A Phase II Trial of Durvalumab (MEDI4736) and Tremelimumab i n Metastatic, Non-Transitional Cell Carcinoma of the Urothelial Tr act

PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a phase II study testing durvalumab and tremelimumab in metastatic, non-transitional cell carcinoma of the urothelial tract. Patients with I) any component of small cell carcinoma (or neuroendocrine features) II) predominant squamous cell carcinoma or III) predominant adenocarcinoma of the urothelial tract will be enrolled. A Simon‟s minimax two-stage design will be carried out. We will enroll 13 patients in the first stage. If we see 1 or more responses in the first stage, we continue to the second stage where we enroll an additional 14 patients for a total sample size of 27 patients. Patients will be treated in 4-week cycles. Patients will receive 4 cycles of the combination of durvalumab and tremelimumab followed by up to 9 cycles of durvalumab maintenance or until lack of clinical benefit or unacceptable toxicity. Cross-sectional imaging will be performed every 8 weeks until the end of treatment. The best, confirmed overall response rate (ORR) by RECIST 1.1 will be determined as the primary endpoint.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

- To determine the efficacy of the combination of durvalumab and tremelimumab in patients with I) carcinoma with a small-cell component (or neuroendocrine features) II) predominant squamous cell carcinoma or III) predominant adenocarcinoma or the urothelial tract as measured by best ORR, which will include the sum of complete response (CR) + partial response (PR) by RECIST v 1.1.

Secondary Objectives:

- To assess for other parameters of clinical outcome of the combination of durvalumab plus tremelimumab in patients with I) carcinoma with a small-cell component (or neuroendocrine features) II) predominant squamous cell carcinoma or III) predominant adenocarcinoma or the urothelial tract including:
    - Progression Free Survival (PFS) and duration of response (DOR) rate by RECIST v1.1
    - Overall survival (OS)
    - Best ORR (CR + PR), PFS, and DOR by Immune-related Response Criteria in Solid Tumors (irRECIST) criteria
    - Clinical benefit (CR + PR + Stable Disease [SD]) rate by RECIST v1.1 and irRECIST
    - Rate of immune-related Adverse Events (irAE)
    - Rate of serious adverse events (SAE)

Exploratory Objectives:

- To determine differences in the immune microenvironment between bladder cancer histologies as determined by PD-L1 staining, immune related gene expression profiles, and multiplex immunofluorescence (IF) for multiple immune cell subsets
- To determine whether bladder cancer histology and the associated immune microenvironment as defined above is predictive of the clinical benefit rate (CBR).
- To determine if T cell clonality in tumors and blood will be associated with the CBR.
- To determine whether immune suppressive cells types in the peripheral blood and in tumors will correlate with a decreased CBR.

3.1 BACKGROUND AND RATIONALE

3.2 Non-Transitional Cell Carcinoma of the Urothelial Tract

Approximately 90% of malignant tumors arising from the urothelial tract are transitional cell carcinoma (TCC) (1). The remainder encompasses a variety of subtypes such as adenocarcinoma, squamous cell carcinoma, small cell/neuroendocrine carcinoma, sarcoma, paraganglioma, carcinosarcoma/sarcomatoid, lymphoma, or melanoma. Adenocarcinoma, squamous cell carcinoma, small cell/neuroendocrine carcinoma are the most common of these non-TCC histologies and compromise 0.5-2%, 3-5%, and 0.5-1% of bladder tumors, respectively (1). TCC plus squamous cell carcinoma, adenocarcinoma, and small cell/neuroendocrine carcinoma are the recognized as distinct clinical entities (2). Although each of these tumors is characterized by unique risk factors and biology, a unifying feature is their aggressive course and dismal prognosis, including in patients with organ-confined disease (3) (Figure 1). For patients with metastatic disease, poor outcomes with standard, front-line chemotherapeutic regimes have been reported in two small prospective and a variety of small retrospective studies (Table 1). For patients with metastatic disease that has progressed despite front-line therapy, clinicians have only case reports and a few retrospective studies to guide management. Outcomes are typically poor, and new therapeutic strategies are urgently needed.

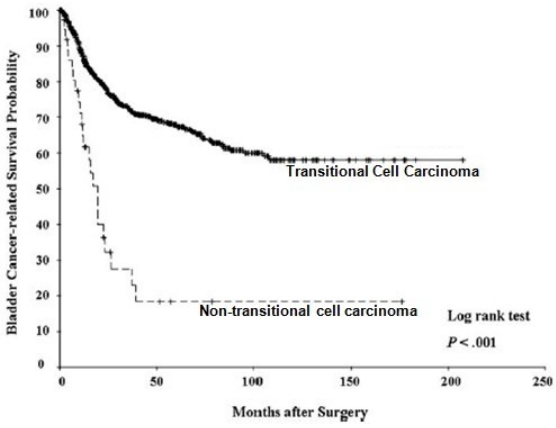

Figure 1 : Non-transitional cell carcinoma is associated with poor outcomes following radical cystectomy (3)

Histology	Regime	ORR (% response; 95% CI)	Median OS (Months)	Citation
Adeno	TIP	4/11 (36%; 15-59%)	24.8 (95% CI, 10.2 to 32.2)	(4)
Adeno	DMF IA/IV	5/8 (62.5%)	10 (95% CI not reported)	(5)
Adeno	Variable*	3/9 (33%)	20 (95% CI not reported)	(6)
Squamous	TIP	2/8 (25%; 3-65%)	8.9 (95% CI, 5.4 to not reached)	(4)
Squamous	Variable**	0/5	11 (95% CI not reported)	(7)
Small Cell	IA and EP	11/12 (92%)	13.3 (95% CI, 8.5 to not reached)	(8)
Small Cell	Variable^	9/12 (75%)	15 (95% CI not reported)	(9)

Table 1. Frontline Chemotherapy Regimes in Non-Transitional Cell Predominant Metastatic Carcinoma of the Urothelial Tract. TIP=ifosfamide, paclitaxel, and cisplatin; IA=Ifosfamide/Doxorubicin; EP= Etoposide/Cisplatin; DMF= intravenous and/or intra-arterial 5-fluorouracil, doxorubicin, and mitomycin-C; *5-fluorouracil or cisplatin containing regimes; **methotrexate/vinblastine/doxorubicin/cisplatin or 5FU/cisplatin or gemcitabine/cisplatin; ^cyclophosphamide/doxorubicin/vincristine or carboplatin/etoposide, or other platinum-based regime

3.3 Rationale for Immune Checkpoint Blockade in Non-Transitional Cell Carcinoma of the Urothelial Tract

Checkpoint blockade is a transformative therapeutic approach to a broad spectrum of malignancies because it increases the power of antitumor immunity to obtain durable responses. Antibodies targeting the programmed death 1 (PD-1) pathway have demonstrated evidence of activity and been approved by the Federal Drug Administraion (FDA) in untreated and pre-treated metastatic TCC (10–15). Although these agents have not yet been investigated in non-TCC histologies, the promising results in small cell and squamous cell lung cancer (Table 2) provide strong rationale for their use in this setting. With regard to adenocarcinoma of the urothelial tract, a recently presented phase I expansion study incorporating immune checkpoint blockade reported that 1 in 4 patients had a partial response (16). Our group has also had success treating patients with adenocarcinoma of the urothelial tract with anti-PD-1 antibodies (personal communication with Dr. Dean Bajorin). Durvalumab is a anti-PDL1 antibody, which demonstrated a toxicity profile similar to other anti-PD-1/anti-PD-L1 agents, and was recently granted accelerated approval by the FDA for pre-treated metastatic TCC (10).

Although treatment with PD-1 blockade has led to dramatic success in patients with previously incurable metastatic TCC, it is still only a minority of patients who benefit. This finding has driven the field toward developing combination therapies to increase response rates. Tremelimumab is an antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is expressed on the surface of T cells, where it primarily suppresses their early stages of activation by inducing inhibitory downstream T-cell receptor (TCR) signaling and counteracting activity of the T-cell costimulatory receptor, CD28 (17,18). The combination of CTLA-4 and PD-1 blockade is FDA approved in melanoma and seems to be more efficacious than CTLA-4 blockade alone (19,20) or PD-1 blockade alone in patients whose tumors do not express PD-L1 (19). In patients with previously treated metastatic urothelial carcinoma who received anti-PD-L1 therapy, our group recently demonstrated that the diversity of the baseline peripheral TCR repertoire was directly correlated with overall survival (21). Importantly, CTLA-4 blockade has also been shown to increase the diversity

peripheral TCR repertoire, which may increase the likelihood that a particular anti-tumor T cell population is present (22,23). In addition, anti-PD-1 monotherapy and the combination of CTLA-4 and PD-1 blockade were evaluated in randomized phase II trial in recurrent small cell carcinoma of the lung (24). The combination demonstrated higher response rates over anti-PD-1 monotherapy is now listed in the NCCN compendium guidelines for the treatment of small cell carcinoma of the lung. Finally, in Checkmate 032, combined CTLA-4/PD-1 blockade in patients with previously-treated, metastatic TCC with nivolumab 1 mg/kg and ipilimumab 3 mg/kg led to an ORR of 38.5%, which compares favorably with 24.4% ORR seen with nivolumab monotherapy (25). Although drug-related adverse events of grade 3 or 4 are more common with the combination of PD-1 and CTLA-4 therapies, most of these events resolve with immunosuppressive medication.

