MD Anderson IND Sponsor Cover Sheet

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ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
AChE	Acetylcholine esterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response
CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state

Abbreviation or special term	Explanation
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICOS	Inducible COStimulator
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event

Abbreviation or special term	Explanation
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
Prometheus	Electronic database
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks

Abbreviation or special term	**Explanation**
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SOC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1.0 INTRODUCTION

Prostate cancer is the second leading cause of cancer death among men in the United States. The first-line treatment for advanced prostate cancer is androgen deprivation therapy (ADT), which initially results in tumor regression; however, the tumor eventually progresses, a clinical state known as castration-resistant prostate cancer (CRPC) to which most men eventually succumb. The taxane chemotherapies (docetaxel and cabazitaxel) and drugs targeting the androgen receptor (AR) signalling pathway (enzalutamide and abiraterone acetate) have been FDA-approved for the treatment of CRPC for their proven survival benefit in definitive Phase III clinical trials (*2-7*). Despite the clinical success of these agents that target the tumor epithelial cells, none of them induce durable responses.

Approximately 80% of patients with advanced prostate cancer have metastatic disease that has spread to the bone. The interaction between the tumor and its microenvironment in the bone promotes plays a key role in metastatic growth of prostate cancer. The significance of the microenvironment has been confirmed by the clinical successes of the following drugs: 1) bone-homing radiopharmaceutical, radium-223 (Xofigo); and 2) the prostate cancer vaccine, sipuleucel-T (Provenge). Sipuleucel-T and radium-223 prolong survival in advanced prostate cancer without decreasing serum prostate-specific antigen (PSA). Agents that target primarily the tumor would be expected to decrease PSA; providing evidence that the above-described drugs target primarily the tumor microenvironment. Unfortunately, in most patients, radium-223 and sipuleucel-T only also prolong survival without providing durable responses. Therefore, there is an unmet need to find therapies that in addition to modulating the cancer epithelial cells and the tumor microenvironment, also induce durable clinical responses.

1.1 Disease Background

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

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir et al, 2008; Park et al, 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and

CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (Zou and Chen, 2008).

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

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

tremelimumab in melanoma (Kirkwood et al, 2010; Ribas et al, 2013). In a large Phase 3 randomized study comparing tremelimumab with dacarbazine (DTIC)/temozolomide in patients with advanced melanoma, the reported median OS in the final analysis was 12.58 months for tremelimumab versus 10.71 months for DTIC/temozolomide (HR = 1.1416, p = 0.1272; Ribas et al, 2013).

Targeting CTLA-4 with ipilimumab in Phase 1 and 2 CRPC trials demonstrated clinical activity (Hodi et al 2010; Schiller et al 2002; Wolchok et al 2013). However, in a phase 3 trial comparing ipilimumab to placebo following radiotherapy in patients with CRPC who received prior treatment with docetaxel, ipilimumab barely failed to improve overall survival (Hodi et al 2010).

Post hoc analyses revealed that treatment with ipilimumab improved the median overall survival in CRPC patients with favorable laboratory values, but without visceral metastases (Hodi et al 2010). Furthermore, studies of other immunotherapies (eg, sipuleucel-T, poxvirus-based vaccine [PROSTVAC]) for CRPC have demonstrated that the extent of tumor burden influences outcome (Mu et al 2011; Nakano et al 2001). Therefore, immunotherapies such as targeting immune checkpoints may be most beneficial in chemotherapy naïve CRPC patients without visceral metastases who are asymptomatic or minimally symptomatic.

We investigated whether the lack of significant therapeutic efficacy with ipilimumab in prostate cancer may be attributed to the immune tumor microenvironment by comprehensively analyzing the immune profile in a number of malignancies, including prostate cancer, melanoma, RCC, and bladder cancer. Prostate cancer, unlike the other malignancies, has very few immune infiltrates and low tumor expression of PD-L1; therefore, it is a relatively non-immunogenic tumor. Interestingly, there is data from three clinical trials suggesting that higher tumor expression of PD- L1 correlates with an increased likelihood of responding to therapies targeting PD-1 or PD-L1 (Mu et al 2011). Thus, it is not surprising that in a phase 1 study targeting PD-1 (nivolumab), treatment was ineffective in patients with CRPC (0/17 responses) (Drake et al 2013).

However, our observations demonstrate PD-L1 expression is an adaptive response to CTLA-4 blockade and support the hypothesis that CTLA-4 plus PD-1 inhibition will be an effective strategy to induce anti-tumor responses in patients with CRPC. We recently observed that following treatment with 2 doses of ipilimumab there is a markedly significant increase in tumor-infiltrating lymphocytes (TILs) and enhanced PD-1 and PD-L1 expression within the prostate tumor microenvironment. This suggests that CTLA-4 blockade has the potential of making prostate cancer immunogenic, but also that resistance to CTLA-4 blockade may be attributed to the PD-1/PD-L1 signaling pathway. Thus, simultaneously targeting CTLA-4 and PD-L1, may overcome resistance to CTLA-4 blockade. Our group was the first confirm this hypothesis in preclinical studies (Iwai et al 2002).

1.1.1 Immunotherapies

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

1.1.2 Durvalumab

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

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1.

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancers. In a number of these cancers, including lung, the expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In lung cancer, only 12% of patients with tumors expressing PD-L1 survived for more than 3 years, compared with 20% of patients with tumors lacking PD-L1 (Mu et al 2011). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance anti-tumor immune responses in patients with cancer. Results of several non-clinical studies using mouse tumormodels support this hypothesis, where antibodies directed against PD-L1 or its receptor PD-1 showed anti-tumor activity (Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Zhang et al 2008).

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

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

of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, > 90% of subjects are expected to maintain PK exposure ≥ 40 µg/mL throughout the dosing interval.

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

1.1.3 Tremelimumab

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

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

Binding of CTLA-4 to its target ligands (B7-1 and B7-2) provides a negative regulatory signal, which limits T-cell activation. Anti-CTLA-4 inhibitors antagonize the binding of CTLA-4 to B7 ligands and enhance human T-cell activation as demonstrated by increased cytokine (interleukin [IL]-2 and interferon [IFN] gamma) production in vitro in whole blood or peripheral blood mononuclear cell (PBMC) cultures (Tarhini and Kirkwood 2008). In addition, blockade of CTLA-4 binding to B7 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and anti-tumor activity in animal models, including killing of established murine solid tumors and induction of protective anti-tumor immunity. (Refer to the tremelimumab IB, Edition 6.0, for more information.) Therefore, it is expected that treatment with an anti-CTLA-4 antibody, such as tremelimumab, will lead to increased activation of the human immune system, increasing anti-tumor activity in patients with solid tumors.

An extensive program of non-clinical and clinical studies has been conducted for tremelimumab both as monotherapy and combination therapy with conventional anticancer agents to support various cancer indications using different dose schedules.

As of the data cutoff dates (1 November 2015 for monotherapy studies and 15 April 2015 to12 July 2015 for combination therapy studies), 34 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these, 13 studies have completedand 21 are ongoing. Eight tremelimumab monotherapy studies have been completed and 3 are ongoing. As of the data cutoff date of 1 November 2015, 973 patients received tremelimumab in completed monotherapy studies and the ongoing Study D4881C00024 and 569 patients have been treated in the ongoing blinded Phase IIb monotherapy Study D4880C00003 [DETERMINE]). In the 3rd

ongoing monotherapy study (D4884C00001), no patients have been treated as of the data cutoff. In addition, approximately 59 patients have been treated with tremelimumab in monotherapy arms of combination studies. Five studies of tremelimumab in combination with other anticancer agents have been completed and 18 are ongoing. In total, 250 patients with a variety of tumour types have received tremelimumab in combination with other anticancer agents in these studies. Details on the safety profile of tremelimumab monotherapy are summarized in Section 0. Refer to the current tremelimumab IB (version 6.0) for a complete summary of non-clinical and clinical information; see Section 6.6 for guidance on management of tremelimumab-related toxicities.

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

1.1.4 Durvalumab in combination with tremelimumab

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

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

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

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

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

agents.

