MSK PROTOCOL COVER SHEET

Radioiodine (RAI) in Combination with Durvalumab (Medi4736) for RAI-avid, Recurrent/Metastatic Thyroid Cancers

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a pilot study with the primary objective to assess the safety of administering the PD-L1 targeting agent durvalumab in combination with recombinant human thyroid stimulating hormone (rhTSH, Thyrogen) stimulated/prepared radioiodine (RAI; ^{131}I) therapy in patients with RAI-avid (RAIA) recurrent and/or metastatic (R/M) thyroid cancer. Secondary objectives are assessing best overall response (BOR) and progression-free survival (PFS). Enrolled patients will be treated with durvalumab 1500 mg IV approximately every 4 weeks. In Cycle 1/Week 3, Thyrogen 0.9 mg IM will be administered on two consecutive calendar days followed by 100 mCi (+/- 10 mCi) of RAI the next calendar day. Durvalumab will be continued approximately every 4 weeks. Only adverse events occurring within 6 weeks of the first durvalumab dose will be counted as dose limiting toxicities (DLTs). If >1 of the first 3 patients or >2 of the first 6 patients develop a DLT related to durvalumab, further accrual to the study will be halted. If this threshold is not crossed, 11 patients in total will be accrued to the pilot study. All adverse events will be graded according to CTCAE v4.0. Tumor assessments according to RECIST v1.1 will be conducted with serial radiologic imaging at baseline and approximately every 2 cycles of durvalumab therapy (or every 8 weeks +/- 1 week). After 6 months of treatment, imaging will be obtained every 3 cycles (or every 12 weeks (+/- 1 week)). Patients will remain on durvalumab treatment until there is confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or if the study physician feels removal from the study is in the patient's best interest. One exception to these discontinuation rules: given the potential for delayed responses following short periods of disease progression with immunotherapy, subjects may continue to receive therapy beyond radiographic progression if the investigator concludes that the subject is tolerating study drug and continued therapy may provide clinical benefit. Subjects who decide to continue to receive therapy beyond radiographic progression will be asked to reconsent. Adverse events will be monitored from the time informed consent is signed until 90 days after the last dose of drug.

It is mandatory that patients agree to undergo two research biopsies, which will be analyzed to evaluate how this experimental approach changes the genomic/transcriptomic landscape of the tumor and the tumor immune infiltrate (exemption from the second biopsy may be considered if after performance of the first biopsy it is felt that a subsequent biopsy is not reasonably safe for the patient). Archival tumor tissue and serial peripheral blood collections will also be analyzed for potential biologic correlates of immune activation and efficacy derived from the combination therapy.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

To assess the safety of administering durvalumab in combination with rhTSH-stimulated RAI therapy in patients with recurrent/metastatic thyroid cancer.

Secondary Objectives

1) To assess the best overall response to durvalumab in combination with rhTSH-stimulated RAI therapy in patients with recurrent/metastatic thyroid cancer.

2) To assess the progression-free survival of durvalumab in combination with rhTSH-stimulated RAI therapy in patients with recurrent/metastatic thyroid cancer.

Exploratory Objective

To explore in tumor specimens, peripheral blood collections (for peripheral blood mononuclear cells (PBMCs), and cell free DNA (cfDNA)) potential biologic correlates of immune response, impact upon the tumor biology/immune cell infiltrate, and efficacy associated with durvalumab in combination with rhTSH-stimulated RAI therapy.

3.0 BACKGROUND AND RATIONALE

Thyroid cancers and radioiodine (RAI; ^{131}I): The majority of thyroid cancers are differentiated carcinomas of follicular origin (also known as "differentiated thyroid cancers" or "DTCs") with papillary thyroid cancer (PTC) being the most common followed by follicular thyroid cancer (FTC) (use of the term "thyroid cancer" in this protocol refers specifically to follicular cell-derived thyroid malignancies). Metastatic disease represents the most frequent cause of thyroid cancer-related death[1], and radioiodine (RAI or ^{131}I) remains a mainstay of therapy for these patients. The capacity of thyroid tumors to concentrate RAI is mediated by the expression of thyroid-specific gene products which in the normal follicular cell function to incorporate iodine into the protein thyroglobulin (Tg) to produce thyroid hormone ("iodine organification"). These genes include Tg, the sodium-iodide symporter (NIS; mediates iodide uptake into cells), pendrin (another iodide transporter), and thyroid peroxidase (TPO). Importantly, thyroid-stimulating hormone (TSH or thyrotropin) engagement of the TSH receptor (TSHR) in follicular cells, and indeed also thyroid cancer cells, upregulates the expression of these genes to promote enhanced iodide concentration. This biology is routinely exploited in standard clinical practice by prescribing thyroid hormone withdrawal or administering recombinant human TSH (rhTSH; thyrotropin alpha; Thyrogen™ (Genzyme))[2] to elevate circulating TSH for the purpose of enhancing tumoral RAI incorporation for diagnostic and therapeutic purposes.

Though ^{131}I can be particularly effective for treating small volume (< 1 cm), metastatic RAI-avid (RAIA; tumors with detectable RAI uptake) disease[3], efficacy is significantly lower for patients with larger, structurally evident disease. Sabra et. al. published a retrospective study evaluating the efficacy of first-line ^{131}I therapy and reported that for these patients the rate of response with RAI was only 22%[4]. This observation is consistent with the 10% to 24% response rates reported in other retrospective series for similar subsets of patients[3,5-7]. Though repeated administration of RAI is often possible, unfortunately many patients with metastatic tumors lose the ability to trap iodine, leading to RAI-refractory (RAIR) disease. This is associated with a worse prognosis (10% 10-year survival[3]), and systemic therapy options being limited to tyrosine kinase inhibitors (TKIs)[8,9].

With regards to clinical terminology, the "RAI-avid" designation is often used to not only describe the ability of tumors to incorporate RAI, but also infers that such tumors are responsive to RAI therapy. However, RAI avidity is not a binary variable, but a continuous one, and the clinical reality is that the degree of avidity encountered varies broadly from patient to patient, and indeed tumor to tumor. Since RAI efficacy is ultimately dependent upon the capability of thyroid tumors to take up and retain sufficient isotope to deliver tumoricidal doses of radiation, some RAI-refractory tumors are still "RAI-avid" in that isotope uptake can be identified on diagnostic scans[10]. In this protocol,

the term "RAI-avid" (RAIA) is limited to designating tumors that retain the ability to take up and retain iodide, and does not communicate the degree of avidity or sensitivity to RAI treatment ("RAI-avid" here can include both RAI-sensitive and –refractory patients). This RAIA patient population is the cohort that will be evaluated in this clinical trial.

Targeting T cell checkpoints as a therapeutic strategy for DTCs: Immunotherapies directed at blocking inhibitory checkpoints to activate T cell immune responses is an effective therapeutic strategy for a variety of human cancers[11]. The efficacy of these therapies for thyroid cancer, however, is not known. Targeting the programmed death protein 1 (PD-1)/PD ligand 1 (PD-L1) checkpoint in DTCs is of particular interest given that PD-L1 expression occurs at a high rate in these tumors and has been correlated to aggressive disease with poorer prognosis[12-14]. Recently reported in abstract form were the preliminary results from a cohort of PD-L1 positive, advanced DTC patients treated on a phase 1b trial with the PD-1 targeting antibody pembrolizumab (Merck)[15]. Among 22 evaluable patients, two partial responses (9.1%), a 64% rate of tumor regression, and 36% 12-month progression-free survival (PFS) rate were observed. While these data validate that targeting immune checkpoints may have therapeutic efficacy against DTC, it also highlights that a better understanding of the thyroid cancer-immune system interaction is needed to develop rational approaches that improve upon the modest activity elicited with PD-1 targeting alone.

Determinants of "foreignness" in DTCs: Tumor "foreignness", specifically tumor presentation of peptides in major histocompatibility complexes (MHCs) that T cells recognize as non-self, is hypothesized to be essential for therapeutic efficacy with immunotherapeutic approaches targeting T cell checkpoints. Clinical trial data support the hypothesis that foreignness is predominantly driven by the presentation of "neoantigens", epitopes which are uniquely generated by the tumor, most commonly via somatic mutations[16]. Published correlations between high mutational load, neoantigen detection, and efficacy with checkpoint blockade suggests a probabilistic process in which a greater somatic mutation rate enhances the likelihood of creating neoantigens to drive tumor response[17,18], a principle convincingly demonstrated by pembrolizumab efficacy in mismatch repair deficient tumors[19].