Therefore, the anti-PD-L1 antibody durvalumab in combination with the anti-CTLA-4 antibody tremelimumab is a logical therapeutic strategy. We hypothesize that it will demonstrate activity in patients with adenocarcinoma, squamous cell carcinoma, small cell/neuroendocrine carcinoma of the bladder. If successful, the proposed trial could change the standard of care for this patient population with very limited treatment options.

Histology	PD-1 Blocking Agent	ORR	Citation
Small Cell (PD-L1+)	Pembrolizumab	7/20 (35%)	(26)
Small Cell	Nivolumab 3 mg/kg	10/98 (10%)	(24)
	Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg	14/61 (23%)	
	Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg	10/54 (19%)	
Squamous	Nivolumab	17/117 (15%)	(27)
Squamous	Nivolumab	27/135 (20%)	(28)
Squamous	Durvalumab	18/88 (21%)	(29)

Table 2. Immune checkpoint Blockade in Recurrent Small Cell and Squamous Cell Lung Cancer

3.4 Rationale for allowing chemo-naïve patients with squamous cell carcinoma and adenocarcinoma

Atezolizumab (anti-PD-L1) and pembrolizumab (anti-PD-1) both have accelerated approval from the FDA for front-line use in chemo-naïve, cisplatin-ineligible patients with metastatic TCC. Approximately 50% of patients with metastatic TCC are cisplatin-ineligible (30). Pembrolizumab demonstrated a 29% ORR with the median duration of response not yet being reached after a median follow-up of 9.5 months (31). Atezolizumab demonstrated an ORR of 23% with a median overall survival of 15.9 months (14), which compares favorably to the 13.8-14.8 month median overall survival of cisplatin-eligible patients with metastatic TCC treated with a front-line cisplatin based regimens (32). These data have provided the rationale for multiple, randomized, front-line clinical trials evaluating immune checkpoint blockade in patients with metastatic TCC. The squamous cell and adenocarcinoma histologies are generally believed to be chemotherapy refractory. Indeed, the NCCN guidelines suggest that patients with muscle-invasive squamous cell and adenocarcinoma of

the bladder proceed directly to cystectomy without receiving the neoadjuvant cisplatin-based chemotherapy that is standard of care for patients with muscle-invasive TCC. Small cell carcinoma, on the other hand, is well known to be chemotherapy sensitive, although it almost uniformly progresses after treatment. Thefore, we will allow patients with squamous cell carcinoma and adenocarcinoma to be chemo-naïve while patients with small cell/neuroendocrine must have been previously treated.

3.5 Durvalumab and tremelimumab

3.4.1 Durvalumab

The non-clinical and clinical experience is fully described in the current version of the durvalumab Investigator‟s Brochure.

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 (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (36). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell dependent mechanism (36). Based on these data, durvalumab is expected to stimulate the patient‟s antitumor immune response by binding to PD L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

Durvalumab has been given to humans as part of ongoing studies as a single drug or in combination with other drugs. To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. No studies have been completed or terminated prematurely due to toxicity.

As of 09Feb2015, pharmacokinetic (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 clearance 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. The PK data on the 4 week dosing of durvalumab is in section 3.3.3.

As of 09Feb2015, a total of 388 subjects provided samples for anti-drug antibody (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 (PDx) in 1 subject in the 3 mg/kg cohort.

Of note, durvalumab has been granted accelerated FDA approval for treatment of patients with platinum-refractory urothelial bladder cancer. The designation was based on the results of a phase I/2 multicenter study evaluating durvalumab in 61 patients (40 PD-L1–positive, 21 PD-L1–negative) (33). The ORR was 31.0% (95% CI, 17.6 to 47.1) in 42 response-evaluable patients, 46.4% (95% CI, 27.5 to 66.1) in the PD-L1–positive subgroup, and 0% (95% CI, 0.0 to 23.2) in the PD-L1–negative subgroup. Responses are ongoing in 12 of 13 responding patients, with median duration of response not yet reached (range, 4.1+ to 49.3+ weeks). The most common treatment-related adverse events (AEs) of any grade were fatigue (13.1%), diarrhea (9.8%), and decreased appetite (8.2%). Grade 3 treatment-related AEs occurred in three patients (4.9%); there were no treatment-related grade 4 or 5 AEs. One treatment-related AE (acute kidney injury) resulted in treatment discontinuation.

3.4.2 Tremelimumab

The non-clinical and clinical experience is fully described in the current version of the tremelimumab Investigator‟s Brochure.

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.

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. To date tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Refer to the current tremelimumab Investigator‟s Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

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.

3.4.3 Durvalumab in combination with tremelimumab

Targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (34) 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.

To date more than 3000 patients have received the combination using a number of doses and dosing schedules.

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 (35). The dosing schedule utilized is durvalumab every 2 weeks (Q2W) up to week 40 or every 4 weeks (Q4W) up to Week 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 recently published results are discussed below.

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 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.

An update of Study D4190C00006 was published in March of 2016 (35). Between Oct 28, 2013, and April 1, 2015, 102 patients were enrolled into the dose-escalation phase and received treatment. At the time of this analysis (June 1, 2015), median follow-up was 18·8 weeks (IQR 11-33). The maximum tolerated dose was exceeded

in the cohort receiving durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg, with two (30%) of six patients having a dose-limiting toxicity (one grade 3 increased aspartate aminotransferase and alanine aminotransferase and one grade 4 increased lipase). The most frequent treatment-related grade 3 and 4 adverse events were diarrhea (11 [11%]), colitis (nine [9%]), and increased lipase (eight [8%]). Discontinuations attributable to treatment-related adverse events occurred in 29 (28%) of 102 patients. Treatment-related serious adverse events occurred in 37 (36%) of 102 patients. 22 patients died during the study, and three deaths were related to treatment. The treatment-related deaths were due to complications arising from myasthenia gravis (durvalumab 10 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), pericardial effusion (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 1 mg/kg), and neuromuscular disorder (durvalumab 20 mg/kg every 4 weeks plus tremelimumab 3 mg/kg). Evidence of clinical activity was noted both in patients with PD-L1-positive tumors and in those with PD-L1-negative tumors. Investigator-reported confirmed objective responses were achieved by six (23%, 95% CI 9-44) of 26 patients in the combined tremelimumab 1 mg/kg cohort, comprising two (22%, 95% CI 3-60) of nine patients with PD-L1-positive tumors and four (29%, 95% CI 8-58) of 14 patients with PD-L1-negative tumors, including those with no PD-L1 staining (four [40%, 95% CI 12-74] of ten patients).

3.4.3.1 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 (PD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

In order to reduce the dosing frequency of durvalumab to align with the Q4W dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety, and efficacy profile, cohorts were narrowed to 15 and 20 mg/kg durvalumab Q4W. PK simulations from the durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W durvalumab. The observed durvalumab PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median C_{max} at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

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

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

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab might 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 (35), of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥3 AEs or treatment-related SAEs. No dose-limiting toxicities were reported.

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

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. A total of 5 of 11 patients in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab cohort were evaluable for efficacy with at least 8 weeks of follow-up. Of these, there were 2 patients (40%) with partial response (PR), 1 patient (20%) with stable disease (SD), and 1 patient (20%) with progressive disease (PD). (The fifth patient had only a single scan, which was conducted outside the window for these evaluations.)

Taken together, the efficacy and toxicity data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

3.4.3.2 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 (31).

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.

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 (28,37,38). 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 (37).

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 (39,40).

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.

3.4.3.3 Fixed Dosing for durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase I 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 the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposures (AUCss,0-28, Cmax,ss, and Cmin,ss) using the population PK model. A fixed dose of 750 mg Q2Wwas selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (based on median body 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 (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady state Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W .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*) (42). 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 (43–45). Zhang 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 PK/PDx parameters(45).

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

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a single-arm, phase II study with a Simon minimax design testing the combination of durvalumab and tremelimumab in patients with non-TCC of the urothelial tract. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients, the study will be stopped. Otherwise, 14 additional patients will be accrued for a total of 27. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients. See section 14 for more details regarding statistical design.

4.3 Intervention

Patients will receive durvalumab 1500 mg and tremelimumab 75 mg IV Q4W for up to 4 doses/cycles, then durvalumab 1500 mg Q4W starting at Week 16 for 9 doses (total treatment duration of 12 months). The rationale for this dosing schedule is explained in section 3.3.

Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of the tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1-hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator"s discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion). The timing is illustrated below.

DURVALUMAB/TREMELIMUMAB COMBINATION TREATMENT PLAN				
TIME:	**0hr – 1hr**	**1hr – 2hr**	**2hr – 3hr**	**3hr – 4hr**
Tremelimumab	X			
Observation		X*		X*
Durvalumab			X	
*If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator"s discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).				

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

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

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

5.2 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 dehydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The normal fill volume is 10mL. 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.

Preparation of durvalumab doses for administration with an IV bag

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

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

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

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (weight per volume [w/v]) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0 mL of durvalumab (i.e., 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.

A fixed dosing of Durvalumab (1500mg) will be used. 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, using a 0.2, or

0.22-µm in-line filter. Longer infusions up to 8 hours are allowed if interruptions are necessary (see below).