1.2 Research hypothesis

To determine whether durvalumab plus tremelimumab can be safely administered and may induce augmented immunological and clinical responses in patients with metastatic castration-resistant prostate cancer.

1.3 Rationale for conducting this study

As an antibody, that blocks the interaction between PD-L1 and its receptors, durvalumab may relieve PD-L1-dependent immunosuppressive effects and, therefore, enhance the cytotoxic activity of anti-tumor T-cells. This hypothesis is supported by emerging clinical data from other mAbs targeting the PD-L1/PD-1 pathway, which provide early evidence of clinical activity and a manageable safety profile (Brahmer et al 2012, Topalian et al 2012). Responses have been observed in patients with PD-L1-positive tumors and patients with PD-L1-negative tumors. In addition, durvalumab monotherapy has shown durable responses in NSCLC in Study 1108 (see Section 1.4.1.1).

The rationale for combining durvalumab and tremelimumab is that the mechanisms of CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity (Pardoll 2012). In fact, combining immunotherapy agents has been shown to result in improved response rates (RRs) relative to monotherapy. For example, the concurrent administration of nivolumab and ipilimumab to patients with advanced melanoma induced higher objective response rates (ORRs) than those obtained with single-agent therapy. Importantly, responses appeared to be deep and durable (Wolchok et al 2013). Similar results have been observed in an ongoing study of durvalumab + tremelimumab in NSCLC (Wolchok et al 2013).

1.3.1 Durvalumab + tremelimumab combination therapy dose rationale

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

Pharmacokinetics/Pharmacodynamics data

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included toalign with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state

($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

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

Clinical data

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes therisk: benefit profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the Q2W schedule, the number of patients reporting any AE, ≥ Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the Q4W regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis, colitis and other immune mediated events, were more commonly seen in cohorts using either 3 mg/kg or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10-mg/kg doses of tremelimumab were eliminated in the final dose selection.

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

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showedstrong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab Q4W cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacydata suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response.

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

1.3.2 Rationale for 4 cycles of combination therapy followed by durvalumab monotherapy

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

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

Nivolumab (anti-PD-1) was dosed q2w for up to 96 weeks in a large Phase I dose-escalation and expansion study, and showed responses were maintained for a median of 22.94 months for melanoma (doses 0.1 mg/kg to 10 mg/kg), 17 months for NSCLC (doses 1, 3, and 10 mg/kg),and 12.9 months for renal cell carcinoma patients (doses 1 and 10 mg/kg) at the time of data analysis

(Hodi et al 2014, Brahmer et al 2014, Drake et al 2013). Furthermore, responses were maintained beyond treatment discontinuation in the majority of patients who stopped nivolumab treatment (either due to protocol specified end of treatment, complete response [CR], or toxicity) for up to 56 weeks at the time of data analysis (Topalian et al 2014).

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

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

1.3.2.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. (For further information on PK observations in Study 006, please see the current IB).

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen.

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg (Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUCss (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median Ctrough,ss is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

Clinical data

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

1.4 Benefit/risk and ethical assessment

1.4.1 Potential benefits

Durvalumab

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

Tremelimumab

In a single-arm, Phase II study (Study A3671008) of tremelimumab administered at 15 mg/kg every 90 days to patients with refractory melanoma, an RR of 7% and a median OS of 10 months in the second-line setting (as compared to approximately 6 months with best supportive care reported from a retrospective analysis; (Korn et al 2008) were observed (Kirkwood et al2010). In a randomized, open-label, first-line Phase III study of tremelimumab (administered at 15 mg/kg every 90 days) versus chemotherapy (dacarbazine or temozolomide) in advanced melanoma (Study A3671009), results of the final analysis showed an RR of 11% and a median OS of 12.58 months in this first-line setting as compared to 10.71 months with standard chemotherapy; however, these results were not statistically significant (Ribas et al 2013). Additionally, a Phase II maintenance study (Study A3671015) in patients with Stage IIIB or IV NSCLC who had responded or remained stable failed to achieve statistical significance. The primary endpoint of PFS at 3 months was 22.7% in the tremelimumab arm (15 mg/kg) compared with 11.9% in the best supportive care arm (Study A3671015).

Durvalumab + tremelimumab

The preclinical and clinical justification for this combination as noted in Section 1.1.4 also supports the synergy of this combination. Available data, such as those presented by (Wolchok et al2013), suggest that the combination of agents targeting PD-1/PD-L1 and CTLA-4 may have profound and durable benefits in patients with melanoma (Wolchok et al 2013). Of the 102 subjects with advanced NSCLC treated with durvalumab in combination with tremelimumab in Study D4190C00006, 63 subjects with at least 16 weeks of follow-up were evaluable for response (defined as measurable disease at baseline and at least 1 follow-up scan; this included discontinuations due to disease progression or death without follow-up scan). Of the 63 evaluable subjects, 17 (27%) had a best overall response of PR, 14 (22%) had SD, 22 (35%) had PD, and 10 (16%) were not evaluable. The ORR (confirmed and unconfirmed CR or PR) was 27% and the DCR (CR, PR, or SD) was 49% as assessed by RECIST v1.1.

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

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

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

1.4.2 Potential risks

Durvalumab

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

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

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current

durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuationof durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

Tremelimumab

Potential risks, based on the mechanism of action of tremelimumab and related molecules (ipilimumab) include potentially immune-mediated gastrointestinal (GI) events including enterocolitis, intestinal perforation, abdominal pain, dehydration, nausea and vomiting, and decreased appetite (anorexia); dermatitis including urticaria, skin exfoliation, and dry skin; endocrinopathies including hypophysitis, adrenal insufficiency, and hyperthyroidism and hypothyroidism; hepatitis including autoimmune hepatitis and increased serum ALT and AST; pancreatitis including autoimmune pancreatitis and lipase and amylase elevation; respiratorytract events including pneumonitis and interstitial lung disease (ILD); nervous system events including encephalitis, peripheral motor and sensory neuropathies, and Guillain-Barré syndrome; cytopenias including thrombocytopenia, anemia, and neutropenia; infusion-related reactions; anaphylaxis; and serious allergic reactions. The profile of AEs and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to patients with melanoma). Overall, 944 of the 973 patients (97.0%) treated with tremelimumab monotherapy as of the data cutoff date of 12

November 2014 (for all studies except D4190C00006 that has a cutoff date of 04 December 2014 and not including 497 patients who have been treated in the ongoing blinded Phase IIb Study D4880C00003) experienced at least 1 AE. The events resulted in discontinuation of tremelimumab in 10.0% of patients, were serious in 36.5%, were Grade ≥3 in severity in 49.8%, were fatal in 67.7%, and were considered to be treatment related in 79.1% of patients. The frequency of any AEs and Grade ≥3 AEs was generally similar across the tremelimumab dose groups. However, a higher percentage of patients in the 10 mg/kg every 28 days and 15 mg/kg every 90 days groups compared with the All Doses <10 mg/kg group experienced treatment-related AEs, SAEs, AEs resulting in discontinuation of investigational product (IP), and deaths.

Durvalumab + tremelimumab

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

Study D4190C00006: The safety profile of durvalumab and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjects treated with durvalumab and tremelimumab combination therapy (not including subjects treated with blinded investigational product). As of 15Apr2015, 95 of 102 subjects (93.1%) reported at least 1 AE. All subjects in the tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; subjects in the durvalumab 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest AE rate (77.8%). Treatment-related AEs were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjects being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each), rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related ≥ Grade 3 AEs reported in ≥ 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment- related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase in 2 subjects; myasthenia gravis in 1 subject; and pericardial effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the MEDI4736 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported SAEs, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty- six subjects (35.3%) experienced treatment-related SAEs. Twenty-seven subjects (26.5%) permanently discontinued treatment due to AEs. Treatment-related AEs resulting in discontinuation in ≥ 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3

subjects), and increased AST (2 subjects).Additional safety results from this study are presented in Section 0 and the durvalumab IB.