However, the relevance of neoantigens in thyroid cancer remains to be investigated. The mutational load for the majority of DTCs (<1 mutation per Mb) is 1-2 logs lower than in other malignancies, such as melanoma and lung cancers (>10 mutations per Mb), diseases for which the existence of neoantigens and significant benefit to PD-1 blockade has been established[16,20]. While acknowledging that low mutational load does not exclude the possibility of neoantigen formation and recognizing that poorly differentiated forms of thyroid cancer are characterized by higher mutation rates[21], we posit that foreignness in DTC may be determined in part by the expression of nonmutated proteins to which T cell tolerance is lost or incomplete. The therapeutic contribution of T cell responses to nonmutated antigens, and the enhancement of these responses by checkpoint blockade, has already been demonstrated in melanoma[22,23]. Along with the observed efficacy of T cell products directed against nonmutated peptide epitopes (e.g. NY-ESO-1), several lines of evidence now suggest that along with neoantigen formation, loss of immune tolerance to native proteins can play a critical therapeutic role in establishing foreignness. This is a particularly appealing hypothesis for DTC given that the thyroid gland is one of the most immunogenic organs in the body, and autoimmune thyroid disease is the most common form of autoimmunity in humans (~5% US prevalence)[19,24]. Subclinical autoimmunity has been estimated to be as high as 10-20% among women[24]. Glandular lymphocytic infiltration in these cases have been shown to include T

cell subsets that proliferate in response to native thyroid proteins[25]. Development of immune-mediated hypothyroidism and hyperthyroidism with CTLA-4 and PD-1 targeting agents provides evidence that clinically targeting T cell checkpoints may be sufficient to augment or stimulate T cell responses against native, immunogenic thyroid epitopes. DTCs to a varying degree maintain the expression of nonmutated thyroid-specific genes, including the biochemical machinery responsible for mediating iodide avidity and therapeutic susceptibility to RAI. In fact, the same genes that govern tumoral RAI avidity have also been shown to be immunogenic antigens relevant to thyroid autoimmunity (e.g. thyroglobulin (Tg), thyroid peroxidase (TPO), and thyroid stimulating hormone receptor (TSHR))[26].

Taken together, our central hypothesis is that in addition to putative neoantigens, nonmutated protein immunogens contribute to thyroid cancer foreignness, and can be upregulated/released to optimize antigenic T cell priming to enhance the efficacy of PD-1 pathway directed therapy.

Rationale for combining TSH-stimulated RAI therapy with PD-1 pathway blockade: Here we propose using TSH-simulated RAI therapy to upregulate the expression and release of nonmutated proteins and putative neoantigens to amplify the therapeutic efficacy of PD-1 pathway blockade for the treatment of RAI-avid recurrent/metastatic thyroid cancers. TSH stimulation globally increases the expression of thyroid-specific genes in DTCs. This effect extends to those genes which mediate RAI avidity, a property that is routinely exploited clinically for diagnostic and therapeutic purposes when recombinant human TSH (rhTSH; Thyrogen (Genzyme)) is administered to patients in order to optimize RAI uptake in normal and malignant thyroid tissue. Consistent with this mechanism of action, rhTSH has been reported to boost circulating TG levels on average ~3 fold or higher[27]. Additionally, dramatic increases in TG have also been documented after RAI administration[28-30], consistent with RAI-induced thyroiditis and tumor lysis leading to the release of thyroid antigens. In this way, RAI may boost PD-1 pathway directed therapies in a manner similar to the "abscopal effect" described with radiation therapy, except that systemically administered RAI may optimize antigen release from not just one irradiated site, but multiple tumor sites, unmasking the full complement of neoantigens accompanying disease heterogeneity. Hence, rhTSH-stimulated RAI may be an effective approach for optimizing nonmutated protein and neoantigen release to optimally prime the T cell response simulated by PD-1 pathway blockade, which we propose to achieve with the PD-L1 targeting antibody durvalumab (AstraZeneca).

Durvalumab: Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of PD-L1 to PD-1 and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

Overview of the clinical experience with durvalumab: As of July 12th, 2018, a total of 5127 subjects have been enrolled and treated AstraZeneca or MedImmune-sponsored interventional studies in multiple tumor types, stages of diseases and lines of therapy. Of the 5127 subjects, 2229 received durvalumab monotherapy, 1573 received durvalumab in combination with tremelimumab, and 1325 received durvalumab in combination with an investigational and or an approved product. An estimated 8252 patients are currently enrolled in blind studies. In addition, 1637 patients have aprticipated in the durvalumab Early Access Programme (EAP; Study D4194C00002 for patients with locally advanced, unresectable non-small cell lung cancer [NSCLC] whose disease has not

progressed following platinum-based chemoradiation therapy). The total post-marketing exposure to durvalumab to 12 July 2018 was estimated to be approximately 1854 patient-years.

Durvalumab safety: The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. Most adverse drug reactions (ADRs) seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues and could occur in any organ system. Adverse events of special interest (AESIs) and immune-mediated AEs (imAEs) observed with anti PD-L1/PD-1 agents such as durvalumab and durvalumab in combination with tremelimumab include diarrhea/colitis, pneumonitis, hepatitis/hepatotoxicity, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), rash/dermatitis, nephritis myocarditis, myositis/polymyositis, pancreatitis and rare/less frequest imAEs including neuropathy/neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with durvalumab monotherapy in key clinical studies are described below.

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

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study

D4191C00003/ATLANTIC. Overall, events reported in ≥ 10% of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in ≥ 2% of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in ≥ 1.0% of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

Safety data have been pooled for 3 durvalumab monotherapy studies (**CD-ON-MEDI4736-1108** [n=970], **ATLANTIC** [n=444] and **PACIFIC** [n=475]) for patients who received a durvalumab dose of 10 mg/kg Q2W; a total of 1889 patients are included in this validated pooled data set.

- Overall, AEs reported in ≥15% of patients were fatigue, cough, decreased appetite dyspnoea, nausea, constipation, diarrhoea and pyrexia; AEs considered by the investigator as related to durvalumab in ≥5% of patients were fatigue, diarrhoea, hypothyroidism, nausea, pruritus, decreased appetite and rash.
- A total of 45.2% patients reported AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher: Grade 3, 4 and 5 (fatal) events were reported in 42.1%, 6.7% and 5.3% patients, respectively; Grade 3, 4 and 5 (fatal) events considered related to durvalumab were reported in 9.4%, 0.7% and 0.6% patients, respectively.
- Grade 3 or 4 events occurring in ≥2% of patients were anaemia, dyspnoea, hyponatraemia, gamma-glutamyltransferase (GGT) increased, pneumonia, fatigue, aspartate aminotransferase (AST) increased and back pain; Grade 3 or 4 events considered related to durvalumab occurring in ≥0.5% patients were fatigue, AST increased, GGT increased, pneumonitis, alanine aminotransferase (ALT) increased and diarrhoea.
- The most common Grade 5 events were general physical health deterioration (0.8% patients), respiratory failure (0.5% patients) and sepsis (0.4% patients) The only Grade 5 event considered related to durvalumab occurring in ≥2 patients was pneumonitis.
- A total of 9.4% patients discontinued from study treatment due to an AE. The most common events leading to treatment discontinuation were pneumonitis, pneumonia, dyspnoea, general physical health deterioration and radiation pneumonitis.

- A total of 5.7% patients had serious AEs (SAEs) that were considered by the investigator as related to durvalumab.
- A total of 56.3% patients experienced an AESI. The most common grouped term AESI was diarrhoea (17.4% patients; of whom 0.7% had events of Grade ≥3). Other common AESIs (>10%; grouped term) were dermatitis (15.8% patients; of whom 0.2% had events of Grade ≥3); rash (15.0% patients; of whom 0.6% had events of Grade ≥3); select hepatic events (12.0% patients; of whom 4.6% had events of Grade ≥3); and hypothyroidism (10.9% patients; of whom 0.1% had events of Grade ≥3).

PACIFIC: Overall durvalumab monotherapy (10 mg/kg Q2W) was well-tolerated and had a manageable safety profile relative to the standard of care (SoC) in this placebo-controlled study where durvalumab or placebo was given to patients following concurrent chemoradiation to the chest for stage IIIA/IIIB unresectable NSCLC. Generally, the type, incidence, and severity of AEs were comparable between the durvalumab and placebo treatment groups. Where not comparable, the type, incidence, and severity of events were consistent with the established durvalumab safety profile to date (safety monotherapy pool). The exception to this was for events of pneumonitis/radiation pneumonitis, for which, as expected in this patient population, there was a high background incidence. However, despite a numerical increase in these events for patients receiving durvalumab over those receiving placebo, most of these events were low grade. Clinically important CTCAE Grade 3 or 4 events were infrequent and balanced between the 2 treatment groups. The data incidences for this study are provided in the format of durvalumab vs placebo arms respectively.