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline or 5% [w/v] dextrose) 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 temperature.

Durvalumab hold and infusion times

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

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

5.2 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 m M 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.

Preparation of tremelimumab doses for administration with an IV bag

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

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

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

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

No incompatibilities between tremelimumab and polyvinylchloride or polyolefin IV bags have been observed. Doses of 75 mg tremelimumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final tremelimumab concentration ranging from 0.1 mg/mL to 10 mg/mL, and delivered through an IV administration set with a 0.2 µm or 0.22 µm in-line filter. Remove 3.8 mL of IV solution from the IV bag prior to addition of tremelimumab. Next, 3.8 mL of tremelimumab (i.e., 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.

A fixed dose of 75mg of Tremelimumab will be used. 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, using a 0.2, or 0.22-µm in-line filter. Longer infusions up to 8 hours are allowed if interruptions are necessary (see below).

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

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

Tremelimuab hold and infusion times

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

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

5.3 Monitoring of dose administration

Patients will be monitored before, during and after the infusion with assessment of vital signs as outlined in section 10.

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 (e.g., 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.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

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

1. Age ≥ 18 years at time of informed consent
2. Body weight > 30 kg
3. Histologically or cytologically confirmed small cell carcinoma, squamous cell carcinoma or adenocarcinoma (confirmed at MSKCC) of the bladder, ureter, urethra, urachus, or renal pelvis. Patients with squamous cell carcinoma and adenocarcinoma are required to have a predominant squamous or adenocarcinoma component as reviewed by the pathologist at MSKCC. However, if any element of small cell or neuroendocrine differentiation is present, the patients will be classified as small cell/neuroendocrine.
4. Confirmation of availability of sufficient tissue from a prior sugery for correlative studies is required prior to enrollment. Patients must have representative non-TCC or the urothelial tract FFPE archival tumor specimens (tumor blocks or 30 unstained slides; preference for tumor blocks). These samples may be submitted between the time of consent and the start of treatment. Patients with < 30 slides may be enrolled after discussion with the principal or co-principal investigators, see Section 9.5.2 for more details.
5. Clinical evidence of metastatic (T4b, any N; any T, N2-3; M1) disease.
6. Life expectancy of 12 weeks of greater based on assessment by the treating investigator.
7. Evidence of measurable disease by RECIST 1.1.
8. Patients with small cell carcinoma must have progressed after at least one prior systemic therapy. Patients with squamous cell carcinoma or adenocarcinoma may be previously

untreated or have progressed after prior systemic therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen. NOTE: There is no maximum number of prior treatments allowed.

9. Patients with brain metastases are allowed onto the study as long as patients have completed their treatment for brain metastasis, no longer require corticosteroids, and are asymptomatic. Subjects with neurological symptoms should undergo a head CT scan or brain MRI to exclude brain metastasis, at the discretion of the treating physician.

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

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

    - Hemoglobin ≥ 9.0 g/dL
    - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L (≥ 1000 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) (≤ 3 x institutional ULN in patients with Gilbert‟s syndrome)
    - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional ULN unless liver metastases are present, in which case it must be ≤ 5 x ULN
    - Calculated creatinine clearance > 30 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

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

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

12. Evidence of post-menopausal status or negative serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

13. Female patients of reproductive potential and non-sterilized males who are sexually active with a female partner of childbearing potential must be willing to adhere to the following restrictions:

    - Females of reproductive potential who are sexually active with a non-sterilized male partner must agree to use at least 1 **highly** effective method of contraception (Table 3) from the time of screening until 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. It is strongly recommended that non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice.

    - Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Not engaging in sexual activity is an acceptable practice. Male patients should refrain from sperm donation throughout this period. It is strongly recommended that female partners (of childbearing potential) of male patients to also use a highly effective method of contraception (Table 3) throughout this period.

    - Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 3.

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

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

14. 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.

6.3 Subject Exclusion Criteria

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

1. Previous enrollment in the present study
2. Participation in another clinical study with an investigational product during the last 14 days
3. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia"s Correction
4. Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab or an anti-CTLA-4, including tremelimumab
5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) < 21 days prior to enrollment.
6. Major surgery within 28 days of starting study treatment. There is no minimum time requirement for minor procedures such as biopsy or vascular access placement.
7. Radiation within 14 days of starting study treatment

8. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:

    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

    - Systemic corticosteroids at physiologic doses not to exceed <<10 mg/day>> of prednisone or its equivalent

    - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

9. Any unresolved toxicity from previous anti-cancer therapy must have resolved to at least ≤ Grade 1 (or baseline) at time of enrollment.

    Patients with irreversible toxicity that is not reasonably expected to be exacerbated by treatment with durvalumab and tremelimumab may be included after consultation with the Principal Investigator or Co-Principal Investigator (e.g. alopecia, hearing loss, peripheral neuropathy).

10. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis, celiac disease, 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 autoimmune disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with diverticulosis
    - Patients with celiac disease controlled by diet alone

11. History of primary immunodeficiency

12. History of allogeneic organ transplant

13. History of hypersensitivity to durvalumab, tremelimumab or any excipient

14. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

15. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice),

hepatitis B (known positive HBV surface antigen (HBsAg) result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

16. History of leptomeningeal carcinomatosis
17. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab or tremelimumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.
18. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
19. Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g. prostate cancer with Gleason score ≤ 6, and prostate-specific antigen [PSA] ≤ 10 mg/mL, etc).
20. Patients should agree to not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab or tremelimumab
21. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or180 days after the last dose of durvalumab + tremelimumab combination therapy.

7.0 RECRUITMENT PLAN

Eligible patients with non-TCC of the urothelial tract will be recruited from the Genitourinary Oncology and Urology Services at MSKCC. Every attempt will be made to recruit women and minorities to participate in this study. Participation is voluntary. The consenting physician will inform patients of their diagnosis, current treatment options including standard treatment, and the risks, benefits, and experimental nature of this treatment program.

8.1 PRETREATMENT EVALUATION

The following studies must be completed within 14 days prior to study registration/ enrollment (unless otherwise indicated):

- Informed consent (within 28 days)
- Review of eligibility criteria
- Medical history and demographics, including tobacco and alcohol use

- Complete physical exam (with height measured at screening only)
- ECOG Performance Status
- Vitals signs including temperature, blood pressure, respiratory rate, heart rate, weight, and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Submission of archival tumor tissue. Patients without archival tumor tissue may be enrolled after discussion with the principal investigator. Repeat biopsies purely for investigational purposes for this study will not be performed. See section 9.5.2 for additional details.
- Review of prior/concomitant medications
- Appropriate radiographic diagnostic procedures (for example CT scan of chest and CT or MRI of the abdomen & pelvis) for evaluation of measurable disease at baseline within 28 days of registration.
- Clinical laboratory tests for:
    - CBC (see Table 4)
    - Clinical chemistry panel (see Table 5)
    - TSH (free T3 and free T4 only if TSH is abnormal)
    - Coagulation (PT, PTT, INR)
    - Estimated Creatinine Clearance using the Cockcroft-Gault formula
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies (Hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody) and HIV antibody screen within 28 days
    - Urinalysis (see Table 6)

- Research bloods as outlined in section 9 and per MSKCC standard operating procedures

Table 4. Complete blood count (CBC)

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

Table 5. Clinical chemistry (Serum or Plasma) Laboratory Tests

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

[a] If Total bilirubin is ≥1.5xULN (and no evidence of Gilbert"s syndrome) then fractionate into direct and indirect bilirubin
*These tests are not part of the standard MSKCC comprehensive metabolic panel and will need to be ordered separately.

Table 6.

Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

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

9.0 TREATMENT/INTERVENTION PLAN

9.1 Intervention

This is a single-arm, phase II study with a Simon minimax design testing the combination of durvalumab and tremelimumab in patients with non-TCC of the urothelial tract.

Patients will receive durvalumab 1500 mg and tremelimumab 75 mg IV Q4W for up to 4 doses/cycles, then durvalumab 1500 mg Q4W starting 4 weeks after the last combination treatment for up to 9 doses. The rationale for this dosing schedule is explained in section 3.3.

9.2 Duration of treatment, treatment beyond progression, and criteria for retreatment

Patients will continue study treatment until lack of clinical benefit, development of unacceptable toxicity, or completion of planned study treatment. Patients may be treated beyond RECIST progression if the investigator deems them to be continuing to derive clinical benefit and if they meet all of the following criteria:

- Absence of symptoms and signs (including worsening of laboratory values [e.g. new or worsening hypercalcemia]) indicating unequivocal progression of disease
- No decline in ECOG performance status from baseline
- Absence of tumor growth at critical anatomic sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
- Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator.