In the literature (Wolchok et al 2013), using the combination of the same class of drugs (eg, anti-PD-1 and anti-CTLA4 antibodies), specifically nivolumab + ipilimumab in a study involving patients with malignant melanoma, the safety profile of this combination had shown occurrences of AEs assessed by the Investigator as treatment-related in 93% of treated patients, with the most frequent events being rash (55% of patients), pruritus (47% of patients), fatigue (38% of patients), and diarrhea (34% of patients). Grade 3 or 4 AEs, regardless of causality, were noted in 72% of patients, with Grade 3 or 4 events assessed bythe Investigator as treatment-related in 53%. The most frequent of these Grade 3 or 4 events assessed by the Investigator as treatment- related include increased lipase (in 13% of patients), AST (in 13%), and ALT levels (in 11%). Frequent Grade 3 or 4 selected AEs assessed by the Investigator as treatment-related in the combination therapy included hepatic events (in 15% of patients), GI events (in 9%), and renal events (in 6%). Isolated cases of pneumonitis and uveitis were also observed.

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 durvalumab (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

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.

2.0 STUDY OBJECTIVE

2.1 Primary objective(s)

- To evaluate the safety and tolerability of durvalumab plus tremelimumab in patients with metastatic castration-resistant prostate cancer.

2.2 Secondary Objective(s)

- To assess the efficacy of durvalumab plus tremelimumab in patients with metastatic castration-resistant prostate cancer.
- To explore immunological changes in peripheral blood and tissue (e.g. peripheral blood cluster of differentiation (CD)4+(Inducible COStimulator (ICOS)+ T cells, CD3 expression in tissue) in response to durvalumab plus tremelimumab in patients with metastatic castration-resistant prostate cancer.

3.0 STUDY DESIGN

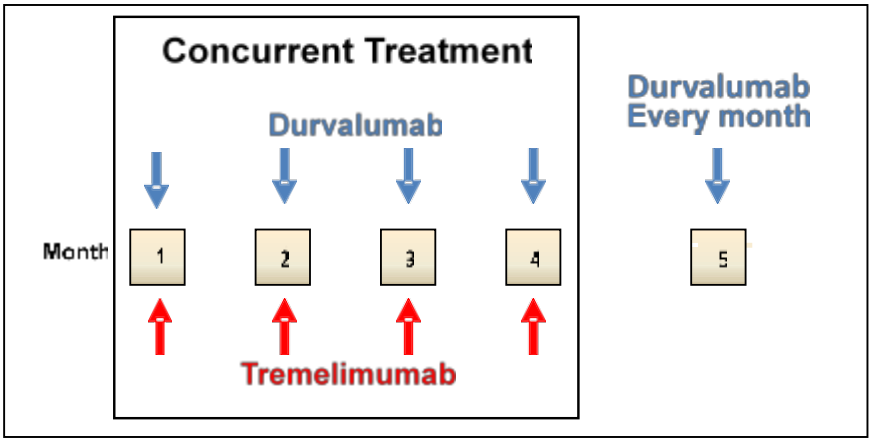
3.1 Overview of study design

This is an open-label, single center, Phase II pilot study to explore the link between immunological changes and efficacy of durvalumab (1500 mg IV q4w) in combination with tremelimumab (75 mg IV q4w) for up to 4 doses/cycles each followed by durvalumab 1500 mg IV q4w for up to a total of 8 months [9 additional doses/cycles]) in chemotherapy-naïve men with metastatic CRPC.

This study will enroll approximately 27 patients.

3.2 Study schema

Figure 1.



3.3 Study Oversight for Safety Evaluation

Toxicity will be monitored in all patients who receive at least one dose of tremelimumab, even if the patient is not evaluable for the biomarker or efficacy endpoint. Further details are included in Section 11.2.2.

4.0 PATIENT SELECTION, ENROLLMENT, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all of the inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Under no circumstances will there be exceptions to this rule.

4.1 Inclusion criteria

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

1. Written informed consent.

2. Age ≥ 18 years at time of study entry.

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

4. Life expectancy of ≥ 52 weeks.

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

   - Hemoglobin ≥ 11.0 g/dL.
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3).
   - Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3).
   - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not

apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.

- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal
- Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

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

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

7. Consent to MD Anderson laboratory protocol PA13-0291and LAB02-152.

8. Willing to have peripheral blood mononuclear cells and bone marrow biopsies to be collected prior to receiving the first dose of durvalumab and tremelimumab, after 2-doses and 4-doses of durvalumab and tremelimumab, after 2nd treatment administration and 4th treatment administration.

9. Histologically or cytologically confirmed adenocarcinoma of the prostate.

10. Evidence of metastatic disease to the bone seen on most recent bone scan, CT scan and/or MRI.

11. Asymptomatic or minimally symptomatic patients (do not require narcotics for prostate cancer-related pain).

12. Tumor progression while on hormone therapy with castrate levels serum testosterone (≤ 1.7 nmol/L or 50 ng/dL) defined by PSA and/or radiographic criteria according to the Prostate Cancer Working Group 3 (PCWG3). Castrate levels of testosterone must be maintained by surgical or medical means throughout the conduct of the study.

4.2 Exclusion criteria

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

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

2. Participation in another clinical study with an investigational product during the last 4 weeks.

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

4. History of another primary malignancy except for:

    - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of study drug and of low potential risk for recurrence.

    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.

    - Adequately treated carcinoma in situ without evidence of disease (eg, superficial bladder cancer).

5. Evidence of visceral metastasis to the liver.

6. Prior use of taxane-based chemotherapy, for treatment of castrate resistant prostate cancer.

7. Receipt of the last dose of anti-cancer therapy (immunotherapy, endocrine therapy [eg, abiraterone acetate, enzalutamide], targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) ≤ 28 days prior to the first dose of study drug. (With the exception of those treatments described in exclusion #3)

8. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of durvalumab or tremelimumab. Note: Local surgery of isolated lesions for palliative intent is acceptable.

9. QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms. Any clinically significant abnormalities detected, require triplicate ECG results and a mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 ms calculated from 3 ECGs.

10. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab or tremelimumab, with the exceptions of:

    - intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid or steroids as pre-medication for hypersensitivity reactions (eg CT scan premedication)

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

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

    - Patients with vitiligo or alopecia.

    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on

hormone replacement.

- Any chronic skin condition that does not require systemic therapy.
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician.
- Patients with celiac disease controlled by diet alone.
- Subjects with history of diverticulitis may be included only after consultation and approval of the study physician

13. History of primary immunodeficiency.
14. History of allogeneic organ transplant.
15. History of hypersensitivity to the combination of durvalumab and tremelimumab.
16. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.
17. Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Known history of positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection.
18. History of leptomeningeal carcinomatosis.
19. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab.
20. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
21. Brain metastases or spinal cord compression unless asymptomatic or treated and stable off steroids and anti-convulsants for at least 28 days prior to study treatment start. Patients with suspected brain metastases at Screening should have a CT/MRI of the brain prior to study entry.
22. Subjects with uncontrolled seizures.
23. Male patients of reproductive potential who are not willing to employ effective birthcontrol from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

24. A malignancy [other than the one treated in this study] which required radiotherapy or systemic treatment within the past 5 years, or has a ≥ 30% probability of recurrence within 24 months (except for non-melanoma skin cancer or Ta urothelial carcinomas).

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.3

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

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of either durvalumab plus tremelimumab or durvalumab.

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

1. Withdrawal of consent or lost to follow-up.
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
4. Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Table 3).
5. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits.
6. Initiation of alternative anticancer therapy including another investigational agent.
7. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab + tremelimumab.
8. Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments

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

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.1 and Table 2, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone per the schedule in table 2 as an alternative.

4.4 Replacement of subjects

A total of 20 biomarker-evaluable patients are planned to be enrolled on this trial. The number is small as a proof-of-concept study utilizing immune biomarkers as important secondary endpoints. To be evaluable for the secondary objectives, a patient needs to receive 2 doses of

durvalumab + tremelimumab, have immune markers measured, and have at least one follow-up for clinical outcome measures. Up to 7 patients who do not remain on study will be allowed to achieve 20 evaluable patients, for a maximum enrollment of 27 patients. All additional patients who received at least 1 dose of study drug will still be counted in safety analyses.