- AEs experienced during the study with an incidence of >15% were cough (35.4% vs 25.2%); fatigue (23.8% vs 20.5%); dyspnoea (22.3% vs 23.9%); radiation pneumonitis (20.2% vs 15.4%); and diarrhoea (18.3% vs 18.8%). Combined events of pneumonitis or radiation pneumonitis occurred in 33.9% vs 24.8% of patients.
- CTCAE Grade 3 or 4 AEs were reported in 32.0% vs 27.8% of patients. CTCAE Grade 3 pneumonitis or radiation pneumonitis occurred in 3.4% vs 2.6% of patients and there were no Grade 4 events.
- SAEs were reported in 28.6% vs 22.6% of patients.
- AEs with an outcome of death were comparable between treatment groups (4.4% vs 6.0%). The only AEs with an outcome of death experienced by >1 patient in the durvalumab arm were pneumonitis and cardiac. Fatal events of pneumonitis or radiation pneumonitis were balanced between the 2 treatment groups.
- A total of 15.4% vs 9.8% of patients had an AE that led to permanent discontinuation of treatment. AEs leading to discontinuation reported in ≥2 patients were pneumonitis (4.8% vs 2.6%), radiation pneumonitis (1.3% vs 1.3%) and pneumonia (1.1% vs 1.3%).
- A total of 66.1% vs 48.7% of patients experienced an AESI. AESIs, grouped terms, with an overall incidence >15% were dermatitis or rash (32.6% vs 17.9%) and diarrhea (18.3% vs 19.2%). A total of 8.2% vs 3.8% of patients experienced CTCAE Grade 3 or 4 AESIs. AESIs with an outcome of death occurred in 4 patients (0.8%) treated with durvalumab (all pneumonitis events) and 4 patients (1.7%) treated with placebo (3 patients [1.3%] with pneumonitis and 1 patient [0.4%] with eosinophilic myocarditis).
- Consistent with the immune-mediated mechanism of action for durvalumab, there was a higher incidence of imAEs for patients receiving durvalumab (24.2% vs 8.1% of patients). ImAEs of CTCAE Grade 3 or 4 were reported for 3.4% vs 2.6% of patients.

Durvalumab efficacy:
Clinical activity has been observed across numerous monotherapy and combination therapy studies for which efficacy data are available.

Study CD-ON-durvalumab-1108: The ORR per BICR was 21.8% (95% CI: 15.4, 29.3) and 6.4% (95% CI: 2.6, 12.8) in PD-L1 high and low/negative patients, respectively. Median OS was 12.4 months (95% CI: 9.3, 15.2). HNSCC: ORR per BICR was 16.7% (95% CI: 3.6, 41.1) and 2.9% (95% CI: 0.1, 14.9) in PD-L1 high and low/negative patients, respectively. Median OS was 8.4 months (95% CI: 5.7, 12.3). UC: ORR was 27.7% (95% CI: 19.3, 37.5) in the PD-L1 high subgroup compared to 5.9% (95% CI: 1.9, 13.2) in the PD-L1 low/negative subgroup. The median OS was 10.5 months (95% CI: 6.9, 15.7). HCC: ORR per RECIST v1.1 was 10% (95% CI: 2.8, 23.7). The median OS was 13.2 months (95% CI: 6.3, 23.0).

Study D4190C00007 (MDS): In the 40 patients with MDS treated in Study D4190C00007, the best overall responses were mCR in 13 patients (32.5%). The median PFS was 32.0 weeks (95% CI: 10.4, 49.6) and median OS was 51.1 weeks (95% CI: 34.0, 71.4).

PACIFIC (NSCLC): The median PFS by BICR was significantly longer with durvalumab treatment (16.8 months [95% CI: 13.0, 18.1]) compared with placebo (5.6 months [95% CI: 4.6, 7.8]); hazard ratio 0.52; 98.9% CI: 0.39, 0.70; p<0.0001. The median OS was not reached for the durvalumab arm and was 28.7 months for the placebo arm; stratified hazard ratio for death, 0.68; 99.73% CI: 0.47, 0.997; p=0.0025). The 24 month OS rate was 66.3% with durvalumab vs 55.6% with placebo.

HAWK: In patients with PD-L1 high (≥25% TC) HNSCC. ORR (per BICR) was 16.2% (95% CI: 9.90, 24.41). The median PFS was 2.1 months (95% CI: 1.9, 3.7). The median OS was 7.1 months (95% CI: 4.9, 9.9); the OS rate at 12 months was 33.6% (95% CI: 24.8, 42.7).

Study D4190C00006 (NSCLC): In the dose expansion Cohort A (treatment-naive NSCLC selected by PD-L1 status), the ORR was 15.6% (7/45; 95% CI: 6.5, 29.5). ORRs were 16.7% (3/18; 95% CI: 3.6, 41.4) and 12.0% (3/25; 95% CI: 2.5, 31.2) in the PD L1 high and PD-L1 low/negative groups, respectively. Median OS was not reached, with an OS rate at 6 months of 83.6%. In the dose expansion Cohort B co-administration group (immunotherapy-naïve, 1L or 2L patients with NSCLC), no objective responses were observed per investigator assessment. A best overall response of SD was observed for 9 of the 19 patients (DCR 47.4%; 95% CI: 24.4, 71.1). In the dose expansion Cohort B sequential administration group (2L patients with non squamous NSCLC), the ORR per BICR was 18.8% (40/213; 95% CI: 13.8, 24.7); ORRs were 35.1% (20/57; 95% CI: 22.9, 48.9) and 11.8% (16/136; 95% CI: 6.9, 18.4) in the PD-L1 high and PD-L1 low/negative subgroups, respectively. Median PFS per BICR was 3.5, 7.1 and 3.3 months in the total, PD-L1 high and PD-L1 low/negative groups, respectively. The median OS was 15.4 months; the OS rate at 12 months was 53.8% and higher in the PD-L1 high (71.6%) vs the PD-L1 low/negative (47.3%) subgroup. In Cohort C (immunotherapy-pretreated, 2L to 4L patients with NSCLC), the ORR by investigator assessment was 5.1% (4/78; 95% CI: 1.4, 12.6); ORRs were 7.7% (2/26; 95% CI: 0.9, 25.1) and 2.9% (1/34; 95% CI: 0.1, 15.3) in the PD-L1 high and PD-L1 low/negative subgroups, respectively. Median PFS was 1.8, 1.7 and 1.7 months in the total, PD-L1 high and PD-L1 low/negative groups, respectively. The median OS was 8.4 months; the OS rate at 12 months was 34.1% and was similar in the PD-L1 high (31.5%) vs the PD-L1 low/negative (29.8%) subgroup.

Study D4190C00022: ORR was 17.5% (95% CI: 7.3, 32.8). The median TTR was 8 weeks (range, 7.6 to 24 weeks). The DCR (defined as any CR + PR + SD >16 weeks) was 57.5% (95% CI: 40.9, 73.0).

Durvalumab fixed dosing: A population PK model was developed for durvalumab using monotherapy data from a Study 1108 and ATLANTIC across dose levels and tumor types *(Model 1; n= 1324, doses ranging from 0.1 mg/kg to 10 mg/kg Q2W or 15 mh/kg Q3W or 20 mg/kg Q4W*).

Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg Q2W was selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W), 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (Appendix 2).

Study overview: The objective of this pilot clinical trial is to assess the safety of administering the PD-L1 targeting agent durvalumab in combination with rhTSH-stimulated RAI in RAIA, recurrent and/or metastatic thyroid cancer patients. Secondary and exploratory objectives will be to collect preliminary efficacy data as well as explore potential biologic correlates in sampled tumors and peripheral blood to clinical efficacy with the combination. Since RAI is being administered for the primary purpose of augmenting the immunotherapeutic response, patients with at least one RAI-avid tumor of any degree will be eligible, including patients who are clinically designated either “RAI-sensitive” or “RAI-refractory.”

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a pilot study with the primary objective to assess the safety of administering the PD-L1 targeting agent durvalumab in combination with recombinant human thyroid stimulating hormone (rhTSH, Thyrogen) stimulated/prepared radioiodine (RAI; ^{131}I) therapy in patients with RAI-avid (RAIA) recurrent and/or metastatic (R/M) thyroid cancer. If >1 of the first 3 patients or >2 of the first 6 patients develop a DLT related to durvalumab, further accrual to the study will be halted. If this threshold is not crossed, 11 patients in total will be accrued to the pilot study. All adverse events will be graded according to CTCAE v4.00. Secondary objectives are assessing best overall response (BOR) and progression-free survival (PFS) RECIST v1.1 criteria.