Patients for whom radiographic disease progression is confirmed at subsequent tumor assessments may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above and have evidence of clinical benefit. Other immunotherapy studies have demonstrated that patients who initially derive clinical benefit from treatment and have progression while off treatment can derive clinical benefit again if they are retreated (40,46,47). 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:

- Patients who achieve and maintain disease control (i.e., CR, PR, or SD) up until the end of the treatment period may restart treatment with durvalumab 1500 mg and tremelimumab 75 mg IV Q4W for up to 4 doses/cycles, then durvalumab 1500 mg Q4W beginning 4 weeks after the last dose of combination therapy for up to 9 doses of durvalumab monotherapy upon evidence of PD (with or without confirmation according to RECIST 1.1) during follow-up provided the study is still on-going. If patients experienced unacceptable toxicity with the combination, they may resume durvalumab 1500 mg Q4W alone.
- Patients who complete the 4 dosing cycles of the combination durvalumab plus tremelimumab with clinical benefit per Investigator judgment but subsequently have evidence of PD during the durvalumab monotherapy portion, with or without confirmation according to RECIST 1.1, may restart treatment with the durvalumab dosing at 1500 mg Q4W with 75 mg of tremelimumab Q4W for 4 doses each followed by durvalumab monotherapy 1500mg Q4W (for 9 additional doses) at the investigator‟s discretion.

For patients who restart combination durvalumab + tremelimumab treatment, before restarting their assigned treatment, the Investigator should ensure that the patient:

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

b. Still fulfills the eligibility criteria for this study, including re-consenting to restart durvalumab and tremelimumab and excluding previous treatment with durvalumab and tremelimumab.

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

d. Has had a baseline tumor assessment within 28 days of restarting their assigned treatment; all further scans should occur with the same frequency as during the initial 13 cycles of treatment until study treatment is stopped (maximum of 13 cycles 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 4 doses each. Patients will then continue with durvalumab monotherapy at 1500 mg Q4W beginning 4 weeks after the last dose of combination therapy for up to 9 doses of durvalumab monotherapy.

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.

Patients must resign the informed consent form to be treated through progression.

Patients who the Investigator determines may not continue treatment will enter follow-up.

9.3 Concomitant Treatment

Patients must inform the treating investigator about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded.

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

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 the section below.

Local therapy (palliative radiotherapy, surgery, radiofrequency ablation) is allowed.

Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

- Any investigational anticancer therapy (other than the protocol specified therapies)
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy).
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers, except when required to treat investigational product-related AEs. 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 (i.e., 30 days prior to the first dose, during treatment with durvalumab and tremelimumab for 30 days post discontinuation of durvalumab and tremelimumab) are not permitted. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Table 7. 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 investigational protocol (IP) treatment
mAbs against CTLA-4, PD-1, or PD-L1	Should not be given whilst the patient is on IP treatment through 90 days after the last dose of IP.
Any concurrent chemotherapy, biologic therapy, or hormonal therapy for cancer treatment. Local therapy (palliative radiotherapy, surgery, radiofrequency ablation) is allowed.	Should not be given whilst the patient is on IP treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable.)

Prohibited medication/class of drug:	Usage:
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. Herbal and natural remedies which may have immune-modulating effects should not be given concomitantly unless agreed by the sponsor.	Should not be given whilst the patient is on IP treatment. 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 during the study

Rescue/supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., 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

Rescue/supportive medication/class of drug:	Usage:
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

Blood donation

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

9.4 End of treatment

The end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures might be completed within ± 28 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.

Every effort should be made to complete the end of treatment visit and all required procedures. However, if the subject is unfit or unwilling to return to clinic during the specified time frame, the assessments can be skipped with permission from the Principal Investigator.

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

Assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in Appendix 3.

9.5 Research blood and tumor specimens

For an explanation of the immune related hypotheses and the exploratory analysis plan, see section 14.3. Please see the clinical laboratory manual (Appendix 6) for further details regarding research blood and archival tissue collection.

9.5.1 Research blood

Blood specimens will be obtained for research purposes on cycle 1 day 1, cycle 1 day 14, and cycle 2 day 1 (+ 4 days). An additional two blood draws at two different time points after cycle 2 day 1 and the last protocol clinic visit are recommended when feasible (as determined by investigator discretion).

Specimens should be collected prior to drug administration. Four (4) tubes of blood are to be collected in BD Vacutainer® CPT™ Cell Preparation Tubes with Sodium Heparin (BD order # 362761 or equivalent) at each research blood draw. Peripheral blood mononuclear cells and plasma will be isolated per institutional practice in the MSK Immune Monitoring Facility (IMF). One EDTA tube should be collected at every research time point for purification of RNA/DNA for TCR analysis and collection of genomic data.

9.5.2 Tumor specimens

For the requirement of submission of pre-treatment tumor tissue, samples collected from fine-needle aspiration, brushing, cell pellet from pleural effusion, bone metastases without a soft tissue component, and lavage are not acceptable. Acceptable samples include transurethral resection of bladder tumor specimens, radical cystectomy specimens, core-needle or excisional biopsies for deep tumor tissue or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Representative non-TCC of the urothelial tract FFPE archival tumor specimens (tumor blocks or 30 unstained slides; preference for tumor blocks) must be provided. Patients with < 30 slides may be enrolled after discussion with the principal or co-principal investigators. Biopsy purely for research purposes for this study will not be allowed. Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. Samples can be submitted during screening any time after the patient signs the informed consent form up until cycle 1, day 1. Exceptions can be provided by the principal investigator or co-principal investigators.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

A cycle is defined as 4 weeks and includes treatment on day 1 followed by 27 days until the start of the next cycle.

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the patient.	**Screening**		**All assessment to be performed pre-infusion unless stated otherwise**		
	Within 28 days	**Within 14 days**	**Cycle 1-4, Day 1 (+/- 4 days)**	**Cycle 1-4, Day 15 (+/- 4 days)**	**Day 1 of Cycle 5 onward (+/- 4 days)**
Written informed consent	X				
Demography and history of tobacco and alcohol use		X			
Previous treatments		X			
Archival tumor tissue collection[1]	X				
Formal verification of eligibility criteria		X			
Medical and surgical history		X			
Serum pregnancy test[2]		X	As clinically indicated		
Durvalumab and trememlimumab co-administration			X		
Durvalumab monotherapy administration					X
Physical examination[3]		X	X	X	X
Vital signs (blood pressure, heart rate, respiratory rate, and temperature; pre-, during and post-infusion)[4]		X	X	X	X
Oxygen saturation (pulse oximetry)		X	X	X	X
Weight		X	X		X
Electrocardiogram (ECG)[5]		X	X		X
Adverse event/serious adverse event assessment[6]		X	X	X	X
Concomitant medications		X	X	X	X
ECOG Performance Status		X	X	X	X
CBC (Table 4)		X	X	X	X
Comprehensive chemistry panel (Table 5)[10]		X	X	X	X
TSH[7]		X	X		X
Coagulation parameters (PTT/PT/INR)		X	As clinically indicated		
Hepatitis B and C; HIV screening	X		As clinically indicated		
Urinalysis (Table 6)		X	As clinically indicated		
Research blood collection[8]			X (C 1 & 2 only)	X (C1 only)	X
Chest CT[9]	X				X
CT or MRI of Ab/Pelvis[9]	X				X[9]

1. See section 9.5.2 for tumor collection details
2. Pre-menopausal female subjects of childbearing potential only.
3. Full physical examination at baseline; targeted physical examination at other time points
4. Vital signs should be collected before, during, and after the infusion according to the treating investigator"s discretion and institutional guidelines and when clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.
5. 3 ECG during screening then 1 ECG with prior to each dose.
6. For AE"s/SAEs reported during the prescreening additional information such as medical history and concomitant medications may be needed.
7. 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.

8. See section 9.5.1 for research blood collection details. Blood specimens will be obtained for research purposes on cycle 1 day 1, cycle 1 day 14, and cycle 2 day 1 (+ 4 days). An additional two blood draws at two different time points after cycle 2 day 1 and the last protocol clinic visit are recommended when feasible (as determined by investigator discretion).
9. Scans to be performed every 2 cycles (+/- 7 days). See section 10.4 for post-treatment follow up. CT chest may be with or without contrast. MRI of the chest may be performed if patients refuse CT. Abdomen/Pelvis imaging should include IV contrast unless there is an extenuating circumstance approved by the PI or co-PI.
10. It is acceptable to proceed with treatment prior to receipt of amylase and/or lipase results for asymptomatic patients. For subsequently noted grade >3 amylase or lipase levels, study drug/study regimen may be continued at the date of the next scheduled treatment if complete workup shows no evidence of pancreatitis.

10.1 Physical examinations

Physical examinations will be performed according to the assessment schedule. A full physical examination will be performed at screening. Height will be measured at screening only. While on treatment, targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Vital signs are to be performed at each assessment. All clinical assessments should occur within +/- 4 days of the intended cycle start date.

10.2 Laboratory Studies During Treatment

Complete blood count (CBC) with differential and platelets and comprehensive panel (Na, K, Cl, CO2, BUN, Cr, Ca, magnesium, glucose, AST, ALT, total protein, Albumin, ALP, total bilirubin) must be performed on day 1 of each cycle. TSH, LDH, amylase, and lipase will be performed at baseline and on day 1 of each cycle.

10.3 Radiographic Studies During Treatment

Patients will undergo cross-sectional imaging every 2 cycles (+/- 7 days) until lack of clinical benefit. CT chest may be with or without contrast. MRI chest may be performed if patients refuse CT. Abdomen/Pelvis imaging should include IV contrast unless there is an extenuating circumstance approved by the PI. CT scans of the abdomen/pelvis and MRI abdomen/pelvis are both acceptable. Imaging will be evaluated using RECIST v1.1.

10.4 Post-Treatment Follow-Up

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

Assessments for subjects who have discontinued durvalumab or tremelimumab treatment due to confirmed PD are presented in Appendix 3.