5.0 INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab and tremelimumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the investigator as a solution for infusion after dilution.

List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	1500 mg, solution, IV	AstraZeneca/MedImmune
Tremelimumab	75 mg, solution, IV	AstraZeneca/MedImmune

5.1.1 Formulation/packaging/storage

Durvalumab

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

Tremelimumab

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

6.0 TREATMENT PLAN

6.1 Subject enrollment

All screening and enrollment procedures will be performed according to the assessment schedule in (Table 1).

Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening/baseline

evaluations. All patients will be required to provide consent to supply a sample of their tumor for entry into this study.

All screening/baseline procedures, must be performed within 28 days before the first dose of treatment. Screening/baseline evaluations may be performed over more than 1 visit. Informed consent may be obtained prior to the 28-day screening window to permit tumor biopsy sample acquisition.

6.2 Dose and treatment regimens

6.2.1 Treatment regimens

Durvalumab + tremelimumab combination therapy

Patients in the combination of durvalumab + tremelimumab portion of the regimen will receive 1500 mg durvalumab via IV infusion q4w and 75 mg tremelimumab via IV infusion q4w for up to 4 doses. Subjects experiencing adverse events (AEs) related to combination dose therapy (Part 1) that do not meet dose discontinuation criteria, may proceed to durvalumab monotherapy dosing (Part 2) without completing all 4 combination doses. A minimum of two combination cycles are required to proceed to durvalumab monotherapy. Additional durvalumab monotherapy doses will be given to complete a total of 13 treatment doses (including combination therapy). Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be conducted at the Investigator's discretion.

Durvalumab monotherapy

Starting on 4 weeks after last dose of combination therapy patients will begin to receive 1500 mg durvalumab via IV infusion q4w for up 11 doses. The duration of the infusion will last approximately 1 hour. The observation period following infusion will be at (suggested 30 minutes post infusion).

6.2.2 Criteria for retreatment

Retreatment is allowed (once only) for patients meeting the retreatment criteria below. The same treatment guidelines followed during the initial 12-month treatment period will be followed during the retreatment period, including the same dose and frequency of treatments and the same schedule of assessments.

Patients may undergo retreatment in 2 clinical scenarios, described below:

1. Patients who achieve and maintain disease control (ie, CR, PR, or SD) through to the end of the 12-month treatment period may restart treatment with the combination upon evidence of PD, with or without confirmation according to RECIST 1.1, during follow-up.

2. Patients who have received at least 2 dosing of cycles of the combination of durvalumab + tremelimumab portion of the regimen (with clinical benefit per Investigator judgment), but subsequently have evidence of PD during the durvalumab monotherapy portion of the regimen, with or without confirmation according to RECIST 1.1, may restart treatment with the combination.

    - Before restarting treatment, the Investigator should ensure that the patient: Does not have any significant, unacceptable, or irreversible toxicities that indicate continuing treatment will not further benefit the patient

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

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

    - Has had a baseline tumor assessment within 28 days of restarting treatment; all further scans should occur with the same frequency as during the initial 12 months of treatment until study treatment is stopped (maximum of 12 months of further treatment).

During the retreatment period, patients receiving durvalumab + tremelimumab may resume durvalumab dosing at 1500 mg q4w with 75 mg of tremelimumab q4w for up to 4 doses. Subjects experiencing adverse events (AEs) related to combination dose therapy that do not meet dose discontinuation criteria, may proceed to durvalumab monotherapy dosing without completing all 4 combination doses. Patients will then continue with durvalumab monotherapy (a minimum of two combination cycles are required to proceed to durvalumab monotherapy) at 1500 mg q4w, beginning at 4 weeks after the last dose of combination therapy (up to a total of 11 durvalumab monotherapy doses).

Treatment through progression is at the Investigator's discretion, and the Investigator should ensure that patients do not have any significant, unacceptable, or irreversible toxicities that indicate that continuing treatment will not further benefit the patient. A patient with 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.

A patient with confirmed progression cannot continue therapy or obtain retreatment with a regimen if dosing for the same regimen is ongoing and the progression occurs in target lesions that have previously shown a confirmed response of complete response or partial response.

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

Study drug preparation of durvalumab and tremelimumab

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

Preparation of durvalumab doses for administration with an IV bag

The dose of durvalumab for administration must be prepared by the Investigator's designated IP manager using aseptic technique.

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 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. Remove 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.1 mL of durvalumab (ie, 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

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

Calculate the dose volume of durvalumab and tremelimumab and number of vials needed for the subject to achieve the accurate dose.

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

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

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

Durvalumab hold and infusion times

Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

In the event that either preparation time or infusion time exceeds the time limits outlined in the

table, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Preparation of tremelimumab doses for administration with an IV bag

The dose of tremelimumab for administration must be prepared by the Investigator's designated IP manager using aseptic technique.

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

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

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

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

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

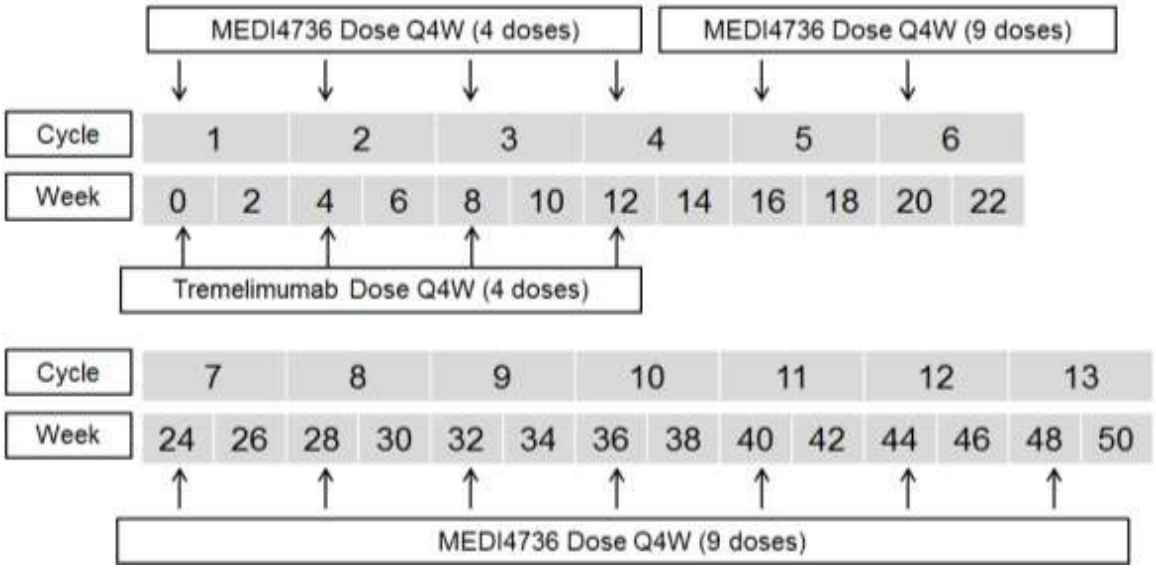
Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature. The table below summarizes time allowances and temperatures.

Tremelimumab hold and infusion times

Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

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

6.2.3 Durvalumab (MEDI4736) + tremelimumab combination therapy dosing schedule



6.2.4 Monitoring of dose administration

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

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

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

6.2.5 Accountability and dispensation

The investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. The study drug administered to the subject must be documented on the drug accountability form. All study drug will be stored and disposed of according to the Investigational Pharmacy standards. Study-site personnel must not combine

contents of the study drug containers.

Study drug must be handled in strict accordance with the protocol and the container label, and must be stored at the study site in a limited-access area or in a locked cabinet under appropriate environmental conditions. Unused study drug must be available for verification by the sponsor's study site monitor during on-site monitoring visits.

Potentially hazardous materials such as used ampules, needles, syringes and vials containing hazardous liquids should be disposed of immediately in a safe manner and therefore will not be retained for drug accountability purposes.