4.3 Intervention

Enrolled patients will be treated with durvalumab 1500 mg IV approximately every 4 weeks. In Cycle 1/Week 3, Thyrogen 0.9 mg IM will be administered on two consecutive calendar days followed by 100 mCi (+/- 10 mCi) of RAI the next calendar day. Durvalumab will be continued approximately every 4 weeks. Only adverse events occurring within 6 weeks of the first durvalumab dose will be counted as dose limiting toxicities (DLTs). Tumor assessments according to RECIST v1.1 criteria will be conducted with serial radiologic imaging at baseline and approximately every 2 cycles of durvalumab therapy (or every 8 weeks +/- 1 week). After 6 months of treatment, imaging will be obtained every 3 cycles (or every 12 weeks (+/- 1 week)). Patients will remain on durvalumab treatment until there is confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or if the study physician feels removal from the study is in the patient's best interest. One exception to these discontinuation rules: given the potential for delayed responses following short periods of disease progression with immunotherapy, subjects may continue to receive therapy beyond radiographic progression if the investigator concludes that the subject is tolerating study drug and continued therapy may provide clinical benefit. Adverse events will be monitored from the time informed consent is signed until 90 days after the last dose of drug. It is mandatory that patients agree to undergo two research biopsies, which will be analyzed to evaluate how this experimental approach changes the genomic/transcriptomic landscape of the tumor and the tumor immune infiltrate (exemption from the second biopsy may be considered if after performance of the first biopsy it is felt that a subsequent biopsy is not reasonably safe for the patient). Archival tumor tissue and serial peripheral blood collections will also be analyzed for potential biologic correlates of immune activation and efficacy derived from the combination therapy.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Durvalumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the investigator as a 500-mg vial solution for infusion after dilution. Durvalumab is an IND agent that is not FDA-approved for any indication.

Formulation/packaging/storage

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

Durvalumab Doses and treatment regimens

Durvalumab will be administered 1500 mg IV approximately every 4 weeks. Two weeks after the first dose and prior to the second dose of durvalumab, Thyrogen and RAI will be administered. Durvalumab will be continued approximately every 4 weeks. Patients will remain on durvalumab until there is confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or if the study physician feels removal from the study is in the patient's best interest. One exception to these discontinuation rules: given the potential for delayed responses following short periods of disease progression with immunotherapy, subjects may continue to receive therapy beyond radiographic progression if the investigator concludes that the subject is tolerating study drug and continued therapy may provide clinical benefit.

Study drug preparation

For patients weighing ≥ 30 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) (based on an average body WT of 75 kg) should be prepared. For subjects <30 kg body weight, dose is determined using body mass, calculating the stock volume of durvalumab to achieve the accurate dose according to Appendix 2.

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 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 1500 mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Remove a volume of IV solution from the IV bag equal to the calculated volume of durvalumab to be added to the IV bag prior to addition of durvalumab. Next, the volume of durvalumab (i.e., 15.0 mL for 750 mgor 30.0 mL for 1500 mgof durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Patient weight at baseline should be used for dosing calculations in patients ≤30 kg unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For patients <30kg, calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose according to Appendix 2.

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

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

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

Durvalumab hold and infusion times

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

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

Monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure)

approximately every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug maybe decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects 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. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 4 hours (otherwise requires new infusion preparation).

As with any antibody, allergic reactions to dose administration are possible.

5.2 Thyrotropin alpha (Thyrogen; Genzyme)

Thyrogen will be given as 0.9 mg IM daily injections administered for two consecutive days prior to RAI. The Thyrogen will be administed in clinic.

5.3 ^{131}I (RAI; sodium iodide; I-131)

100 mCi (+/- 10 mCi) of ^{131}I will be administered a day after Thyrogen injections have been administered for two consecutive calendar days. This is a low, empiric ^{131}I activity recommended for the treatment of loco-regional or metastatic RAIA thyroid cancer, even in patient populations at increased risk of ^{131}I therapy (elderly, patients with renal insufficiency)[31]. ^{131}I has a half-life of 8 days and relatively high principal photon energy of 364 keV accompanied by beta particle emissions. It is administered orally in the form of capsules or liquid. Pregnancy and breastfeeding are contraindications to radioiodine treatment. A beta-HCG pregnancy test must be performed up to 2 days prior to the administration of ^{131}I (for woman of child-bearing potential). ^{131}I is an FDA-approved agent for the treatment of thyroid cancer. The ^{131}I will be administed in clinic.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

The protocol will enroll patients with RAI-avid recurrent/metastatic thyroid cancer.

6.2 Subject Inclusion Criteria

- Patients must have histologically or cytologically confirmed thyroid carcinoma of follicular origin (including papillary, follicular, hurthle cell or poorly differentiated subtypes and their respective variants).
- Diagnosis of recurrent and/or metastatic thyroid cancer.
- At least one RAI-avid lesion identified on the most recent radioiodine scan (a diagnostic, post-therapy, or post-ablation scan) **OR** at least one lesion on the most recent FDG PET scan with an SUVmax of 10 or less. (Both RAI-sensitive and RAI-refractory patients are eligible if at least one tumor with RAI avidity of any degree can be identified within one of these parameters.)

- Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 20 mm with conventional techniques or as ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. See Section 12 for the evaluation of measurable disease. Tumors in previously irradiated fields may be considered measureable if there is evidence of tumor progression after radiation treatment.

- ECOG Performance Status (PS) 0 or 1. (or Karnofsky ≥60%)

- Age ≥ 18 years at time of study entry

- Adequate normal organ and marrow function as defined below:

  - Hemoglobin ≥ 9.0 g/dL

  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (≥ 1500 per mm^3)
  - Platelet count ≥ 100 x 10^9/L (≥100,000 per mm^3)
  - Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). (This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.)
  - AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5x ULN
  - Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

    Males:

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

    Females:

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

- Female subjects must either be of non-reproductive potential (i.e., post-menopausal by history: ≥60 years old and no menses for ≥1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.

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

- Patients must agree to undergo two research biopsies of (a) malignant lesion(s). Biopsies do not need to be done if the investigator or person performing the biopsy judges there is no tumor accessible for biopsy, the only accessible tumor must be used for RECIST measurement, or the biopsy poses too great a risk to the patient. . If the patient has only one RECIST measureable target lesion for response assessment, research biopsies must not be performed on that target lesion.

- Availability of archival tumor tissue from the thyroid cancer primary or metastasis (a tissue block or a minimum of 30 unstained slides would be required. Patients with less archival tissue available may still be eligible for the study after discussion with the MSK Principal Investigator.)

6.3 Subject Exclusion Criteria

- ^{131}I therapy < 6 months prior to initiation of therapy on this protocol. A diagnostic study using < 10 mCi of ^{131}I is not considered ^{131}I therapy. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.

- History of pneumonitis.

- External beam radiation therapy < 4 weeks prior to initiation of therapy on this protocol..

- Chemotherapy, immunotherapy, targeted therapy, monoclonal antibodies, tumor embolization, or other investigational agent within 28 days prior to the first dose of study drug.

- Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.

- Any unresolved toxicity CTCAE grade $\geq$ 2 from previous anti-cancer therapy. Exceptions include hearing loss, peripheral neuropathy, and alopecia.

- Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.

- Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with a history of autoimmune thyroid disease are not excluded. Subjects with vitiligo or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

- History of primary immunodeficiency.

- History of allogeneic organ transplant.

- History of hypersensitivity to durvalumab or any excipient.

- History of hypersensitivity to thyrotropin alpha (Thyrogen).

- Patients unable to follow a low iodine diet or requiring medication with high content in iodide (amiodarone).

- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses, acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

- Known history of active tuberculosis
- Symptomatic brain metasteses, leptomeningeal carcinomatosis, or spinal cord compression (treated metastatic brain, leptomeningeal carcinomatosis, or spinal cord compression are allowed). Note: Patients must be off steroids used for brain metasteses, leptomeningeal carcinomatosis, or spinal cord compression.
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.
- Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
- Subjects with uncontrolled seizures.

7.0 RECRUITMENT PLAN

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team. Patient recruitment most likely will occur in the medical oncology and endocrinology clinics of the Head and Neck Disease management team. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study. Investigators will discuss the study and review/sign the informed consent documents with the patient.

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

8.1 PRETREATMENT EVALUATION

Within 4 weeks of starting on study, the following tests/evaluations need to be done:

- Signing the Informed Consent Form.
- History and Physical Examination.
- Vital signs (pulse, blood pressure), including weight.
- Performance Status (Eastern Cooperative Oncology Group (ECOG) or Karnofsky Performance Status (KPS)) designation.
- Electrocardiogram (ECG or EKG) in triplicate.
- Radiology studies (CT(s) without contrast and/or MRI(s)) for disease assessment).
- Recording concurrent medications.