11.1 TOXICITIES/SIDE EFFECTS

The common terminology criteria for adverse events version 4.0 (CTCAE v4.0) will be used to grade the severity of adverse events.

11.1 Schedule modification and toxicity management

For adverse events (AEs) that are considered at least possibly due to administration of durvalumab or tremelimumab the following 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 durvalumab or tremelimumab along with appropriate continuing supportive care. If medically appropriate, modifications to the schedule are permitted for durvalumab and tremelimumab (see Appendix 1).
- All schedule modifications should be documented with clear reasoning and documentation of the approach taken.
- Dose reductions are not permitted.

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

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

Schedule modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendix 1. As outlined in Appendix 1, patients may temporarily suspend study treatment for up to 12 weeks beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If study drug is held because of AEs for $>$ 12 weeks beyond the scheduled date of infusion, the patient will be discontinued from study therapy. 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/regimen will result in study discontinuation. Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing will result in study discontinuation. Patients who discontinue study therapy due to toxicity will be followed as outlined in Appendix 2 or 3. Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the Sponsor.

11.2 Definition of adverse events

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

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

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

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

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

The description and reporting of serious adverse events (SAEs) are outlined in section 17.2.

11.3 Durvalumab + tremelimumab adverse events of special interest

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

AESIs for durvalumab ±tremelimumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to

support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the Principal Investigator or Co-Principal Investigator.

AESIs observed with durvalumab ± tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / Transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator"s Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please see Appendix 1). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1) will be applied. The results of the full diagnostic workup (including high-

resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- SpO2
  - Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible and deemed appropriate by the treating physician:
    - (i) ILD Markers (KL-6, SP-D) and β-D-glucan
    - (ii) Additional Clinical chemistry: CRP, LDH

11.4 Immune-related adverse events

Based on the mechanism of action of durvalumab and tremelimumab leading to T-cell activation and proliferation, there is a possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), pneumonitis, and endocrinopathies (49–51). 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 (e.g., 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 Appendix 1, it is recommended that irAEs are managed according to the general treatment guidelines outlined for ipilimumab (52). These guidelines recommend the following:

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

11.5 Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients will be assessed every cycle by physical examination for response for disease progression. Patients will have appropriate radiographic diagnostic procedures (CT scan of chest and CT or MRI of abdomen and pelvis) for evaluation of measurable disease at baseline within 28 days of initiation of the study. Imaging will be repeated to evaluate the disease every 2 cycles while patients are on study.

12.2 Response Criteria

The response evaluation criteria in solid tumors (RECIST 1.1) will be used as presented in Appendix 4. The immune-related RECIST (irRECIST) criteria will also be used as a response

assessment as described in Appendix 5.

12.3 Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

13.1 CRITERIA FOR REMOVAL FROM STUDY

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

- Withdrawal of consent or lost to follow-up. If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Note that patients may withdraw from treatment without withdrawing consent for the study. Such patients will receive no further investigational treatment but can be followed for progression and survival. Documentation distinguishing these two outcomes should be placed in the patient"s chart.
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
- Pregnancy or intent to become pregnant
- Any AE that meets criteria for discontinuation as defined in Section 11.0
- Grade ≥ 3 infusion reaction
- Subject noncompliance that, in the opinion of the investigator, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- Initiation of alternative anticancer therapy including another investigational agent

- Prolonged duration of therapy-related toxicity as defined in section 11.2.
- Patients may be permitted to continue study treatment after RECIST v1.1-defined progressive disease if they meet all of the following criteria:
    - Absence of symptoms and signs (including worsening of laboratory values [e.g. new or worsening hypercalcemia]) indicating unequivocal progression of disease
    - No decline in ECOG performance status from baseline
    - Absence of tumor growth at critical anatomic sites (e.g. leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions
    - Evidence of clinical benefit (defined as the stabilization or improvement of disease-related symptoms) as assessed by the investigator.

  Patients for whom radiographic disease progression is confirmed at subsequent tumor assessments may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above and have evidence of clinical benefit.

  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 per section 9.4 for safety, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

14.1 BIOSTATISTICS

14.2 Primary Endpoint and Sample Size Justification

The three histologic groups (Small-Cell, Squamous Cell Carcinoma, and Adenocarcinoma) will be part of the same cohort given they are expected to have similar response rates. With an unacceptable rate of 5% and acceptable rate of 20%, and setting type I error to 5% and power to 80%, with Simon"s minimax two-stage design, we will enroll 13 patients in the first stage. Non-transitional cell carcinoma of the urothelial tract is a rare entity. Single, arm phase II studies have been published, but only in the front-line setting and only in small cohorts of patients (summarized in table 1). To our knowledge, there is no published data on response rates to second-line chemotherapy in patients with non-transitional cell carcinoma of the urothelial tract. The patient population under study has no standard treatment options and, in our group"s clinical experience, rarely experiences a meaningful clinical benefit from chemotherapy. Therefore, we have elected to set the null hypothesis at an ORR of 5%. If no

patients in the first 13 have achieved a response, enrollment for stage 2 will be halted until the 13 subjects in the first stage have been assessed for response (window of 2 disease assessment scans following initiation of treatment). If we see 1 or more responses in any of the histologies in the first stage, we continue to the second stage where we will enroll additional 14 patients. If, at the end of the study, we see 4 or more responses out of the total of 27 patients, we will consider the therapy promising. As an exploratory analysis, we will also estimate the response rate of the small cell/neuroendocrine, predominant squamous, and predominant adenocarcinoma cohorts separately as a proportion of responders with the corresponding confidence interval, although formal comparisons between the three cohorts are not planned.

The response evaluable population is defined as all patients with a baseline disease assessment who have received at leat one treatment with durvalumab and tremelimumab on study and have had either at least one post-baseline disease assessment or withdrawn from study treatment prior to post-baseline disease assessment due to clinical progression or death.

As described in section 9.2, patients may undergo retreatment after disease progression. The primary endpoint of best overall response is based on the best response from the first round of treatment.

Patients who discontinue protocol therapy for toxicity will be followed for response per Appendix 2. Patient who come off study for withdrawal of consent prior to having one post-baseline disease assessment will be considered inevaluable and will be replaced. All treated patients will remain evaluable for toxicity.

With an estimated patient accrual of 1 patient every month, it would take approximately 13-30 months to complete accrual to the trial.

14.3 Secondary Endpoint Justification

1. Safety and tolerability: Adverse events and immune-related adverse events by the current version of Common Terminology Criteria for Adverse Events version 4 (CTCAE v4.03) will be tabulated in order to assess the safety profile and tolerability therapy in treated patients.

2. Progression-free survival (PFS): PFS will be defined as the duration of time from start of treatment to time of recurrence, progression, or death due to any cause, whichever occurs first. Patients will be censored at last follow up date. The Kaplan Meier estimate of median PFS will be reported, as well as the PFS rate at 24 weeks (+/- 1 week).

3. Overall survival (OS): Overall survival will be evaluated using the Kaplan Meier Method.

4. Duration of response (DOR): Duration of response will be determined for each patient with time origin at the first occurrence of confirmed response (CR, PR) until the first occurrence of progression or date of death if the patient dies due to any cause before progression. Duration of response will be evaluated using the Kaplan Meier Method.

5. Clinical benefit rate (CBR): Clinical benefit rate will be defined as the percentage of patients with complete response (CR) + partial response (PR) + stable disease (SD) by 24 weeks from the start of treatment will be reported and the 90% confidence interval will be estimated using exact binomial proportions.

6. Best confirmed ORR, PFS, CBR, and DOR according to immune-related RECIST (irRECIST) as presented by Bohnsack et al.(53) and as proposed in Appendix 5. The methodology is the same as described for RECIST 1.1 except for new lesions do not automatically denote disease progression and the measurement of longest diameter of new measurable lesions are included in the sum of the measurement of the original target lesions. This method accounts for some of the delayed response patterns seen with immune checkpoint blockade. The efficacy endpoints based on irRECIST will be estimated using the same methods for these endpoints based on RECIST.

14.4 Exploratory analyses

Listed below are immune related hypotheses and the plan for exploratory analyses. Additional or different investigational methods will be used to characterize and measure components of the immune response based upon the latest available technology at the time of analysis. Specimens will also be stored for future studies related to non-TCC of the urothelial tract immunity for those patients who have consented to an institutional biobanking protocol (e.g. 06-107, 12-245, etc). If tissue availability or funding is limited, assay priority will be determined at the investigators discretion.

The exploratory hypotheses listed below are hypothesis generating. As such, all four of the exploratory analyses will be descriptive and graphical in nature. To test the associations between binary CBR or subtypes and biomarkers we will use Fisher"s exact or Wilcoxon rank sum tests for binary or continous variables respectively.

Immune Hypothesis 1: The tumor microenvironment will vary based on the histologic subtype of non-TCC of urothelial tract.

Proposed biomarker evaluation: Analysis of immune infiltrate will be performed using immunohistochemistry (IHC), immunofluorescence (IF), and computational approaches based upon RNA sequencing data. Immune regulatory molecules and populations of cells analyzed may include, but will not be limited to PD-L1, CD4, CD8, Tregs, B cells, macrophages, and dendritic cells and expression of biologically relevant/phenotypic markers thereof. The Ventana SP263 assay (performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT) should be used to measure PD-L1.