Study drug should be dispensed under the supervision of the investigator or a qualified member of the study-site personnel, or by a hospital/clinic pharmacist. Study drug will be supplied only to subjects participating in the study. The site will account for all investigational study drug dispensed and also for appropriate destruction.

6.3 Dose Modification and Toxicity Management

6.3.1 Durvalumab and tremelimumab

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

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab or tremelimumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab and tremelimumab (see Table 3).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

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

Following the first dose of durvalumab or tremelimumab, subsequent administration of durvalumab or tremelimumab can be modified based on toxicities observed. Dose reductions are not permitted.

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

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Table 3.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Table 3. All toxicities will be graded according to NCI CTCAE v4.03 other version.

7.0 RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

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

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

Restrictions relating to concomitant medications are described in (Section 7.2).

Highly Effective Methods of Contraception[a]

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

[a] Highly effective (i.e. failure rate of <1% per year)

[b] This is also considered a hormonal method

Blood donation

All patients: Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab or until alternate anti-cancer therapy is started.

7.2 Concomitant treatment(s)

The concurrent use of all other drugs, over-the-counter medications, or alternative therapies

including herbal supplements will be captured in the electronic medical record.

The patient will provide a list of medications, including over the counter agents, herbal preparations, taken prior to enrollment, and will update the list during clinic visits while on treatment. Concurrent medications related to co-morbidity (e.g. hypertension, diabetes, etc.) will be recorded in Prometheus. The name, dose, date start and stop (as accurately as possible) along with indication of the medication will be collected.

Supportive medications, pre-medications routinely prescribed prior to chemotherapy or immunotherapy infusion to mitigate reactions, hydration, or routine surgical drugs will not be recorded in the Prometheus.

Restricted, prohibited, and permitted concomitant medications are described below. See Table 3 for guidance on management of IP-related toxicities.

7.2.1 Permitted concomitant medications

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

7.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

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

2. Any concurrent chemotherapy, radiotherapy (except when radiotherapy is used to palliate bone lesions involving ≤ 25% of the bone marrow), immunotherapy, biologic or hormonal therapy for cancer treatment, other than any stated comparator or combination regimens. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy)
3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).

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

Prohibited and Rescue Medications

Prohibited medication/class of drug:	**Usage:**
Additional investigational anticancer therapy concurrent with those under investigation in this study	Should not be given whilst the patient is on IP treatment
mAbs against CTLA-4, PD-1, or PD-L1other than those under investigation in this study	Should not be given whilst the patient is on IP treatment through 90 days after the last dose of IP.
Any concurrent chemotherapy, local therapy (except palliative radiotherapy for non-target lesions, eg, radiotherapy, surgery, radiofrequency ablation), biologic therapy, or hormonal therapy for cancer treatment	Should not be given whilst the patient is on IP treatment (including SoC). (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.)
Immunosuppressive medications, including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or its equivalent, methotrexate, azathioprine, and tumor necrosis factor α blockers	Should not be given whilst the patient is on IP treatment (including SoC). (Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC) during the study

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

8.0 STUDY PROCEDURES

8.1 Schedule of study procedures

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

8.1.1 Screening Phase

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

. TABLE 1: SCHEDULE OF STUDY ASSESSMENTS

Assessments to be performed at the times stipulated in the table and as clinically required in themanagement of the subject.	**Screening**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Refer to Section**
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days													
Day	**-28 to+1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	
Week	**-4 to +1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Written informed consent/assignment of subject identification number	X														
Previous treatments for prostate cancer	X														
Formal verification of eligibility criteria	X														
Medical and surgical history	X														
Durvalumab and Tremelimumab Combination Administration[j]		X	X	X	X										Section 6.3.1
Durvalumab Administration(Mono therapy)				Xj	Xj	X	X	X	X	X	X	X	X	X	Section 6.3.1

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Screening**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Refer to Section**
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days													
Day	**-28 to +1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	
Week	**-4 to+1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Physical examination[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs (pre-, during and post-infusion vital signs assessments)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Electrocardiogram[c]	X	As clinically indicated													
Adverse event/serious adverse event assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 10.1
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 7.3
Palliative radiotherapy	As clinically indicated														Section 7.3
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Serum chemistry (complete clinical chemistry panel including liver enzymes)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Screening**	**C1**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**	**C13**	**Refer to Section**
		Window for each assessment: ±3 days, window for tumor assessment: ±7 days													
Day	**-28 to+1**	**1**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	
Week	**-4 to +1**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	
Thyroid function tests (TSH and T3 and fT4)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ESR amd CRP	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[f]	X	As clinically indicated													
Coagulation parameters[g]	X	As clinically indicated													
Tumor assessment (CT or MRI); Bone Scan (^{99m}Tc)[h]	X	X[h]		X[h]		X[h]		X[h]		X[h]		X[h]		X[h]	Section 9.0
PSA[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Section 9.3

[a] Full physical examination at day 1 of cycle 1; targeted physical examination at other time points. Body weight recorded at all physical examinations. Height is only measured at screening.

[b] Subjects will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a total treatment infusion):

- At the beginning of the treatment administration infusion (at ±30 minutes)
- Once during treatment administration
- At the end of treatment administration (±30 minutes)
- 60 minutes post-treatment administration : (±30 minutes) –if no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation and vital signs period can be conducted at the Investigator's discretion.

[c] ECG during screening. Thereafter as clinically indicated. Baseline and abnormal ECG at any time in triplicate others single infusion. (Clinically significant abnormalities detected require triplicate EKG's).

[d] If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion.

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

[f] Urinalysis performed at Screening, then as clinically indicated

[g] Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.

[h] CT or MRI scans will be performed every 8 weeks for the first 48 weeks and then every 12 weeks until confirmed PD. Variations, alterations, and deletions will not be considered deviations from the protocol.

[i] Does not have to be repeated if done within 2 weeks of Cycle 1 Day

j: A minimum of two combination cycles are required. Subjects experiencing adverse events (AEs) related to combination dose therapy (Part 1) that do not meet dose discontinuation criteria, may proceed to durvalumab monotherapy dosing (Part 2) without completing all 4 combination doses, Additional durvalumab monotherapy doses will be given to complete 13 treatment cycles(up to 11 durbalumab monotherapy cycles).

Table 2. Schedule of study procedures: follow-up for subjects who have completed durvalumab and tremelimumab treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued durvalumab or tremelimumab due to toxicity in the absence of confirmed progression of disease

Evaluation			
Time Since Last Dose of Durvalumab[E]	30 days	3 months	12 months
	Day (±7)	(±2 weeks)	~~Every 6 Months~~ (±2 weeks)
Physical examination[a]	X		
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X		
Weight	X		
AE/SAE assessment	X	X	
Concomitant medications	X	X	
Palliative radiotherapy (as clinically indicated)			
World Health Organization ECOG performance status	X	X	
Subsequent anti-cancer therapy	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X[d]	X
Hematology	X	X	
Serum chemistry	X	X	
Thyroid function tests (TSH, and fT3 and fT4)[b]	X		
ESR and CRP	X	X[c]	
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 12 months of treatment**, tumour assessments should be performed every 12 weeks relative to the date of **first infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Assessments for timings of confirmatory scans. For subjects who **discontinue Durvalumab due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the relative to the date of **first infusion** as follows: every 8 weeks for the first 48 weeks per Schedule of Assessments, then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Schedule of Assessments for timings of confirmatory scans.		

[a] Full physical exam

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

[C] ESR and CRP should be collected for the first 3 follow-up visits (Day 30, Month 3)

[d] Survial status will be evaluated by phone /or in person at 30 day, 3 month and 12 month visit

[E] If EOT is greater than 30 days after last dose, EOT will serve as 30 day visit. Subsequent follow up visits will occur at allocated time from EOT date and not last dose date.

8.1.2 End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue durvalumab or tremelimumab prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

8.2 Biological sampling procedures

8.2.1 Correlative studies

The correlative studies will be obtained from patients participating other MD Anderson IRB approved biospecimen protocols.