- Confirm availability of archival tumor tissue (if tissue is not already available at MSK, physical receipt of tissue is not required for study enrollment or initiation).
- Research tumor biopsy: The research biopsy will be performed any time prior to Week 1 Day 1 (can completed ≥ 4 weeks before starting on study). Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered safe for the patient (image-guided biopsies will be performed by a radiology physician with the appropriate expertise).
- Research blood draw: Any time prior to start of study, approximately 10 mL of blood, preferably in a lavender top tube (with EDTA).
- Hematology tests (see Section 10).
- Clinical chemistry tests (see Section 10).
- Urinalysis (see Section 10).
- Pregnancy test in women of child-bearing potential (serum or urine beta-hCG within 7 days of starting the study).

9.1 TREATMENT/INTERVENTION PLAN

9.2 Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy.

2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment, other than TSH suppressive therapy and/or bisphosphonates and/or denosumab.

3. 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. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).

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

Contraception

Females of childbearing potential who are sexually active with a nonsterilised male partner must use at least 1 highly effective method of contraception (Table 1) from the time of screening, and must agree to continue using such precautions at least 90 days following the last infusion of durvalumab and avoid pregnancy for 9 months after RAI (^{131}I) administration; 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.

1. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).

2. Subjects must use 2 acceptable methods of effective contraception as described in Table 1.

3. Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 1) from Day 1 and for 90 days after receipt of the final dose of investigational product. Males should avoid impregnating females partners for 9 months after RAI (^{131}I).

Table 1: Highly Effective[a] Methods of Contraception

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

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

[b] This is also considered a hormonal method

Blood donation

Subjects should not donate blood while participating in this study for at least 90 days following the last infusion of durvalumab and a minimum 12 months after administration of RAI.

9.3 Schedule of Events

- Patients will initiate treatment with durvalumab on Week 1, Day 1. The required evaluations and laboratory tests (detailed in **Section 10**) can be performed up to 7 days prior to initiation of treatment. It is unnecessary to repeat laboratory tests if the screening assessments of the same tests were performed within 7 days prior to first dose of therapy. Durvalumab 1500 mg IV

approximately every 4 weeks will be administered (adjustment to the dose may be necessary for patients weighing <30 kg). All other Week 1 evaluations (detailed in **Section 10**) may be performed up to 3 days prior to initiation of study treatment.

- In Cycle 1/Week 3, Thyrogen 0.9 mg IM will be administered on two consecutive calendar days followed by 100 mCi (+/- 10 mCi) RAI the next calendar day (these agents will be administered in clinic). The laboratory tests detailed in **Section 10** are to be drawn prior to the first Thyrogen injection.

- Research tumor biopsy: If after performance of the first research biopsy the investigator judges that it is safe to proceed with a second research biopsy, it is preferred that the procedure be performed during Cycle 2, Week 3 or 4 (though alternate timing for this second biopsy during Cycle 2 or later is allowed per investigator discretion or for safety reasons related to RAI administration). Biopsy of the same tumor that was sampled previously is preferred, but not required. Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered safe for the patient (image-guided biopsies will be performed by a radiology physician with the appropriate expertise).

- DLT monitoring and evaluations (including research blood collections) are to be conducted according to the schedule detailed in **Section 10**. Guidelines for holding durvalumab will be performed as outlined in **Section 11** and **Appendix 1**.

9.4 Definition of Dose-Limiting Toxicity (DLTs)

The period of DLT monitoring will be 6 weeks beginning from the first durvalumab dose administered. Patients who are removed from the study for reasons other than DLT prior to the administration of the first Thyrogen injection will be replaced with another subject. Patients who do not complete the 6 week period of monitoring beginning from the first durvalumab dose for reasons other than DLT will also be replaced. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

If >1 of the first 3 patients or >2 of the first 6 patients develop a DLT related to durvalumab, further accrual to the study will be halted. If this threshold is not crossed, 11 patients in total will be accrued to the pilot study.

With the exception of specific AEs discussed below, a DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period felt to be possibly, probably, or definitely related to durvalumab. For ≥ Grade 3 adverse events that occur in patients during the DLT monitoring period, investigators must use their discretion to decide if the adverse event is a DLT (e.g., alkaline phosphatase elevation in the context of known progression of hepatic and/or bone metastases might be attributed to progression of disease per investigator discretion).

Any AE requiring discontinuation of durvalumb will also be considered a DLT. Durvalumab-related AEs that occur during the 6-week DLT evaluation period and delay the administration of the second durvalumab dose and/or Thyrogen/RAI therapy by more than two weeks will also be considered DLTs.

Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this DLT definition.

The following will be DLTs:

- Any Grade 4 immune related Adverse Event (irAE)
- Any ≥ Grade 3 colitis
- Any ≥ Grade 3 noninfectious pneumonitis
- Any ≥ Grade 3 nephritis or renal dysfunction (elevated serum creatinine)
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE (excluding colitis, pneumonitis, thyroiditis, or nephritis) that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management, including systemic corticosteroids, or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8x ULN or total bilirubin > 5x ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The DLT definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Any grade hypothyroidism or elevation of TSH
- Grade 3 endocrine disorder (pituitary, thyroid, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc)
- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

The following toxicities are excluded from the definition of DLT if observed within 30 days of RAI administration:

- Grade 3 low white blood cell count
- Grade 3 or 4 neutropenia
- Grade 3 thrombocytopenia

Regarding immunosuppression, the laboratory parameter for DLT determination will be absolute neutrophil count (not total white blood cell count).

9.5 Correlative Studies

Tumor Analysis: (These studies will be conducted in collaboration with Drs. Timothy Chan, Luc Morris, and James Fagin.)

Exploratory objective: To investigate potential tumor predictors/correlates of benefit to durvalumab plus rhTSH-stimulated/prepared RAI therapy.

Rationale: We hypothesize that interfering with the PD-1/PD-L1 axis in thyroid cancers can result in the loss of tolerance to immunogenic thyroid antigens, which can be augmented by rhTSH stimulated RAI therapy. Other predictors of benefit to immunotherapeutic approaches delineated in other settings include PD-L1 expression, tumor mutation burden, and neoantigen load. To evaluate the potential correlation of these tumor features with the efficacy of durvalumab plus rhTSH-prepared RAI, we will perform whole exome and transcriptome analysis in fresh research biopsies and/or archival tissues.

Of particular importance is the lack of data addressing how immune checkpoint inhibition and RAI therapy impacts the dynamics of the thyroid cancer immune microenvironment and genomic landscape. For the latter, immunotherapy induced changes to the tumor genome could provide insights into the "immunoediting" induced by therapy and potentially identify epitopes of particular significance for efficacy. The only approach that will provide new insight into these biologic processes is the analysis of serial research biopsies performed during therapy. On this study, biopsies will be performed pre-treatment and after durvalumab/RAI in Cycle 2. These tissues will be analyzed with next-generation sequencing of DNA and RNA. For cases in which sufficient tissue is collected, the immune microenvironment may be characterized by cytometric techniques, including flow cytometry or mass cytometry (CyTOF; MIBI). Protein based approaches, including IHC (e.g. for PD-L1, PD-L2 status), will also be employed. We hypothesize that durvalumab and RAI will increase tumoral immune infiltration characterized by enhanced markers of T cell activation (increased granzyme/perforin expression, enrichment of the IFN-gamma signaling pathway, decreased Treg/CD8+ ratio). Beyond characterizing the tumor-associated T cell infiltrate, therapy induced changes of other immune cell popoulations will be examined (e.g. macrophages, NK cells, B-cells). Additionally, how durvalumab/RAI impacts the status of other immune checkpoint molecules (e.g. LAG-3, CTLA-4, TIM-3) may provide insights into putative mechanisms of resistance to this therapeutic approach. Such studies will be essential for rationally developing future immunotherapy based therapeutic approaches for advanced thyroid cancer patients.

Approach: The research biopsy samples will be divided for fixation and flash freezing at the discretion of the Principle Investigator. These samples will be used to evaluate the genomic and transcriptomic landscape of the tumors. Archival tissues may also be used if of sufficient quantity and quality.

DNA and RNA will be extracted from frozen samples and/or paraffin tissue. The research peripheral blood sample collected on the study will be used as a control, matched normal sample (microdissection of normal tissue in the tumor samples may also be used for this purpose). DNA will be submitted for next generation sequencing, possibly whole exome or whole genome sequencing. The specific assay that will be employed to analyze for genomic alterations will be dependent upon the technology available at the time of analysis. Comparisons of DNA between tumor and normal tissue (from the research blood draw) will be performed as appropriate, thus generating germline sequence data. There is no intention to analyze the germline data beyond

utilizing it as a normal control for the tumor tissue analysis, and generally germline data will not be communicated to the patient. This data will be used to quantitate mutation load and identify candidate neoantigens.

