxic chemotherapy is planned. Subjects will receive either whole brain radiation treatment (WBRT) or stereotactic radiosurgery (SRS), as per standard of care, with tremelimumab administered at 75 mg and durvalumab administered at 1500 mg every 28 days for 4 cycles. After the 4$^{th}$ cycle, patients will continue to receive 1500 mg durvalumab every 28 days until disease progression or unacceptable toxicity. Patients will continue to receive HER2 directed therapy at a NCCN-guideline-endorsed dose and schedule, as determined by the investigator. Study design parameters and safety rules are similar to those that were used to the previously enrolled study subjects who did not require concurrent HER2 directed therapy.

## 14.2 Subjects for analysis

- **All Enrolled Subjects:** All subjects who signed an informed consent form and were registered into the IVRS.
- **All Treated Subjects:** All subjects who received at least one dose of any study medication.
- **Biomarker Subjects:** All assigned subjects with available biomarker data.

## 14.3 Definitions of endpoints

### 14.3.1 Primary endpoint

The primary endpoint will be assessed by RECIST1.1 criteria as described in section 12.1. The non-CNS disease control rate (CR+PR+SD) at 12 weeks will be calculated with a 95% confidence interval. Subjects who clinically progress or die prior to the 12 week assessment will be included in the analysis as failures.

### 14.3.2 Secondary endpoints

#### *14.3.2.1 Immune-related response*

Objective response (CR + PR), disease control (CR + PR + SD), non-CNS objective response, and non-CNS disease control rates will be evaluated at 12 weeks utilizing the immune-related response criteria. (Wolchok,

Hoos et al. 2009) The irRC calls for confirmation of radiographic progression with a repeat scan 4 weeks after initial scan, and allows for the presence of new lesions when evaluating for possible response. These rates will be calculated with a 95% confidence interval.

Immune-related progression free survival (irPFS) will be defined as the time from the first dose of tremelimumab until death or progressive disease, as measured by irRC. Non-CNS irPFS will also be measured. PFS endpoints will be evaluated using Kaplan-Meier methods, and if necessary, using a cumulative risk approach that adjusts for competing risks.

#### *14.3.2.2 Other response parameters using RECIST1.1*

In addition to the primary endpoint, RECIST1.1 will be used to assess the above listed response parameters (see section 14.3.2.1).

#### *14.3.2.3 CNS response*

CNS-only responses will be assessed using the RANO criteria as detailed in section 12.2.2.

#### *14.3.2.4 Overall Survival*

Overall survival is defined as the time from first dose of tremelimumab until death from any cause. This will be evaluated using Kaplan-Meier methods.

#### *14.3.2.5 Exploratory Endpoints*

All exploratory endpoints will be analyzed descriptively and graphically. Any statistical test will be performed using nonparametric methods and interpreted with caution.

## 15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

### 15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

### 15.2 Randomization

In this single-arm study, no randomization will take place.

# 16.0 DATA MANAGEMENT ISSUES

A MSKCC Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the study team.

The Clinical Research Database (CRDB) will be used for data collection. The data will be report to the MSKCC (IRB) and the drug manufacturer (MedImmune) as appropriate.

## 16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals, protocol compliance, eligibility verification, informed consent procedure, data accuracy, and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

## 16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/learningabout/patientsafety/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smskpsps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf .
There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and *the Data and Safety Monitoring Board (*DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

# 17.0 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Every effort will be made to keep study records private. Neither the patient's name nor anything else that could identify the patient will be used in any reports or publications that result from this study. Trained staff at Memorial Hospital, the Food and Drug Administration, or the study supporters will be able to review the medical records if necessary. The patient may terminate her participation in the study at any time during the trial.

### 17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

### 17.2 Serious Adverse Event (SAE) Reporting

An adverse event is any undesirable sign, symptom or medical condition occurring after starting study drug, even if the event is not considered to be related to study drug. Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected, recorded and followed as appropri ate. Medical conditions/diseases present before starting study treatment are only considered adverse events if they worsen after starting study treatment (any procedures specified in the protocol). Adverse events occurring before starting study treatment but after signing the informed consent form are recorded. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, require changes in study medication(s), or require therapy, and are recorded. Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found.