Upon treatment completion, biospecimens available will be analyzed per each approved protocol. In addition, new technologies have been developed. Exosomes are vesicles secreted from cells and function as mediators of intercellular communication. They have been shown to play a key role in the cross-talk between the immune and non-immune components in the local and distant tumor microenvironment. Exosomes will be isolated from the plasma and bone marrow of patients, and molecular analyses will be performed, which will be associated with clinical outcomes.

8.2.2 Informed consent for donated biological samples

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

Waiver

The additional correlative research involves reviewing medical records of patients who were treated at the MD Anderson Cancer Center on this trial. The samples which will be used were previously collected on other laboratory trials with signed informed consent. The trials with available samples are: LAB02-152, PA13-0291, PA13-0247, PA11-0852, PA12-1099, PA15-0956. Now that patients have completed treatment phase it would be difficult to obtain additional informed consent. We are requesting a waiver of informed consent and waiver of Authorization to Use and Disclose Protected Health Information for the retrospective portion of this study. A Waiver of Informed Consent and a Waiver of Authorization is requested because the data review and sample analysis involve no additional diagnostic or therapeutic intervention, as well as no direct patient contact. It would be impractical to obtain additional consent from patients because they are no longer in treatment, have died or may be lost to follow-up.

The Principal Investigator:

- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn

consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site

- Ensures that the subject is informed about the sample disposal.

8.3 Other assessments

8.3.1 ECOG performance status

ECOG performance status will be assessed at the times specified in the assessment schedules () based on the following:

0 = Fully active; able to carry on all pre-disease performance without restrictions

1 = Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work

2 = Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.

3 = Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry on any self-care. Totally confined to bed or chair

5 = Dead

9.0 DISEASE EVALUATION AND METHODS

Imaging performed prior to informed consent may be used as baseline assessment if it was performed within 28 days prior to study drug administration. Scans should be scheduled in such a way that the scan results are available at the regularly scheduled visit.

CT or MRI scans will be performed every 8 weeks for the first 48 weeks and then every 12 weeks until confirmed PD.

Additional imaging may be performed at any time to confirm suspected progression of disease. Study films (abdominopelvic CT/MRI and bone scan) should be read on site. The principal investigator or a sub-investigator will evaluate the images for all subjects for the duration of the study.

The same imaging method used for an individual subjects at baseline should be used throughout the entire study for that subject, unless for medical reasons the method must be changed (e.g. inability to receive contrast agent).

If a subject is unable to return for restaging scans due to symptoms of progressive disease, he may have scans done by a local facility. These scans should be sent to the investigator for review.

PET scans should not be used to determine disease progression.

Radiographic evaluation of metastatic disease is determined separately for soft -tissue and bone disease.

9.1 Radiographic disease assessment for soft tissue tumor deposits

9.1.1 Definition of measurable and non-measurable tumor deposits

Radiographic disease assessment for soft tissue tumor deposits is based on CT or MRI scan imaging. Soft tissue tumor deposits are described as measurable or non-measurable as defined in RECIST version 1.1:

- To be considered measurable, soft tissue tumor deposits (other than lymph nodes) must be accurately measured in at least one dimension with a minimum size of 10mm by CT or MRI scan (scan slice thickness no greater than 5mm).
- To be considered pathologically enlarged and measurable a lymph node must be ≥15mm in short axis when assessed by CT or MRI scan (scan slice thickness no greater than 5mm).
- All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) as well as truly non-measurable lesions will be considered non-measurable.

9.1.2 Calculation of tumor burden

- At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (Σp-diam) of all index lesions (up to 5 lesions per organ, up to 10 lesions in total that are representative of all involved organs) is calculated and recorded. Non-measurable tumor lesions will be recorded.
- At each subsequent tumor assessment, the Σp-diam of the index lesions and of new, measurable lesions (up to 5 new lesions per organ, up to 10 lesions in total that are representative of all involved organs) are added together to provide the total tumor burden:
    - Tumor burden= Σp-diam index lesions + Σp-diam new, measurable lesions
- Non-measurable tumor lesions should also be recorded at baseline and at each subsequent tumor assessment.
- At the end of study for that subject, maximum percent reduction from baseline in tumor burden will be graphed

9.1.3 Definition of radiographic PD for soft tissue tumor deposits

- An increase in tumor burden of ≥ 20% relative to nadir (minimum recorded tumor burden, including the baseline Σp-diam if that is the smallest on study). In addition to the

relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

- In patients classified as having PD within 12 weeks of last tremelimumab dose, confirmation of PD by a second scan ≥ 4 weeks later in the absence of rapid clinical deterioration will be required, as long as the patient does not show other signs or symptoms of disease progression as judged by the investigator.
- The appearance of one or more new lesions (measurable or non-measurable) will not be considered evidence of PD as long as all of the following criteria are met:
    - The increase in tumor burden remains <20% relative to nadir.
    - There are no signs nor symptoms of disease progression (including laboratory parameters, e.g. worsening liver function tests attributable to liver metastases) as judged by the investigator.
    - There is no further increase in tumor burden observed in a repeat, consecutive assessment obtained ≥ 4 weeks later.
    - For non-measurable tumor lesions an increase in overall disease burden comparable in magnitude to the increase that would be required to declare PD for measurable disease (i.e. ≥20%) will be considered evidence of PD.
    - If repeat scans confirm PD, then progression should be declared using the date of the initial scan.

9.2 Radiographic disease assessment for bone tumor deposits

Radiographic disease assessment for bone lesions is based on standard bone scintigraphy following technetium-99m-MDP injection.

9.2.1 Definition of radiographic PD for bone tumor deposits

- Radiographic disease progression for bone lesions is defined as the appearance ≥2 new areas compared to the baseline bone scan that can unequivocally be attributed to prostate cancer (i.e. not attributable to healing or flare of pre-existing lesions).
- Confirmation of PD by a second scan ≥4 weeks later in the absence of rapid clinical deterioration will be required, as long as the patient does not show other signs or symptoms of disease progression as judged by the investigator.
- Equivocal progression on bone scan must be confirmed by other imaging modalities (e.g. CT or MRI) and/or confirmatory bone scan ≥4 weeks later.
- If repeat scans confirm PD, then progression should be declared using the date of the initial scan.

9.3 PSA

Samples for PSA will be collected and analyzed at the treating institution laboratory. PSA testing will be performed as per the schedule of assessment. The PSA test performed at the screening visit does not need to be repeated on C1D1 if visit occurs within 2 weeks of screening.

9.4 Definition of progression of disease

For the purposes of this study, progression of disease (PD) is a composite endpoint, consisting of clinical deterioration and/or radiographic progression as defined below. Subjects with PSA progression alone will not be considered to have PD.

9.4.1 Clinical deterioration

Clinical deterioration is defined as any symptomatic clinical event attributable to disease progression that, in the investigator's opinion, indicates that the subject is not benefiting from study treatment. Examples include:

- Need for palliative radiation involving more than one site
- Surgery or kyphoplasty to any neoplastic bone lesion
- Cancer associated persistent decrease in performance status (eg, lasting for more than 14 days) of at least 2 points from baseline
- New bladder outlet or ureteral obstruction attributable cancer progression
- Any change of anti-neoplastic therapy for prostate cancer

9.4.2 Radiographic progression

Radiographic progression in soft tissue tumor deposits and/or bone as defined in (Sections 9.1.3 and 9.2.1) above will be considered evidence of disease progression.

PSA progression alone will not be used to define progression.

10.0 ASSESSMENT OF SAFETY

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

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

10.1 Safety Parameters

10.1.1 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 supporter. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

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

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

AESIs observed with durvalumab and tremelimumab include:

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

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

Pneumonitis

AEs of pneumonitis are also of interest for AstraZeneca, as pneumonitis has been observed with use of anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for the management of patients with immune-related AEs (irAEs) including pneumonitis are provided in Table 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 Table 3.

Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in

death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in Table 3.

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 objectiveevidence 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 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 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 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 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 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 3.