Extracted RNA will be analyzed with RNAseq technology, or alternative assays, depending on technical limitations and assay availability. RNAseq data will be used to define a set of expressed neoepitopes and explore gene expression signatures that may correlate with response. RNAseq data analysis may include:

- Quantification of the following: 1) Markers of the MAPK pathway transcriptional output (e.g. Etv1, Etv4, Etv5, Spry2, Spry4, Dusp6); 2) Genes required for thyroid hormone biosynthesis (e.g. Nkx2.1, Pax8, Foxe1, Tg, Tpo, TshR, Nis, Pendrin, Dio2); 3) PD-L1 expression (PD-L1 expression will also be analyzed by IHC).
- Analysis to characterize tumor (a) immune cell infiltration and (b) immunologic gene signatures.

For patients in whom two serial research biopsies are obtained, evolution of the mutation, neoantigen, and gene expression landscape in pre- and post-treatment samples will be analyzed to gain insights into immunoediting that may occur and infer what epitopes may be critical for efficacy. RNAseq data will also be used to explore changes in the expression of nonmutated thyroid gene expression (e.g. TG, THSR, TPO, etc…) with therapy for the same purpose. The same data can be analyzed to evaluate how immune cell tumoral infiltration and immunologic gene signatures may change with therapy.

Frozen tissues from the research biopsy may be evaluated for relevant protein targets by Western blot or other proteomic assays that may be available at time of analysis.

Fixed archival and/or research biopsy tissues may also be evaluated by immunohistochemistry to assess changes in tumor immune infiltrates and tumor/immune cell protein expression (e.g. PD-L1 status). For patients in whom sufficient fresh tissue can be collected in the research biopsies, the tumor immune cell infiltrate (or tumor infiltrating lymphocytes (“TILs”) may be extracted and characterized by cytometric techniques, including flow cytometry or mass cytometry (CyTOF).

Note regarding next generation sequencing analysis performed on this protocol: In the course of this research it is possible that some patients whose tumors are analyzed through investigational “next-generation” profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the

treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #
- Contact: ocrgapirb@mskcc.org

Peripheral Blood Analysis:

Exploratory Objective #1: To investigate changes in peripheral blood populations that occur with durvalumab and rhTSH-prepared RAI.

Rationale: We hypothesize that disruption of the PD-1/PD-L1 axis with durvalumab in combination with rhTSH-prepared RAI therapy will alter peripheral blood immune populations. Additionally, T cell receptor repertoire may be analyzed.

Approach: (These studies will be conducted in collaboration with the MSK immune monitoring core facility.) At the time points indicated in **Section 10**, peripheral blood samples will be collected: 4 CPT tubes (BD, 8-ml capacity, total blood volume collected ~32 ml for PBMC purification for flow cytometric analysis) and 1 PAXgene tube (BD order #762165 or equivalent) (for purification of RNA/DNA for TCR analysis). Changes to these methods may be adapted depending upon the most recent, generally accepted protocols. Flow cytometry will be used to evaluate changes in T cell subsets at different time points. Alternative approaches to this analysis may be pursued depending upon the availability of new technologies, platforms, or approaches. Specifically, assays investigating the immunogenicity of tumoral antigens in *ex vivo* assays utilizing these collected PBMCs may be of value and will be performed to identify potential neoantigens or self antigens that are critical for mediating therapeutic efficacy.

Exploratory Objective #2: To investigate changes in cell free DNA (cfDNA) that occur with durvalumab and rhTSH-prepared RAI.

Rationale: We hypothesize that rhTSH-prepared RAI therapy will enhance expression and release of thyroid-specific antigens/neoantigens critical for augmenting immunotherapeutic responses to PD-L1 targeting with durvalumab. Here, we propose using tumor cfDNA as a surrogate marker of tumor lysis and antigen release.

Approach: (These studies will be conducted in collaboration with the MSK Departement of Laboratory Medicine, MSK cfDNA extraction facility, and Kravis Center for Molecular Oncology (CMO).) At the time points indicated in **Section 10**, peripheral blood samples will be collected. Whole blood will be collected in 10-ml Cell-Free DNA BCT tubes (STRECK) and centrifuged in two steps to separate plasma from cells. Cell-free plasma will then be aliquoted and frozen at minus 80°C until ready to extract. Extraction of cfDNA will be performed using a fully automated QIAGEN platform, QIAsymphony SP, and QIAsymphony DSP Virus/Pathogen Midi Kit (catalog #937055). This is a bead-based custom protocol, optimized to work with 3 ml of plasma as starting material. The extraction process includes lysis, binding, wash and elution steps. The final product is a 60 µl

elution of cfDNA with an average size ~170-200 bp. Quality and quantity of cfDNA will be evaluated with automated electrophoresis using either TapeStation with High Sensitivity D1000 ScreenTape and Reagents (Agilent Technologies) or Fragment Analyzer with High Sensitivity genomic DNA Analysis Kit (Advanced Analytical).

The resulting cfDNA can then be further analyzed to detect and quantify amounts of tumor driver oncogenes (BRAF mutations, RAS mutations, etc…) or other gene mutations if appropriate. These cfDNA results will be analyzed in an exploratory/descriptive manner.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

	Pre-Study[f]	Cycle 1 Week 1[t]	Cycle 1 Week 3	Cycle 2+ Week 1[u]	Off Study[l]
Durvalumab[a]		X		X	
Adherence to low iodine diet			X[h]		
Thyrogen			X[i]		
100 mCi (+/- 10 mCi) ^{131}I (RAI)			X[i]		
Concurrent meds	X	X	X	X	X
Physical exam	X	X[g]	X	X	X
Vital signs (pulse, blood pressure)	X	X[g]	X	X	X
Weight	X	X[g]	X	X	X
Performance status	X	X[g]	X	X	X
EKG[s]	X		X		
Hematology tests[b]	X	X[g]	X[j]	X	X
Clinical chemistry tests[b]	X	X[g]	X[j]	X	X
Urinalysis[b]	X	X[g]		X	
TSH, TG, and antibody serologies for TG, TPO, TSHR[r]		X	X[r]	X	X
Beta-HCG (serum or urine)	X[c]		X[k]		
Research peripheral blood collection[o]		X	X	X[p]	X[p]
DLT Monitoring[d]		X---------- X			
Adverse event evaluation		X---------- (Monitored for 90 days following the last dose of durvalumab.)			---------- X
Radiologic evaluation (CT(s) and/or MRI(s)) for tumor measurements[e] NO IODINATED CONTRAST IS ALLOWED PRIOR TO RAI ADMINISTRATION	X	CT and/or MRI will be performed every 8 weeks (+/- 1 week) (or approximately every 2 cycles). After 6 months, scans will be performed every 12 weeks (+/- 1 week)(or approximately every 3 cycles). Objective responses should be confirmed with a second assessment performed at least 4 weeks later. Iodinated contrast may be used after RAI has been administered.			
Research blood draw[m]	X				
Research tumor biopsy[n]	X	X[n]			
Archival tissue collection[q]	X				

a: 1500 mg IV durvalumab will be administered during week 1 of every cycle. Dose adjustment is required for patients weighing <30 kg as detailed in Appendix 2. Patients will remain on durvalumab treatment until there is confirmed progression of disease, unacceptable toxicity, withdrawal of consent, or if the study physician feels removal from the study is in the patient's best interest. One exception to these discontinuation rules: given the potential for delayed responses following short periods of disease progression with immunotherapy, subjects may continue to receive therapy beyond radiographic progression if the investigator concludes that the subject is tolerating study drug and continued therapy may provide clinical benefit. If a dose of durvalumab is missed or held for unforeseen scheduling conflicts (e.g. extreme weather related issues, etc…), medical issues unrelated to study drug toxicities, or patient's personal conflicts (e.g. personal travel, holidays, etc…), durvalumab may be restarted at the investigator's discretion. The week that durvalumab dose is restarted will be considered Week 1; subsequent treatments/evaluations may then be scheduled accordingly.

b: For components of the hematology tests, see Table 1 below. For components of the clinical chemistry test, see Table 2 below. For components of the urinalysis, see Table 3 below.

c: Serum or urine Beta-hcg (for women of childbearing potential): for pre-study evaluation, this should be obtained within 7 days of starting the study.

d: The DLT monitoring period will be 6 weeks beginning from the first durvalumab dose.