Immune Hypothesis 2: The composition and phenotype of the tumor microenvironment at baseline will correlate with the clinical benefit rate (CBR).

Proposed Biomarker Evaluation: See immune hypothesis 1.

Immune Hypothesis 3: High T cell clonality in the tumor plus peripheral expansion of dominant tumor-resident T cell receptor clones will be associated with the CBR.

Proposed Biomarker Evaluation: We will perform high throughput DNA sequencing of the CDR3 region of the TCR beta chain in baseline tumors and pre- and post-treatment peripheral blood.

Immune Hypothesis 4: High levels of myeloid derived suppressor cells (MDSCs) and T regulatory cells (Tregs) in the peripheral blood and high levels of immunosuppressive tumor associated myeloid cells and T regulatory cells in will correlate with a decreased CBR.

Proposed Biomarker Evaluation: We will perform a whole blood flow cytometry based assay to determine the MDSC and Treg percentage in pre- and post-treatment blood samples. We will analyze tumor associated myeloid cells and T regulatory cells in the tumor using immunohistochemistry (IHC), immunofluorescence (IF), and computational approaches based upon RNA sequencing data.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

N/A

16.0 DATA MANAGEMENT ISSUES

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

The data collected for this study will be entered into a MSKCC secure database (CRDB). Source documentation will be available to support the computerized patient record.

16.1 Quality Assurance

Weekly registration reports may be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, accuracy of evaluations, and follow-up will be monitored periodically throughout the study period. Potential problems will be brought to the attention of the study team.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center (MSKCC) were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials report to the Center‟s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

Potential risks to human subjects include drug-related toxicity, pain and discomfort associated with durvalumab and tremelimumab, placement of IV catheters, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan). The side effects and potential toxicities of durvalumab and tremelimumab are listed in the informed consent form**.** All efforts will be made to avoid any complication by completely reviewing patients‟ symptoms, providing appropriate management, and monitoring blood tests. If an adverse medical event occurs, the patient will first contact the primary oncologist or the principal investigator. At nights and weekends, there is an oncology physician on call at all times. Patients may either call or come directly to

the urgent care center at Memorial Hospital (or to their local emergency room) to be seen. Patients suffering serious adverse reactions must be carefully followed and all follow-up information recorded.

Alternatives/Options for treatment

Patients can elect to receive chemotherapy or supportive/hospice care. They can also elect to participate in another clinical trial. Participation in a clinical trial is voluntary.

Costs

The patient will be responsible for all costs related to treatment and complications of treatment. Durvalumab and tremelimumab will be provided without charge. Costs to the patient (or third party insurer) will include the cost of hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, other medications such as antibiotics and doctor"s fees. Tests done solely for research purposes will not be billed to the patient.

17.2 Privacy

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

17.3 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant"s last investigational treatment or intervention. Any

events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

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

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

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

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

Data needing to be entered:

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

The PI or Co-PI"s signature and the date it was signed are required on the completed report.

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

17.3.1 Requirement SAE Reporting to AstraZeneca/MedImmune

17.2.1.1 Serious adverse events

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

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

The study PI will request additional information for any subject with ongoing AE(s) / SAE(s) at the end of the study, if judged necessary

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

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.

17.2.1.2 Reporting of deaths to AstraZeneca

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 to AstraZeneca as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as a SAE within 24 hours. 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.

17.2.1.3 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 (AE MailboxClinicalTrialTCS@astrazeneca.com). If the overdose results in an AE, the AE must also be recorded as an AE. 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 17.2). There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

The investigator will use clinical judgment to treat any overdose.

17.2.1.4 Hepatic function abnormality

Hepatic function abnormality (as defined per Hy"s law in Section 11.5) 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 (AEMailboxClinicalTrialTCS@astrazeneca.com), 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.

17.2.1.5 Maternal Exposure

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

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

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

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

The same timelines apply when outcome information is available.

It is the MSK IRB stance that pregnant partners are out of our human subject protection (HSP) purview since the pregnant partners are not our patients. If notified, MSK will provide the external sponsor the information for their further action, but MSK will not be involved in the consent or data oversight of that pregnant individual.

18.1 INFORMED CONSENT PROCEDURES

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

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

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

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

19.0 REFERENCES

1. Dahm P, Gschwend JE. Malignant Non-Urothelial Neoplasms of the Urinary Bladder: A Review. Eur Urol. 2003 Dec;44(6):672–81.

2. Eble JN, Sauter G, Epstein JI, Sesterhen IA, editors. The Classification of Tumors of the Urinary System and Male Genital Organs. Lyon, France: WHO; 2002.

3. Galsky MD, Iasonos A, Mironov S, Scattergood J, Donat SM, Bochner BH, et al. Prospective Trial of Ifosfamide, Paclitaxel, and Cisplatin in Patients with Advanced Non-transitional Cell Carcinoma of the Urothelial Tract. Urology. 2007 Feb;69(2):255–9.

4. Logothetis CJ, Samuels ML, Ogden S. Chemotherapy for adenocarcinomas of bladder and urachal origin: 5-fluorouracil, doxorubicin, and mitomycin-C. Urology. 1985 Sep;26(3):252–5.

5. Siefker-Radtke AO, Gee J, Shen Y, Wen S, Daliani D, Millikan RE, et al. Multimodality management of urachal carcinoma: the M. D. Anderson Cancer Center experience. J Urol. 2003 Apr;169(4):1295–8.

6. Hong JY, Choi MK, Uhm JE, Park MJ, Lee J, Park SH, et al. Palliative chemotherapy for non-transitional cell carcinomas of the urothelial tract. Med Oncol. 2008 Nov 6;26(2):186–92.

7. Siefker-Radtke AO, Kamat AM, Grossman HB, Williams DL, Qiao W, Thall PF, et al. Phase II Clinical Trial of Neoadjuvant Alternating Doublet Chemotherapy With Ifosfamide/Doxorubicin and Etoposide/Cisplatin in Small-Cell Urothelial Cancer. J Clin Oncol. 2009 Jun 1;27(16):2592–7.

8. Mukesh M, Cook N, Hollingdale AE, Ainsworth NL, Russell SG. Small cell carcinoma of the urinary bladder: a 15-year retrospective review of treatment and survival in the Anglian Cancer Network. BJU Int. 2009 Mar 1;103(6):747–52.

9. Massard C, Gordon MS, Sharma S, Rafii S, Wainberg ZA, Luke J, et al. Safety and Efficacy of Durvalumab (MEDI4736), an Anti–Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J Clin Oncol. 2016 Sep 10;34(26):3119–25.

10. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. The Lancet [Internet]. [cited 2016 Mar 5]; Available from: http://dx.doi.org/10.1016/S0140-6736(16)00561-4

11. O"Donnell PH, Plimack ER, Bellmunt J, Berger R, Montgomery RB, Heath K, et al. Pembrolizumab (Pembro; MK-3475) for advanced urothelial cancer: Results of a phase IB study. J Clin Oncol [Internet]. 2015 [cited 2015 Feb 27];33(suppl 7; abstr 296). Available from: http://meetinglibrary.asco.org/content/141989-159

12. Apolo AB, Infante JR, Hamid O, Patel M, Wang D, Kelly K, et al. Safety, clinical activity, and PD-L1 expression of avelumab (MSB0010718C), an anti-PD-L1 antibody, in

patients with metastatic urothelial carcinoma from the JAVELIN Solid Tumor phase Ib trial. J Clin Oncol [Internet]. 2016 [cited 2016 Mar 6];34((suppl 2S; abstr 367)). Available from: http://meetinglibrary.asco.org/content/157130-172

13. Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. The Lancet. 2017 Jan 13;389(10064):67–76.

14. Balar A, Bellmunt J, O"Donnell PH, Castellano D, Grivas P, Vuky J, et al. Pembrolizumab (pembro) as first-line therapy for advanced/unresectable or metastatic urothelial cancer: Preliminary results from the phase 2 KEYNOTE-052 study. Ann Oncol [Internet]. 2016 Oct 1 [cited 2017 Feb 21];27(suppl_6). Available from: https://academic.oup.com/annonc/article/27/suppl_6/LBA32_PR/2800534/Pembrolizumab-pembro-as-first-line-therapy-for

15. Apolo AB, Mortazavi A, Stein MN, Pal SK, Davarpanah NN, Parnes HL, et al. A phase I study of cabozantinib plus nivolumab (CaboNivo) and ipilimumab (CaboNivoIpi) in patients (pts) with refractory metastatic urothelial carcinoma (mUC) and other genitourinary (GU) tumors. J Clin Oncol [Internet]. 2017 [cited 2017 May 20];35(suppl 6S; abstract 293). Available from: http://meetinglibrary.asco.org/content/179687-197

16. Schwartz RH. Costimulation of T lymphocytes: the role of CD28, CTLA-4, and B7/BB1 in interleukin-2 production and immunotherapy. Cell. 1992 Dec 24;71(7):1065–8.

17. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med. 1995 Aug 1;182(2):459–65.

18. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Jul 2;373(1):23–34.

19. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and Ipilimumab versus Ipilimumab in Untreated Melanoma. N Engl J Med. 2015 May 21;372(21):2006–17.