10.1.2 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 (Hodi et al 2010, Brahmer et al 2012, Topalian et al 2012). These AEs are inflammatory in nature and can affect any organ. With anti-PD-L1 and anti-CTLA-4 combination therapy, the occurrence of overlapping or increasing cumulative toxicities that include irAEs could potentially occur at higher frequencies than with either durvalumab or tremelimumab monotherapy. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, pneumonitis, hepatitis, and endocrinopathy. In addition to the dose modification guidelines provided in Table 3, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (Weber et al 2012). These guidelines recommend the following:

- Patients should be evaluated to identify any alternative etiology.
- In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered immune related.
- Symptomatic and topical therapy should be considered for low-grade events.
- Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
- More potent immunosuppressive 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.
  Assessment of safety parameters

Table 3. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (Durvalumab Monotherapy or Combination therapy with Tremelimumab or Tremelimumab Monotherapy) 19 August 2016 Version

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be madeto manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-relatedAE following resumption of dosing Grade 1 No dose modification Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. Grade 4 Permanently discontinue study drug/studyregimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen	It is recommended that management of irAEs follows the guidelines presented in this table: − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, and infections). − In the absence of a clear alternative etiology, all events should be considered potentially immune related. − Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. − For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). − More potent immunosuppressives such as TNF inhibitors (eg, infliximab) (also refer to the individual sections of the irAE for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. − Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumorresponse (eg, inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit/risk analysis for that patient.

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

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	**Any Grade**	General Guidance	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider pulmonary and infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (eg, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PCP treatment (refer to current NCCN guidelines for

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			treatment of cancer-related infections (Category 2B recommendation)[a] – Consider pulmonary and infectious disease consult. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain pulmonary and infectious disease consult. – Hospitalize the patient. – Supportive care (eg, oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patients is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation).[a]
Diarrhea/Enterocolitis	**Any Grade**	General Guidance	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event.

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (stool frequency of <4 over baseline per day)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (stool frequency of 4 to 6 over baseline per day)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consult study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 or 4 (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	**Any Grade**	General Guidance	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications).
	Grade 1 AST or ALT > to 3 × ULN and/or TB > to 1.5 × ULN)	No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4.	**For Grade 2:** – Regular and frequent checking of LFTs (eg, every 1 to 2 days) until elevations of these are improving or resolved.

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	(AST or ALT > 3 to 5 × ULN and/or TB >1.5 to 3.0 × ULN)	• If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	– If no resolution to Grade ≤1 in 1 to 2 days, discuss with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: AST or ALT >5 to 20 × ULN and/or TB >3.0 to 10 × ULN) (Grade 4: AST or ALT >20 × ULN and/or TB >10 × ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to **4** mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	General Guidance	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1	No dose modifications.	**For Grade 1:**

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	(Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)		– ~~Monitor serum creatinine weekly and anyaccompanying~~ symptoms. • If creatinine returns to baseline, resume itsregular monitoring per study protocol. • If creatinine worsens, depending on theseverity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, includinghydration, electrolyte replacement, and diuretics.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, includinghydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptlystart prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring perstudy protocol.
	Grade 3 or 4 (Grade 3: serum creatinine	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on dailybasis.

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	>3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)		– ~~Consult nephrologist and consider renal biopsy if clinically~~ indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream). – Consider moderate-strength topical steroid.

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		• If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	– If no improvement of rash/skin lesions occurs within 3 to **5** days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, and adrenal insufficiency)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** – Consult endocrinologist. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension, and weakness.

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, or infections). – Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study	**For Grade 2 (including those with symptomatic endocrinopathy):** – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Initiate hormone replacement as needed for management. – Evaluate endocrine function, and as clinically indicated, consider pituitary scan. – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term corticosteroids (eg, 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones). - – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals,

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.	**For Grade 3 or 4:** – Consult endocrinologist. – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Once the patient is improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Discuss with study physician.
Neurotoxicity (to include but not be limited to limbic encephalitis and	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03	General Guidance	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes, or medications).

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	for defining the CTC grade/severity)		– Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Discuss with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 3 or 4:** – Discuss with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	– If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	General Guidance	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1	No dose modifications.	**For Grade 1:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Discuss with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.

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

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

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

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

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

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

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

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

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

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

10.2 Assessment of relationship

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

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

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

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

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

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

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

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

If a subject discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments (per Table 2), drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

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

Follow-up of unresolved adverse events

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

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

Post study events

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

10.4 Reporting of Serious Adverse vents

Serious Adverse Event (SAE) Reporting for MD Anderson-sponsored IND Protocols

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

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

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

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas MD Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of study drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 90 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

10.4.1 Reporting to FDA

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

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

10.4.2 Investigator Communication with Supporting Companies

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

The investigator and/or sponsor must inform the FDA, via the M.D. Anderson 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 M.D. Anderson SAE form must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the M.D. Anderson 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-15-11590)

***** 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

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- 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 using the MD Anderson form for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

10.4.3 Reporting of deaths

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

- Death that is clearly the result of disease progression should be documented but and be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to as a SAE within **24 hours** . The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

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

10.5 Other events requiring reporting

10.5.1 Overdose

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

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

The investigator will use clinical judgment to treat any overdose.

10.5.2 Hepatic function abnormality/Hy's Law

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

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

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

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

10.5.3 Paternal exposure

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

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

10.5.4 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new or progression of existing metastasis to the primary cancer under study should be considered as diseaseprogression and not an AE. Events that are unequivocally due to disease progression should not be reported as an AE during the study

10.5.5 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study treatment and have been identified after the patient's inclusion in this study.

11.0 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

11.1.1 Safety analysis set

All patients who receive at least 1 dose of study drug will be included in the safety reporting and interim safety monitoring.

11.1.2 Efficacy analysis set

To be evaluable for the secondary objectives, a patient needs to receive 2 doses of drug, have immune markers measured, and have at least one follow-up for clinical outcome measures. Patients who do not meet this level of evaluability will be described separately to establish any

trends in patient evaluability and comparability of compliant patients with the intended patient population based on available information.

11.2 Methods of statistical analyses

11.2.1 Primary safety analyses

For the interim safety monitoring described below, an extreme toxicity (TOX) will be defined as any grade 3 or higher adverse event that is possibly, probably, or definitely related to any therapy received on this protocol and occurs within the first 8 weeks of therapy (2 cycles) with one exception. Any grade 3 or higher adverse event that is potentially treatable with steroids will only count as an extreme toxicity if it does not improve to grade 1 or better within 2 weeks of steroid therapy.

At the end of the trial, all adverse events will be tabulated by their CTCAE v4.03 name, counted once at the worst grade and the ultimate attribution within the patient. Exploration of these measures by cycle may also be presented.

11.2.2 Efficacy analyses

Efficacy of this combination will be measured by PSA progression-free survival (PFS), radiographic PFS, and maximal decline of PSA from baseline. PSA PFS, radiographic PFS, and time to maximal PSA decline will start at the first day of treatment and will be summarized by Kaplan-Meier. The numeric PSA value at maximal decline will be summarized by a boxplot and as a scatter plot of maximal decline by baseline PSA.

11.2.3 Biomarker endpoint analyses

For continuous data, summary statistics including n, mean, standard deviation, median, minimum and maximum or IQR will be computed. Prostatic T cell infiltration pre-and-post biopsy will be described and graphed over time. Differences in either time point compared to baseline will be compared with a t-test or non-parametric alternative. Cox models will be implemented to explore the relationship of treatment combination, prostatic T cell infiltration, and progression-free survival.

11.2.4 Interim analyses

Toxicity will be monitored in all patients who receive at least one dose of durvalumab + tremelimumab, even if the patient is not evaluable for the efficacy or biomarker endpoints. Based on the method of Thall et al. (1995) continual monitoring after the 6th patient is planned. Calculations were performed in Multc Lean 2.1.