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A Life threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or requi re hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- Note: Hospital admission for a planned procedure/disease treatment is not considered a SAE

Events not considered to be serious adverse events are hospitalizations for:

- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition,
- treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen,
- treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission.

Pregnancy, although not itself a serious adverse event, should also be reported on a serious adverse event form or pregnancy form and be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB office within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report to be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.
    - If the SAE is an Unanticipated problem.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FFA by the SAE staff through the IND Office.

### 17.2.1 Serious Adverse Event (SAE) Reporting responsibilities to AstraZeneca/MedImmune

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 30 days after the last dose of study drug or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator and/or sponsor must inform the FDA, via CRDB SAE form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the CRDB SAE form must be emailed 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 CRDB SAE 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-##-#####)

******* 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.

**Reporting of deaths to AstraZeneca**

All deaths that occur during the study, or within the protocol-defined 30-day post-last dose of study drug safety follow-up period must be reported to AstraZeneca as follows:

- Death that is clearly the result of disease progression should be documented per institutional standards but should not be reported as a SAE to AstraZeneca.

- 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**. 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.

## 18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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# 20.1 APPENDICES

## 20.2 Guidance on Contraception

Females of childbearing potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use a highly effective method of contraception prior to the first dose of investigational product, and must agree to continue using such precautions for 180 days after the final dose of investigational product; cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. They must also refrain from egg cell donation for 180 days after the final dose of investigational product;

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause);
- A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. The acceptable methods of contraception are described in table 20.1;

Males

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a highly effective method of contraception (see Table ) from Days 1 through 90 post last dose. In addition, they must refrain from sperm donation for 90 days after the final dose of investigational product;

**Table 20.1: Highly Effective Methods of Contraception**

| Barrier Methods | Hormonal Methods |
|---|---|
| • Male condom with spermicide<br>• Copper T intrauterine device<br>• Levonorgestrel-releasing intrauterine system (e.g., Mirena®) [a] | • Implants<br>• Hormone shot or injection<br>• Combined pill<br>• Minipill<br>• Patch |

[a] This is also considered a hormonal method.