20. Funt S, Charen AS, Yusko E, Vignali M, Benzeno S, Boyd ME, et al. Correlation of peripheral and intratumoral T-cell receptor (TCR) clonality with clinical outcomes in patients with metastatic urothelial cancer (mUC) treated with atezolizumab. J Clin Oncol [Internet]. 2016 [cited 2016 Oct 5];34(suppl; abstr 3005). Available from: http://meetinglibrary.asco.org/content/167312-176

21. Robert L, Tsoi J, Wang X, Emerson R, Homet B, Chodon T, et al. CTLA4 blockade broadens the peripheral T-cell receptor repertoire. Clin Cancer Res Off J Am Assoc Cancer Res. 2014 May 1;20(9):2424–32.

22. Cha E, Klinger M, Hou Y, Cummings C, Ribas A, Faham M, et al. Improved Survival with T Cell Clonotype Stability After Anti–CTLA-4 Treatment in Cancer Patients. Sci Transl Med. 2014 May 28;6(238):238ra70-238ra70.

23. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016 Jul;17(7):883–95.

24. Ott PA, Fernandez ME, Hiret S. Pembrolizumab (MK-3475) in patients (pts) with extensive-stage small cell lung cancer (SCLC): Preliminary safety and efficacy results from KEYNOTE-028. J Clin Oncol [Internet]. [cited 2015 Dec 3]; Available from: http://meetinglibrary.asco.org/content/148558-156

25. Rizvi NA, Mazières J, Planchard D, Stinchcombe TE, Dy GK, Antonia SJ, et al. Activity and safety of nivolumab, an anti-PD-1 immune checkpoint inhibitor, for patients with advanced, refractory squamous non-small-cell lung cancer (CheckMate 063): a phase 2, single-arm trial. Lancet Oncol. 2015 Mar;16(3):257–65.

26. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123–35.

27. Rizvi NA, Brahmer JR, Ou S-HI, Segal NH, Khleif S, Hwu W-J, et al. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand 1 (PD-L1) antibody, in patients with non-small cell lung cancer (NSCLC). J Clin Oncol [Internet]. [cited 2015 Dec 13]; Available from: http://meetinglibrary.asco.org/content/147607-156

28. Massard C, Gordon MS, Sharma S, Rafii S, Wainberg ZA, Luke J, et al. Safety and Efficacy of Durvalumab (MEDI4736), an Anti-Programmed Cell Death Ligand-1 Immune Checkpoint Inhibitor, in Patients With Advanced Urothelial Bladder Cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2016 Sep 10;34(26):3119–25.

29. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012 Apr;12(4):252–64.

30. Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, et al. Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: a multicentre, phase 1b study. Lancet Oncol. 2016 Mar;17(3):299–308.

31. Schadendorf D, Hodi FS, Robert C, Weber JS, Margolin K, Hamid O, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Oncol. 2015 Feb 9;JCO.2014.56.2736.

32. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, et al. Survival, Durable Tumor Remission, and Long-Term Safety in Patients With Advanced Melanoma Receiving Nivolumab. J Clin Oncol. 2014 Apr 1;32(10):1020–30.

33. Motzer RJ, Rini BI, McDermott DF, Redman BG, Kuzel TM, Harrison MR, et al. Nivolumab for Metastatic Renal Cell Carcinoma: Results of a Randomized Phase II Trial. J Clin Oncol. 2014 Dec 1;JCO.2014.59.0703.

34. Herbst RS, Soria J-C, Kowanetz M, Fine GD, Hamid O, Gordon MS, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014 Nov 26;515(7528):563–7.

35. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013 Jul 11;369(2):122–33.

36. Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res. 2015 Sep;3(9):1052-62.

37. Wang E, Kang D, Bae K-S, Marshall MA, Pavlov D, Parivar K. Population pharmacokinetic and pharmacodynamic analysis of tremelimumab in patients with metastatic melanoma. J Clin Pharmacol. 2014 Oct;54(10):1108–16.

38. Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res. 2006 Jun;23(6):1275–84.

39. Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009 Sep;49(9):1012–24.

40. Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol. 2012 Jan;52(1):18–28.

41. Lipson EJ, Sharfman WH, Drake CG, Wollner I, Taube JM, Anders RA, et al. Durable cancer regression off-treatment and effective reinduction therapy with an anti-PD-1 antibody. Clin Cancer Res Off J Am Assoc Cancer Res. 2013 Jan 15;19(2):462–8.

42. Hamid O, Robert C, Daud A, Hodi FS, Hwu W-J, Kefford R, et al. Safety and Tumor Responses with Lambrolizumab (Anti–PD-1) in Melanoma. N Engl J Med. 2013;369(2):134–44.

43. Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. Biometrics. 2005 Jun;61(2):540–5.

44. Brahmer JR, Tykodi SS, Chow LQM, Hwu W-J, Topalian SL, Hwu P, et al. Safety and Activity of Anti–PD-L1 Antibody in Patients with Advanced Cancer. N Engl J Med. 2012 Jun 28;366(26):2455–65.

45. Hodi FS, O"Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. N Engl J Med. 2010;363(8):711–23.

46. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer. N Engl J Med. 2012;366(26):2443–54.

47. Weber JS, Kähler KC, Hauschild A. Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab. J Clin Oncol. 2012 Jul 20;30(21):2691–7.

48. Pawel J von, Schiller JH, Shepherd FA, Fields SZ, Kleisbauer JP, Chrysson NG, et al. Topotecan Versus Cyclophosphamide, Doxorubicin, and Vincristine for the Treatment of Recurrent Small-Cell Lung Cancer. J Clin Oncol. 1999 Feb 1;17(2):658–658.

49. Bohnsack O, Hoos A, Ludajic K. Adaptation of the immune response criteria: irRECIST. Ann Oncol 2014 [Internet]. 2014 ESMO;25 (suppl_4):iv361-iv372.10.1093/annocn/mdu342. Available from: http://oncologypro.esmo.org/Meeting-Resources/ESMO-2014/Immunotherapy-of-Cancer/Adaptation-of-the-immune-related-response-criteria-irRECIST

20.1 APPENDICES

Appendix 1 Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) - (1 November 2017 Version)

General Considerations

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myo-carditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of
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.	

Appendix 1 Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) - (1 November 2017 Version)

General Considerations

Dose Modifications		Toxicity Management
Grade 3	Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids.
Grade 4	Permanently discontinue study drug/study regimen.	– With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.
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.		– Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.
Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper		
Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).		

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

Pediatric Considerations

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after last dose of study drug/study regimen	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. – The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious disease 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 (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or

			anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [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 [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Diarrhea/Colitis	**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 (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. – Use analgesics carefully; they can mask symptoms of

Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	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.
Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not

baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)	improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.		– 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 (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider

		additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN: • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any	**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 (i.e., 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-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

		alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Grade 1 (Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

Grade 2 (Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to 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 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, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	• 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 Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	**For Grade 3:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate 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 4 (Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above** **(except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise** - **Grade 3-4: 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 (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying

to 1.5 × baseline; > ULN to 1.5 × ULN)		symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

			– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP 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 (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until	**For Grade 3 or 4:** – Consult dermatology.

		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.	– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.

Grade 1	No dose modifications.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 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.
Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes

		mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 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.	function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with 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:** – Consider, as necessary, discussing with the study physician. – Obtain neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or

		medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such

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

Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)
	Grade 1 (asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen).

with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	– If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Myositis/Polymyositis ("Poly/myositis")	**Any Grade** **General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing

		may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Grade 3 or 4 (pain associated with severe weakness;	**For Grade 3:** Hold study drug/study regimen dose until	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation.

limiting self-care ADLs)	resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	– Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[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; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

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

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

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

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

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

Appendix 2 Schedule of study procedures: follow-up for subjects who have completed durvalumab and tremelimumab treatment and achieved disease control (no confirmed progression of disease) or 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

	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Full physical examination	X	X	X					
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Oxygen saturation (pulse oximetry)	X							
Weight	X							
Urine hCG or serum βhCG	X							
AE/SAE assessment[a, b]	X	X	X					
Concomitant medications[a]	X	X	X					
Palliative radiotherapy	As clinically indicated →							
ECOG performance status	X	X	X	At time points consistent with tumor assessments until loss of clinical benefit				
Subsequent anti-cancer therapy[a]	X	X	X	X	X	X	X	X
Survival status[a]				X	X	X	X	X (every 2 months)
CBC	X	X	X					
Serum chemistry	X	X	X					
Research blood tests	A total of 2 additional research blood draws after the first 3 research blood draws may be performed at the discretion of the study physician							
Thyroid function tests (TSH, and fT3 and fT4 if TSH is abnormal)[c]	X	X	X					
Tumour assessment (CT or MRI)	For subjects who **achieve disease control following 48 weeks of treatment**, tumour assessments should be performed every 12 weeks (+/- 14 days) relative to the date of **first infusion** thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to section 10 and 12 for timings of confirmatory scans. For subjects who **discontinue treatment due to toxicity (or symptomatic deterioration)**, tumour assessments should be performed relative to the date of **first infusion** as follows: every 8 weeks for the first 48 weeks , then every 12 weeks until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Section 10 and 12 for timings of confirmatory scans.							

[a] Can be collected by phone.

[b] Patients with ongoing ≥ grade 2 or serious AEs will continue to be followed until the event is resolved to baseline or deemed irreversible or clinically insignificant by the site investigator, or start of new therapy.