Denote the probability of TOX by Θ E. We assume Θ E ~ beta (0.8, 1.2). Our stopping rule is given by the following probability statement: Pr(Θ E > 0.40 | data) >0.90. That is, we will stop

if, at any time during the study, we determine that there is more than a 90% chance that the extreme toxicity rate is more than 40%, a constant rate that is the maximum acceptable for TOX. The stopping boundaries for this toxicity rule are to terminate if the number of TOX events compared to the number of patients who have received at least one dose of treatment exceeds the limits in this table. Continual monitoring will be carried out monthly after the 6th patient is treated according to the following table:

Table 4. Toxicity monitoring rules (after the 6 patient is treated)

If there are this many patients with TOX:	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Stop if there are this many or fewer patients treated with ≥1 dose of study drug:	**7**	**9**	**11**	**13**	**15**	**17**	**20**	**22**	**24**	**26**

If the trial enrolls 27 patients, the trial will stop there regardless of the number of patients with TOX. However, the trial may stop between 20 and 27 patients once 20 evaluable patients are enrolled unless the trial stops for toxicity first. This means the probability of stopping early is over-estimated in the operating characteristics below since the trial may stop for evaluability after 24 patients are enrolled. In this case, the probability of stopping for TOX is overestimated by the probability of stopping at 25 or 26 patients. Similarly, the median, 25th, and 75th percentile of the sample sizes may be slightly overestimated.

Table 5. Operating Characteristics for the Toxicity Monitoring Rule assuming all 27 patients are enrolled

True TOX rate	Probability of Stopping Early	Probability of Enrolling ≥ 20 Patients	Average Number of Patients	Average Number of Patients with TOX	Median (25^{th} %ile, 75^{th} %ile)
25	0.02	0.98	26.6	6.6	27 (27, 27)
30	0.06	0.95	26.0	7.8	27 (27, 27)
35	0.13	0.89	25.0	8.7	27 (27, 27)
40	0.25	0.80	23.3	9.3	27 (27, 27)
45	0.41	0.67	21.0	9.5	27 (13, 27)
50	0.59	0.53	18.3	9.2	20 (11, 27)
55	0.75	0.47	15.5	8.5	13 (7, 26)

MDACC Investigational New Drug (IND) office will review Efficacy/Toxicity data with Principal Investigator (and statistician if needed) at a predetermined interval as indicated next: The first analysis will occur after the first 6 subjects are treated for at least 2 cycles, and reports submission will continue in cohort size of 2 subjects, thereafter. On every report submission, the information from previous reported patients will need to be updated.

11.3 Determination of sample size

The selection of 20 evaluable patients was intended as a pilot sample size with sufficient numbers to establish safety in this population as shown in Table 5 above while providing sufficient numbers for the secondary endpoints. This will allow investigation of a few marker endpoints and establish safety and feasibility of measuring the markers of interest while being able to accrue within 6 months. No formal hypotheses are planned. These patients will form the basis of designing a hypothesis-driven study in the future. However, we can make a statement about what might be detected in secondary endpoints at this sample size. The association between CD3 change and PSA PFS will be explored with a Cox model with CD3 as a continuous measure. Assuming that

75% (80%) of patients will progress by the end of the study, 20 patients will have 80% power to detect a regression coefficient of 0.72 (0.70) at a 2-sided 5% significance level, assuming the change in CD3 has a standard deviation of 1. The regression coefficient of 0.72 (0.70) is equivalent to a hazard ratio of 2.1 (2.0) or a doubling of risk per unit increase in CD3 (Calculations performed in NCSS-PASS 2005). This would hold true for both biomarker and any model of PSA PFS or Radiological/Clinical PFS.

Even if fewer than 20 patients have information available, this is the first look at these measures. Therefore, the descriptive information gathered on biological markers and outcomes, as well as the feasibility of collecting such information in future trials will be valuable.

12.0 STUDY MANAGEMENT

12.1 Monitoring of the study

This study will be monitored for compliance by the IND Office.

12.2 Study Completion/End of Study

The study is considered completed with the last study assessment for the last subject participating in the study. The final data from the study site will be sent to the sponsor (or designee) after completion of the final subject assessment at that study site, in the time frame specified in the clinical trial agreement.

12.3 Records and Reports

An Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) on each individual treated. The investigator is required to retain, in a confidential manner, the data pertinent to the study. Prometheus will be used as the electronic case report form for this study. All protocol specific data, including adverse events, will be entered into Prometheus. This study will be monitored for compliance by the IND Office.

12.4 Privacy of Personal Data

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to fulfill the objectives of the study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be

put in place. Personnel whose responsibilities require access to personal data agree to keep the identity of subjects confidential.

Data will be entered into MD Anderson institutionally approved and compliant database(s). The database(s) have secure portal that requires users to login with validated credentials, uses approved encryption protocols as defined by institutional information security standards.

Systems have granular data access controls to ensure that the minimal amount of information required to complete a task is presented, can handle de-linking and de-identification of patient information to maintain patient confidentiality if necessary. The system(s) are 21 CFR 11 compliant. Standard data collection, storage procedures, and quality assurance procedures will be followed, to ensure integrity and auditability of all information entered.

All patients will be registered in the University of Texas MD Anderson Cancer Center Office of Research Administration database. Registration will occur following informed consent process and prior to initiation of investigational intervention(s). All eligibility criteria must be satisfied.

12.5 Record Retention

The Investigator must retain study drug disposition records, source documents, and case histories designed to record all observations and other data pertinent to the investigation (e.g. case report form) for the maximum period required by applicable regulations and guidelines, or Institution procedures.

If the Investigator withdraws from the study (e.g. relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g. another Investigator, IRB). Documentation of such transfer must be provided to MedImmune.

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APPENDIX 1. ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section_____and_____of the protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3 × Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥2 × ULN at any point during the study following the start of study medication, irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥3 × ULN **together with** TBL ≥2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥3 × ULN
- TBL ≥2 × ULN

The Investigator will without delay review each new laboratory report, and if the identification criteria are met will:

- Determine whether the patient meets PHL criteria (see Section Definitions of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.

The Study Physician contacts the Investigator, to provide guidance, discuss, and agree on an approach for the study patient's follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.
- Complete the 3 Liver eCRF Modules as information becomes available.
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

- No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the

IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

- If the alternative explanation is an AE/SAE, record the AE /SAE in the eCRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term "Hy's Law") according to AstraZeneca standard processes.

  – The "Medically Important" serious criterion should be used if no other serious criteria apply.

  – As there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term "Potential Hy's Law"), applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment, having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required.
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described is Section Potential Hy's Law Criteria metof this Appendix.

[#]A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study, eg, chronic or progressing malignant disease, severe infection, or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at his or her first on-study treatment visit as described in Section Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Section Potential Hy's Law Criteria metof this Appendix.

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change, no action is required.

- If there is a significant change, follow the process described in Section Potential Hy's Law Criteria met of this Appendix.

#A "significant" change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX 2. DURVALUMAB DOSE CALCULATIONS

For durvalumab dosing done depending on subject weight:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

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

4. Dose to be added into infusion bag:

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

Where 50 mg/mL is durvalumab nominal concentration.

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

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

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

Example:

1. Cohort dose: 10 mg/kg

2. Subject weight: 30 kg

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

4. Dose to be added into infusion bag:

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

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

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

Appendix 3. DURVALUMAB DOSE VOLUME CALCULATIONS

For durvalumab flat dosing:

1. Cohort dose: X g

2. Dose to be added into infusion bag:

Dose (mL) = X g × 1000 / 50 (mg/mL)

Where 50 mg/mL is durvalumab nominal concentration.

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

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

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

Example:

1. Cohort dose: 1.5 g

2. Dose to be added into infusion bag:

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

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

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

APPENDIX 4. TREMELIMUMAB DOSE CALCULATIONS

For tremelimumab dosing done depending on subject weight:

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

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

4. Dose to be added into infusion bag:

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

Where 20 mg/mL is tremelimumab nominal concentration.

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

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

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

Example:

1. Cohort dose: 1 mg/kg

2. Subject weight: 30 kg

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

4. Dose to be added into infusion bag:

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

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

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

APPENDIX 5. TREMELIMUMAB DOSE VOLUME CALCULATIONS

For tremelimumab flat dosing:

1. Cohort dose: X mg

2. Dose to be added into infusion bag:

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

Where 20 mg/mL is tremelimumab nominal concentration

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

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

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

Example:

1. Cohort dose: 75 mg

2. Dose to be added into infusion bag:

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

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

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

The footnotes below need to be placed below the toxicity management guidelines -