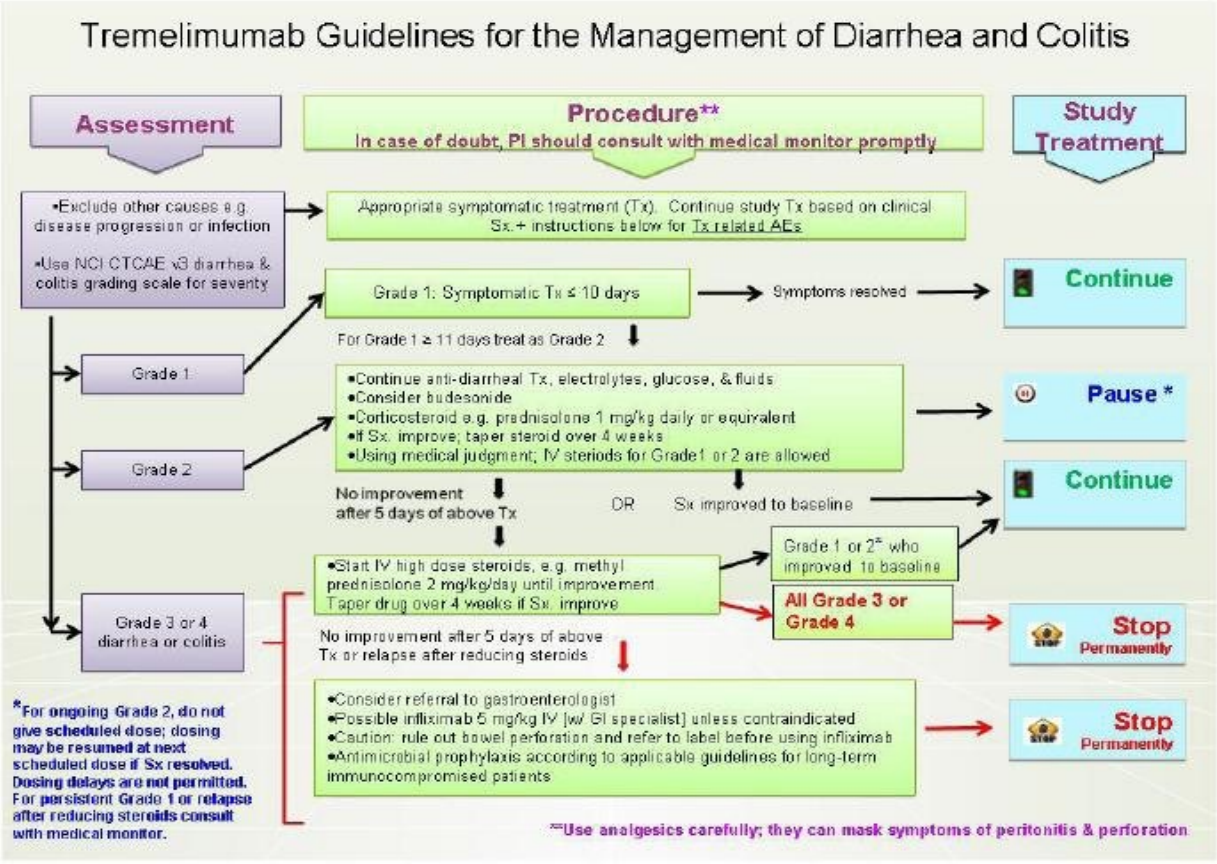
## 20.1.1 Blood donation

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

## 20.2 Management Algorithms

These recommendations have been provided by MedImmune LLC and constitute guidance to the investigator and may be supplemented by discussions with MedImmune LLC representatives. The recommendations are not a representation of benefit/risk. A general principle is that differential diagnoses should be diligently evaluated according to the standard medical practice.

Non-inflammatory etiologies should be explored and appropriately treated. Corticosteroids are a primary therapy for immune related events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low grade toxicity and good oral tolerance. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids. Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.




## 20.3 Dose Modification and Toxicity Management Guidelines

| Table 20.3. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions | | |
|---|---|---|
| **Grade (NCI CTCAE version** | **Dose Modifications** | **Toxicity Management** |

| **4.03)** | |
|---|---|
| **Pneumonitis/ILD:**<br>– 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<br>– 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 | – No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies<br>– Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated<br>– Consider pulmonary and infectious disease consult |
| Grade 2 | – Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1<br>– If toxicity worsens then treat as Grade 3 or Grade 4<br>– If toxicity improves to grade ≤1 then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.<br>– Monitor symptoms daily and consider hospitalization<br>– Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent)<br>– Reimaging as clinically indicated<br>– If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started<br>– If still no improvement within 3-5 days despite IV methylprednisone at 2-4/mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab<br>– Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii1]<br>– Consider pulmonary and infectious disease consult<br>– Consider, as necessary, discussing with study physician |
| Grade 3 or 4 | – Permanently discontinue study drug/study regimen<br>– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent<br>– Obtain pulmonary and infectious disease consult<br>– Hospitalize the patient<br>– Supportive Care (oxygen, etc.)<br>– If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to |

[1] ASCO Educational Book 2015. Michael Postow MD. "Managing Immune Checkpoint Blocking Antibody Side Effects"

| | | |
|---|---|---|
| | | current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii] |
| **Diarrhea/ Enterocolitis:**<br>– 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)<br>– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections) including testing for clostridium difficile toxin, etc.<br>– 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<br>– Use analgesics carefully; they can mask symptoms of perforation and peritonitis | | |
| Grade 1 | No dose modification | – Close monitoring for worsening symptoms<br>– Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment. |
| Grade 2 | – Hold study drug/study regimen until resolution to ≤ Grade 1<br>– If toxicity worsens then treat as Grade 3 or Grade 4<br>– If toxicity improves to grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.<br>– Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper | – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide<br>– Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent<br>– If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 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 2-4mg/kg/day started.<br>– If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5mg/kg once every 2 weeks[2]. **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab<br>– Consult study physician if no resolution to ≤ Grade 1 in 3-4 days<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |
| Grade 3 or 4 | – Permanently discontinue study drug/study regimen | – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent<br>– Monitor stool frequency and volume and maintain hydration<br>– Urgent GI consult and imaging and/or colonoscopy as |