[c] Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an endocrine related AE.

Appendix 3 Schedule of study procedures: follow-up for subjects who have discontinued durvalumab and tremelimumab treatment due loss of clinical benefit at the investigator discretion

Evaluation	Time Since Last Dose of durvalumab							
	Day (±3)	Months (±1 week)						12 Months and Every 6 Months (±2 weeks)
	30	2	3	4	6	8	10	
Full physical examination	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Oxygen saturation (pulse oximetry)	X							
Weight	X							
AE/SAE assessment[a,b]	X	X	X					
Concomitant medications[a]	X							
Palliative radiotherapy	As clinically indicated →							
ECOG performance status	X							
Subsequent anti-cancer therapy[a]	X	X	X	X	X	X	X	X
Survival status[a]		X	X	X	X	X	X	X (every 2 months)
Urine hCG or serum βhCG	X							
CBC	X							
Serum chemistry	X							
Thyroid function tests (TSH, and fT3 and fT4 if TSH is abnormal)[c]	X							
Pharmacokinetic assessment, if applicable								
Research blood test	A total of 2 additional research blood draws after the first 3 research blood draws may be performed at the discretion of the study physician							
Tumour assessment (CT or MRI)	For subjects who **continue treatment post-confirmed progression** at the investigator's discretion, tumour assessments should be performed relative to the date of **first infusion** per section 10 until durvalumab is stopped. For subjects who **discontinue durvalumab following loss of clinical benefit**, **scans should be conducted according to local clinical practice** and submitted for central review until a new treatment is started (these scans are optional).							

[a] Can be collected by phone.

[b] Patients with ongoing ≥ grade 2 or serious AEs will continue to be followed until the event is resolved to baseline or deemed irreversible or clinically insignificant by the site investigator, or start of new therapy.

[c] Free T3 and free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an endocrine related AE.

Appendix 4 The Response Evaluation Criteria in Solid Tumors (RECIST 1.1)

Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

I. Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

A. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

B. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread,

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

C. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions: Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions: Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment: Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

II. <u>Target Lesions: Specifications by Methods of Measurements</u>

A. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

B. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, <u>if not, the patient should be considered not evaluable from that point forward.</u> Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

III. Tumor Response Evaluation

A. Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

B. Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline

sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

IV. Response Criteria

A. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

- **Complete response (CR):** disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- **Partial response (PR):** at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- **Progressive disease (PD)**: at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline

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

  The appearance of one or more new lesions is also considered progression.

  Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study.

B. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to <10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis <10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

C. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- **Complete Response (CR):** disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)

  All lymph nodes must be non-pathological in size (< 10 mm short axis).
- **Non-CR/Non-PD:** persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits

- **Progressive Disease (PD):** unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.
-

D. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from “trace” to “large” or an increase in lymphangitic disease from localized to widespread or may be described in protocols as “sufficient to require a change in therapy.” If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

E. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient‟s baseline lesions

show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

V. Evaluation of Response

A. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1.

Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2. Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

B. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table 3. Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

C. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to “normal” size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of “zero” on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “symptomatic deterioration.” Every effort should be made to document objective progression even after

discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1 – 3.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5 Immune-Related RECIST Criteria

Immune-related RECIST (irRECIST) is derived from RECIST 1.1 conventions (Eisenhauer et al, 2009). The implementation of irRECIST (Perrone, 2016) is identical to RECIST 1.1 until progressive disease (PD) is identified. Upon demonstration of PD per RECIST 1.1, patients may remain on study per Investigator discretion, assuming the patient remains clinically stable, as defined in the protocol. Patients that remain on study will have an imaging disease assessment performed at least 4 weeks after the initial PD is demonstrated in order to confirm PD.

EVALUATION OF LESIONS

1.1 Evaluation of Target Lesions

- Immune-related Complete Response (irCR): **Disappearance of all target lesions.** Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Immune-related Partial Response (irPR): At least a **30% decrease in the sum of diameters of target lesions** (i.e., Percentage Change in Tumor Burden), taking as reference the baseline sum diameters.
- Immune-related Progressive Disease (irPD): Same requirements for PD as standard RECIST 1.1, with exception that progressive disease must be confirmed. After demonstration of PD by standard RECIST 1.1 criteria, patients remain on study and are re-imaged after >4 weeks. Confirmation of target lesion PD is constituted by the following:
    - Sum of linear diameters (SLD) reaches PD threshold of ≥ 20% increase from nadir

    OR

    - SLD remains ≥ 20% increased above baseline (if already ≥ 20% increased at initial PD)
- Immune-related Stable Disease (irSD): Neither sufficient shrinkage to qualify for irPR nor sufficient increase to qualify for irPD, taking as reference the smallest sum diameters while on study.

1.2 Special Notes on the Assessment of Target Lesions

Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of **a short axis of ≥ 15 mm by CT scan.** Only the *short* axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Target Lesions that Become "Too Small to Measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm. However, when such a lesion becomes difficult to assign an exact measure to then:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness **(but should not be changed with varying CT slice thickness).**

Target Lesions that Split or Coalesce on Treatment

When non-nodal lesions „fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

1.3 Evaluation of Non-target Lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- Immune-related Complete Response (irCR): Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).
- Immune-related Non-CR/Non-PD (ir-Non-CR/Non-PD): Persistence of one or more non-target lesion(s). This also includes non-target lesions that demonstrated unequivocal progression at the initial demonstration of PD but then stabilized or regressed on subsequent scans.
- Immune-related Progressive Disease (irPD): Unequivocal progression of existing non-target lesions on a disease assessment subsequent to initial demonstration of PD. Therefore, irPD by non-target lesions requires one of the following on a disease assessment >4 weeks after the initial demonstration of PD:
    - New unequivocal progression

    OR

- Further unequivocal progression (if unequivocal progression present at initial PD)

1.4 New Lesions

Recording of New Target Lesions

The longest diameters of new non-nodal measurable lesions and short axes of new nodal measurable lesions will be recorded. They will be added into the sum of diameters of target lesions (i.e. incorporated into the total Tumor Burden) for this and all subsequent follow-up assessments.

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

Recording of New Non-Target Lesions

All new lesions not selected as new measurable lesions are considered new non-target lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new nonmeasurable lesions prevent irCR.

Progression by New Lesions

irPD by new lesions requires one of the following on a disease assessment >4 weeks after the initial demonstration of PD:

- New lesions appear

  OR

- Additional new lesions appear

  OR

- Prior new lesions grow (if new lesions were present at initial PD)

1.5 Confirmation of Progressive Disease

As described above, irPD requires that an initial demonstration of PD is confirmed in a subsequent disease assessment performed >4 weeks after the initial demonstration of PD. The above section describes what constitutes irPD with respect to Target Lesions, Non-target Lesions and New Lesions. For the sake of clarity, the presence of ALL of the following >4 weeks after initial PD means that PD IS NOT confirmed:

- Target lesions

- SLD is <20% increased from nadir

- Non-target lesions
  - No additional unequivocal progression from prior scan
- New lesions
  - No additional new lesions
  - Any prior new lesions are stable or shrinking (qualitatively)
- Clinical status
  - Patient remains clinically stable

RESPONSE CRITERIA

2.1 Time Point Response

A response assessment should occur at each time point specified in the protocol.

- **Immune-related Complete Response (irCR):** Complete disappearance of all tumor lesions (target and non-target), together with no new measurable or unmeasurable lesions, for at least 4 weeks from the date of documentation of irCR. All lymph nodes short axes must be < 10 mm.
- **Immune-related Partial Response (irPR):** The sum of the linear diameters (SLD) of all target lesions is measured and captured as the sum of diameters at baseline. At each subsequent tumor assessment, the SLD of all target lesions is calculated. A decrease in SLD, relative to baseline SLD, of 30% or greater is considered an irPR, in the absence of irCR or irPD.
- **Immune-related Stable Disease (irSD):** irSD is defined as the failure to meet criteria for irCR, irPR or irPD.
- **Immune-related Progressive Disease (irPD):** It is recommended for patients that are clinically stable to confirm PD at the following tumor assessment. Any of the following will constitute progressive disease:
  - Overall ir-response of irPD (per Table 1) after confirmation of PD with disease assessment >4 weeks after initial demonstration of PD
  - PD per RECIST 1.1 in a patient that is not clinically stable enough to remain on study for confirmation

Table 1: irRECIST 1.1 Definitions

Target Lesion Response per RECIST 1.1	Non-target Lesion Response	New Lesions	Overall ir-response
CR	CR	None OR completely resolved	irCR
PR	Ir-Non-CR/Non-PD	None OR stable/shrinking relative to first PD scan	irPR
SD	Ir-Non-CR/Non-PD	None OR stable/shrinking relative to first PD scan	irSD
PD (with confirmation)	Any	Any	irPD
Any	Presence of unequivocal progression ≥ 4 weeks after initial PD scan	Any	irPD
Any	Any	Appearance of new lesions after initial PD scan	irPD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, ir= Immune-related

2.2 Best Overall Response: All Time Points

Best Overall Response and Date of Progression Using irRECIST 1.1 (irBOR): The investigator will be asked to provide all responses on study and date(s) of progression, if applicable, and the best overall response will be calculated based on the time point responses and tumor measurements provided by the investigator.