e: The treating physician may reschedule radiology scans due to treatment delays at his or her discretion. If the patient has CT and/or MRI scans completed early for any reason (i.e. suspicion of disease progression), the next set of scans may be ordered in 8 weeks (+/- 1 week) from that assessment (or in 12 weeks (+/- 1 week) for patients who are on treatment for more than 6 months).

f: All Pre-Study evaluations must be done within 4 weeks prior to the start of durvalumab unless otherwise specified.

g: These Week 1 evaluations may be performed up to 7 days prior to starting treatment. It is unnecessary to repeat these laboratory tests if the screening assessments of the same tests were performed within 7 days prior to the first dose of therapy.

h: Patients should start a low iodine diet for 5 days prior to the first Thyrogen injection, and maintain the diet through 1 day after RAI is given.

i: 0.9 mg Thyrogen will be administered intramuscularly in 2 consecutive calendar days. RAI is administered the calendar day after the second Thyrogen injection. Performance of a post-RAI whole body scan will be done as per standard of care per investigator discretion. The administration of these agents and evaluations will be performed in clinic. **If modification of durvalumab dose schedule is required prior to RAI therapy, a delay in the schedule of Thyrogen and RAI administration is allowed as long as it is given prior to the second durvalumab dose.**

j: These laboratory tests preferably will be performed prior to the first Thyrogen injection (not required).

k: Serum or urine beta-hcg (for women of childbearing potential) is to be completed within 2 days prior to administration of RAI.

l: Off-study evaluation will be performed within 30 days of the patient's last dose of durvalumab.

m: The research blood sample can be obtained any time (for germline DNA).

n: Radiologic guidance (CT, MRI or ultrasound guided) approaches and obtaining multiple cores to ensure sufficient biopsy material (at least 3 cores preferred) are allowed as long as it is considered safe for the patient (image-guided biopsies will be performed by a radiology physician with the appropriate expertise). The first research biopsy will be performed any time prior to Week 1 Day 1; the second research biopsy will preferably be conducted during Cycle 2, Week 3 or 4 (though alternate timing during Cycle 2 or later is allowed per investigator discretion or for safety reasons related to RAI administration).

o: Peripheral blood samples will be collected for peripheral T cell analysis as well as cfDNA analysis. For peripheral T cells, blood will be collected in 4 CPT tubes (BD, 8-ml capacity, total blood volume collected~32 ml for PBMC purification for flow cytometric analysis) and 1 PAXgene tube (BD order #762165 or equivalent) (for purification of RNA/DNA for TCR analysis). For cfDNA analysis, blood will be collected in 10-ml Cell-Free DNA BCT tubes (STRECK). These blood samples (peripheral T cells and cfDNA) will be collected Cycle 1/Week 1 (prior to durvalumab). In Cycle 1/Week 3 or 4, only the cfDNA sample will be drawn at various time points: on the day of first Thyrogen injection (but prior to Thyrogen injection) and on the day of RAI administration (but prior to RAI ingestion) .

p: Research blood collection (for peripheral T cell analysis and cfDNA analysis) after Cycle 1 will be conducted on Week 1 of Cycles 2, 3, and 4 (preferably prior to durvalumab administration, if possible), as well as Off Study. Cycle 2 cfDNA collection does not have to be performed if it the Principle Investigator decides that it is redundant given the cfDNA collections performed for **footnote o**.

q: Confirm availability of archival tumor tissue (if tissue is not already available at MSK, physical receipt of tissue is not required for study enrollment or initiation).

r: TSH, thyroglobulin (TG), and antibody serologies for TG, thyroperoxidase (TPO), and TSH receptor (TSHR) will be drawn Cycle 1/Week 1 (prior to durvalumab). In Cycle 1/Week 3, TSH and TG will be drawn at various time points: on the day of first Thyrogen injection (but prior to Thyrogen injection) and on the day of RAI administration (but prior to RAI ingestion). Subsequently, TSH and TG will be drawn on Week 1 of every cycle. Additionally, antibody serologies for TG, TPO, TSHR will be required to be drawn on Week 1 of every even numbered cycle, up to and including Cycle 6.

s. EKG will be performed in triplicate. Repeat the EKG in Cycle 1 (Week 3)(only 1 EKG required at that time point).

t. If Cycle 1 Week 1 labs fall below screening requirements, the patient can start treatment at the discretion of the treating investigator if safety is not compromised.

u. Week 1 evaluations/tests and research collections during Cycles 2 and beyond may be performed up to 3 days prior to the patient being treated.

NOTE: Timing/scheduling of the administration of Thyrogen, RAI, and subsequent durvalumab doses beyond the first one, as well as the requisite evaluations listed in the calendar, may be rescheduled at different days due to delays related to durvalumab toxicity, holiday schedules, patients' personal commitments or conflicts.

Table 1. Hematology Laboratory Tests

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

Table 2. Clinical chemistry (Serum or Plasma) Laboratory Tests

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

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

Table 3. 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.

11.1 TOXICITIES/SIDE EFFECTS

For adverse events (AEs) that are considered related to administration of durvalumab, the following may be applied:

- Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (see **Appendix 1**). Dose reductions are not permitted.
- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care according to guidelines outlined in **Appendix 1**.
- If modification of durvalumab treatment is required prior to the administration of RAI, delay in giving Thyrogen and RAI therapy prior to the second dose of durvalumab is allowed if the patient remains on study.
- In addition, there are certain circumstances in which durvalumab should be permanently discontinued.
- Cycle 2 and 3 doses of durvalumab will not be held for hematologic cytopenias (leukopenia, anemia, neutropenia, thrombocytopenia), which can occur following RAI therapy.
- Re-starting of durvalumab administration after holding therapy for toxicity can be done at the investigator's discretion as long as criteria in **Appendix 1** are fulfilled. The week that durvalumab is re-started will then considered to be Week 1. Subsequent treatments and evaluations can then be scheduled accordingly.

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

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions related to durvalumab are detailed in Appendix 1. In addition, management guidelines for adverse events of special interest **(AESIs) are detailed in Appendix 1. All toxicities will be** graded according to NCI CTCAE v4.0.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Please refer to Section 10 regarding the timing of tumor measurement assessments.

Documentation (radiologic) must be provided for patients removed from study for progressive disease (not necessary if removed based on criteria for clinical progression).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (uni dimensional

measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there has been demonstrated progression in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in 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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

'Cystic lesions' thought to represent cystic metastases can be considered as 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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that 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 which can be measured reproducibly should be selected. 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 diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the

presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

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

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If 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 in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

Ultrasound Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

12.4 Response Criteria

12.4.1 Evaluation of 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 the diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis). Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR

Any	PD***	Yes or No	PD
Any	Any	Yes	PD

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: 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 the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

13.1 CRITERIA FOR REMOVAL FROM STUDY

- Disease progression.
- Development of unacceptable toxicity.
- Participants can be removed from the study at any time if the study doctor feels that it is in their best interest to do so.
- Patients may withdraw consent from the study at any time.

Treatment Beyond Progression

Given the potential for delayed responses following short periods of disease progression with immunotherapy, subjects may continue to receive therapy beyond radiographic progression if the investigator concludes that the subject is tolerating study drug and continued therapy may provide clinical benefit.

If treatment is continued beyond initial evidence of radiographic progression, study therapy should be discontinued if further evidence of progression is subsequently observed, defined as an additional 10% or greater increase in tumor burden (by RECIST v1.1 criteria) from time of initial progression (including all target lesions and new measureable lesions).

14.0 BIOSTATISTICS

The primary objective of this pilot study will be to assess the safety of administering durvalumab in combination with Thyrogen-stimulated RAI therapy in patients with recurrent/metastatic thyroid cancer. The period of dose limiting toxicity (DLT) monitoring will be 6 weeks beginning from the first durvalumab dose. Definitions for DLT are in Section 9.3. Subjects who are removed from the study for reasons other than DLT prior to the administration of the first Thyrogen injection will be replaced with another subject. Patients who do not complete the 6 week period of monitoring beginning from the first durvalumab dose for reasons other than DLT will also be replaced. If >1 of the first 3 patients, or >2 of the first 6 patients, develop DLT related to durvalumab, further accrual to the study will be halted. If this rule is not met, we plan to accrue 11 patients in total to this pilot study (see table below). All toxicities will be graded according to CTCAE v4.0.