[2] ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

| | | |
|---|---|---|
| | | appropriate<br>– If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks).<br>– **Caution:** Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |
| **Hepatitis (Elevated LFTs) - Infliximab should not be used for management of Immune Related Hepatitis:**<br>– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin<br>– Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications) | | |
| Grade 1 | – No dose modification. If it worsens, treat as Grade 2 event | – Continue LFT monitoring per protocol |
| Grade 2 | – Hold Study drug/study regimen dose until grade 2 resolution to ≤ Grade 1<br>– If toxicity worsens then treat as Grade 3 or Grade 4<br>– If improves to ≤ Grade 1, resume study drug/study regimen after completion of steroid taper. | – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved.<br>– If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician.<br>– If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent.<br>– If still no improvement within 3-5 days despite 1-2mg/kg/day PO of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day.<br>– If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[3] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**.<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |
| Grade 3 | For elevations in transaminases ≤8 x ULN, or elevated bilirubin ≤5 x ULN:<br>– Hold study drug/study regimen dose until resolution to ≤ Grade | – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent<br>– If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive |

[3] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" , by Michael Postow MD

| | | |
|---|---|---|
| | 1 or baseline<br>– Resume study drug/study regimen administration if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days for elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinuestudy drug/study regimen<br>– Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[iv] | therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**<br>– Hepatology consult, abdominal workup, and imaging as appropriate.<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |
| Grade 4 | – Permanently discontinue study drug/study regimen | |
| **<u>Nephritis or Renal Dysfunction (Elevated Serum Creatinine):</u>**<br>– Consult with Nephrologist<br>– Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.)<br>– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)<br>– 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 | – No dose modification | – Monitor serum creatinine weekly and any accompanying symptom<br>– If creatinine returns to baseline, resume its regular monitoring per study protocol.<br>– If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4<br>– Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. |
| Grade 2 | – Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline<br>– If toxicity worsens then treat as Grade 3 or Grade 4<br>– If toxicity improves to grade ≤ 1 or baseline, then resume study drug/study regimen after | – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.<br>– Carefully monitor serum creatinine every 2-3 days and as clinically warranted<br>– Consult Nephrologist and consider renal biopsy if clinically indicated<br>– If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent |

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| | completion of steroid taper. | – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started.<br>– Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).<br>– When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol. |
| Grade 3 or 4 | – Permanently discontinue study drug/study regimen | – Carefully monitor serum creatinine on daily basis<br>– Consult Nephrologist and consider renal biopsy if clinically indicated<br>– Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent<br>– If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started.<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation] |
| **Rash (excluding Bullous skin formations):** **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****<br>– Monitor for signs and symptoms of dermatitis (rash and pruritus) | | |
| Grade 1 | – No dose modification | – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream) |
| Grade 2 | – For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline<br>– If toxicity worsens then treat as Grade 3<br>– If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. | – Obtain dermatology consult<br>– Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)<br>– Consider moderate-strength topical steroid<br>– If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent<br>– Consider skin biopsy if persistent for >1-2 weeks or recurs |
| Grade 3 | – Hold study drug/study regimen until resolution to ≤ Grade 1 or | – Consult dermatology<br>– Promptly initiate empiric IV methylprednisolone 1 to 4 |

| | | |
|---|---|---|
| | baseline<br>– 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 | mg/kg/day or equivalent<br>– Consider hospitalization<br>– Monitor extent of rash [Rule of Nines]<br>– Consider skin biopsy (preferably more than 1) as clinically feasible.<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<br>– Discuss with Study Physician |
| Grade 4 | – Permanently discontinue study drug/study regimen | |
| **Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.):**<br>– Consult Endocrinologist<br>– Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness.<br>– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.)<br>– Monitor and evaluate thyroid function tests: TSH, free $T_3$ and free $T_4$ and other relevant endocrine labs depending on suspected endocrinopathy.<br>– If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing | | |
| Grade 1 | – No dose modification | – Monitor patient with appropriate endocrine function tests<br>– If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult. |
| Grade 2 | – For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable<br>– If toxicity worsens then treat as Grade 3 or Grade 4<br>– Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.<br>– 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 judgment. 3) | – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids<br>– Initiate hormone replacement as needed for management<br>– Evaluate endocrine function, and as clinically indicated, consider pituitary scan<br>– For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. Levothyroxine, hydrocortisone, or sex hormones).<br>– Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) |

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| | Doses of prednisone are at less than or equal to 10mg/day or equivalent. | – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated. |
| Grade 3 or 4 | – For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled<br>– Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. | – Consult endocrinologist<br>– Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids<br>– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent<br>– Administer hormone replacement therapy as necessary.<br>– For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity<br>– Once improving, gradually taper immunosuppressive steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])<br>– Discuss with study physician |
| **<u>Neurotoxicity (to include but not limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre):</u>**<br>– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.)<br>– Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness)<br>– Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations)<br>– Symptomatic treatment with neurological consult as appropriate | | |
| Grade 1 | – No dose modifications | – See recommendations above. |
| Grade 2 | – For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1<br>– For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1.<br>– If toxicity worsens then treat as Grade 3 or Grade 4<br>– Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper. | – Discuss with the study physician<br>– Obtain Neurology Consult<br>– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.)<br>– Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent<br>– If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG) |
| Grade 3 | – Hold Study drug/study regimen dose until resolution to ≤ Grade | – Discuss with study physician |

<table>
<tr><td></td><td>1<br>– Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.</td><td rowspan="2">– Obtain Neurology Consult<br>– Consider hospitalization<br>– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent<br>– If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG)<br>– Once stable, gradually taper steroids over ≥4 weeks</td></tr>
<tr><td>Grade 4</td><td>– Permanently discontinue study drug/study regimen</td></tr>
<tr><td colspan="3"><u>Peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis:</u><br>– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability<br>– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult<br>– 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<br>– Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG</td></tr>
<tr><td>Grade 1</td><td>– No dose modification</td><td>– Discuss with the study physician<br>– Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above<br>– Obtain a neurology consult unless the symptoms are very minor and stable</td></tr>
<tr><td>Grade 2</td><td>– Hold study drug/study regimen dose until resolution to ≤ Grade 1<br>– 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</td><td>– Discuss with the study physician<br>– Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above<br>– Obtain a Neurology Consult<br>– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.)<br><u>MYASTHENIA GRAVIS</u><br>– Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.<br>– Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a</td></tr>
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| | | neurologist, taking into account the unique needs of each patient.<br>– If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (ACh E) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.<br>*GUILLAIN-BARRE:*<br>– Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG. |
| Grade 3 | – Hold study drug/study regimen dose until resolution to ≤ Grade 1<br>– Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability | – Discuss with study physician<br>– Recommend hospitalization<br>– Monitor symptoms and obtain neurological consult<br>*MYASTHENIA GRAVIS*<br>– Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist.<br>– Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG.<br>– If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.<br>*GUILLAIN-BARRE:*<br>– Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG |
| Grade 4 | – Permanently discontinue study drug/study regimen | |

[i] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

[ii] NCI CTCAE version 4.03

[iii] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

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

## 20.3.1 Infusion Related Reactions

**Table 20.3.1 Dosing Modification and Management Guidelines for Infusion Related Reactions**

| Grade (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
|---|---|---|
| **General Guidelines:**<br>– Manage per institutional standard at the discretion of investigator.<br>– 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 | The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. | – Aceta minophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator.<br>– Consider premedication per institutional standard prior to subsequent doses.<br>– Steroids should not be used for routine premedication of Grade ≤2 infusion reactions. |
| Grade 2 | The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event.<br>– Subsequent infusions may be given at 50% of the initial infusion rate. | – Aceta minophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator.<br>– Consider premedication per institutional standard prior to subsequent doses.<br>– Steroids should not be used for routine premedication of Grade ≤2 infusion reactions. |
| Grade 3 or 4 | Permanently discontinue study drug/study regimen. | Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid). |

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

## 20.3.2 Non-Immune Mediated Reactions

| Table 20.3.1 Dosing Modification and Management Guidelines for Non-Immune Mediated Reactions | | |
|---|---|---|
| **Grade (NCI CTCAE version 4.03)** | **Dose Modifications** | **Toxicity Management** |
| **General Guidelines:**<br>– 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. | | |
| 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. |

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| Grade 3 | Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.<br><br>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. |

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