Number of DLTs to stop in first **3** patients	Number of DLTs to stop in first **6** patients	Number of DLTs to stop in all **11** patients	Acceptable toxicity rate (H0)	Unacceptable toxicity rate (H1)	Type I error rate	Power
>1	>2	>2	0.10	0.35	0.101184466	0.80748277

Secondary objectives will be determining the best overall response rate (BOR; CRs plus PRs per RECIST v1.1 criteria) and progression-free survival (estimated using Kaplan-Meier methodology with time origin at the start of the treatment; PFS). For PFS, patients will be followed until progression of disease or death, whichever come first. Patients who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression, and are subsequently removed from study within the

next radiographic assessment for progression, will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

Exploratory objectives:

Mutation burden, neoantigen landscape, and immunoediting analysis: While the low DTC mutation burden implies a low likelihood of neoantigen formation, neoantigen analysis has never been conducted for DTC. Whole-exome sequencing data will be analyzed using the neoepitope bioinformatics pipeline developed by Dr. Chan's group. Mutation calling is performed by analyzing FASTQ files with four mutation callers and filtering by allelic frequency, call quality and other empiric measures. Mutations are validated with an orthogonal next-gen sequencing panel. Candidate neoantigens are identified based on peptide sequences and predicted binding to patient-specific MHC Class I alleles. RNAseq data will be used to define a set of expressed neoepitopes and explore gene expression signatures that may correlate with response. Evolution of the mutation, neoantigen, and gene expression landscape in pre- and post-treatment samples will be analyzed to gain insights into immunoediting that may occur and infer what epitopes may be critical for efficacy. RNAseq data will also be used to explore changes in the expression of nonmutated thyroid gene expression (TG, THSR, TPO, etc…) with therapy for the same purpose. Biostatistical analysis: Categorical pre- and post-treatment measures will be summarized by 2-by-2 tables; continuous pre- and post-treatment measures will be summarized by mean and standard deviation of the change as well as graphical method.

Immune cell infiltrate and immunologic gene signature analysis: Tumor RNAseq data will be used to analyze changes in (a) immune cell infiltration and (b) immunologic gene signatures with therapy. First, we will estimate the relative infiltration levels of individual immune cell populations in tumor samples using two computational approaches. The first was developed by Yasin Senbabaoglu and Chris Sander at MSK which uses single set enrichment analysis (ssGSEA) to determine the abundance of T cell and other immune cell populations in the tumor microenvironment[32]. A related but alternative approach uses support vector regression to model cellular populations based on a reference expression matrix[33]. These techniques provide efficient and accurate alternatives to flow cytometry sorting. In addition, RNAseq data permits quantification of related immunologic gene expression signatures such as IFNγ signaling, granzyme B, and antigen presenting machinery genes.

Intratumor heterogeneity analysis: Recently we have developed a technique to characterize the intratumor genetic heterogeneity of tumors based on sequencing data[32]. Using copy number and mutational data, our computational pipeline infers subclonal populations in tumors. Here, we propose to characterize the evolution of tumors under the selective pressure of rhTSH-stimulated RAI and durvalumab treatment, and examine subclonal expansions that are associated with an immune escape phenotype, by comparing the subclonal architecture of pre- and post-treatment samples.

PBMCs: In addition to the research biopsies, peripheral blood samples will be collected serially for flow cytometry to evaluate changes in T cell subsets at different time points of therapy. *Biostatistical analysis:* Proportions of T cell subsets will be summarized at each time point and plotted to reveal any trend.

cfDNA: Collected cfDNA will be analyzed to detect and quantify total cfDNA and the amounts of tumor driver oncogenes (BRAF mutations, RAS mutations, etc…) or other gene mutations present

as appropriate. *Biostatistical analysis:* Changes in these parameters that occur with therapy will be analyzed by graphical method.

Accrual to the trial is anticipated to be approximately 1 patient per month.

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

Not applicable.

16.1 DATA MANAGEMENT ISSUES

A 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 coordinating the activities of the protocol study team.

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

16.2 Quality Assurance

Weekly registration reports will 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 and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: *http://www.cancer.gov/clinicaltrials/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:

https://one.mskcc.org/sites/pub/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 is assessed for the 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

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority is already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

Risks, Benefits, Toxicities/side effects

Potential risks to human subjects include drug related toxicity, placement of IV catheters, phlebotomy, and possible psychological discomfort from the stresses associated with obtaining imaging studies (e.g., CT scan, PET scan). 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 on 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 also recorded.

Alternatives/options

Participation in this trial is voluntary. Depending on the specific details of the situation, patient options without being in a study might include:

- Other palliative chemotherapy off study.
- Participation in a different clinical trial
- Best supportive care

Financial Costs/Burdens

The patient will be responsible for all costs related to treatment and complications of treatment. Costs to the patient (third party insurer) will include hospitalizations, routine blood tests and diagnostic studies, office visits, baseline EKG, Thyrogen, RAI (^{131}I) and doctor's fees. Patients will

not be charged the cost of analysis for the research correlates. The patient also will not be charged for the subsequent research analysis of these specimens. Durvalumab is provided by AstraZeneca and therefore is not billable to research participants.

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 starts investigational treatment/intervention. 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.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or a procedure (i.e., a screening biopsy) must be reported.

All SAEs must eb submitted in PIMS. If an SAE requires submission to the HRPP 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. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event

- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- 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

For IND/IDE protocols:
The SAE report should be completed as per above instructions. If appropriate, the report will the forwarded to the FDA by the IND office.

17.2.1 SAE reporting for Sponsor

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

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

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

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-15-11685)

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

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

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

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

17.2.2 Definition of adverse events of special interest (AESI)

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

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

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

AESIs observed with durvalumab include:

- Pneumonitis
- Hepatic events (ALT/AST increases / hepatitis / hepatotoxicity)
- Colitis/diarrhea
- Intestinal perforation
- Endocrinopathies (i.e. events of hyper- and hypothyroidism, adrenal insufficiency, hypophysitis, hypopituitarism, and Type 1 diabetes mellitus)
- Nephritis
- Rash/dermatitis
- Myocarditis
- Myositis/polymyositis
- Pancreatic events (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)
- Rare or less frequenst AESIs and imAEs (i.e. pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hemaetological, rheumatological events, vasculitis, non-infectious meningitis, and non-infectious encephalitis)

- Infusion related/hypersensitivity reactions (includes cytokine release syndrome, and immune-complex disease)
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Renal events

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs (Topalian et al, NEJM 2012). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Appendix 1.

Hypersensitivity Reactions

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

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Appendix 1.

Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies. Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Appendix I.

Cases where a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving durvalumab are provided in Appendix 1.

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix 1. Hypothyroidism on this study will not be considered an AESI.

Pancreatic disorders

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

Neurotoxicity

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

Nephritis

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

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

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

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.

Other events requiring reporting

Overdose

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

Any overdose of a study subject with durvalumab, 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 (see Section 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 17.2). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

Hepatic function abnormality

Hepatic function abnormality (as defined in Section 17.2.2) 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 (see Section 10.3.2 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

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

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

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

Pregnancy

Maternal exposure

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

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

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

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

The same timelines apply when outcome information is available.

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.

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

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

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.

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20.1 APPENDICES

Appendix 1: Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy

Appendix 2: Durvalumab Dose Calculations

APPENDIX 1: Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-Related, and Non Immune-mediated Reactions related to Durvalumab Monotherapy

Appendix 1 Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy 1 November 2017 Version

General Considerations

Dose Modifications

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

Grade 1 No dose modification

Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.

If toxicity worsens, then treat as Grade 3 or Grade 4.

Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper.

Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:

1. The event stabilizes and is controlled.
2. The patient is clinically stable as per Investigator or treating physician's clinical judgement.
3. Doses of prednisone are at ≤10 mg/day or equivalent.

Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.

Grade 4 Permanently discontinue study drug/study regimen.

Toxicity Management

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 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.
- With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP,

Appendix 1 Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion-Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy 1 November 2017 Version

General Considerations

Dose Modifications	Toxicity Management
Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: 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).	formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

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

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 perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.

diagnostic observations only)		
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 baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indi-cated, peritoneal signs; Grade 4 colitis: life-threatening	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not 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.	– – –

	consequences, urgent intervention indicated)		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. **Infliximabshould 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)	**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	**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.,

	(Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	• 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 alternative cause.[b] **For Grade 4:** Permanently discontinue study drug/study regimen.	mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximabshould 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]
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	**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

of either **increasing bilirubin or signs of DILI/liver decompensation**			– 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. **Infliximabshould NOT be used.**
	Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal 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	**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

	(Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	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]	– 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. **Infliximabshould 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 isolatedbut (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 instructedfor Grade 2 transaminase rise** - **Manage dosing for Grade 2 transaminase rise as instructedfor 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 to 1.5 × baseline; > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [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/studyregimen after completion of steroid taper.	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:**	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

		Permanently discontinue study drug/study regimen.	– 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.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 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.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism 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	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.

		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.	– 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.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization.

		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.	– 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	**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

		insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	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	No dose modifications required unless clinical suspicion is	**For Grade 1 (no definitive findings):**

(asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)	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.	- Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.	
Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IVmethylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [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; limiting self-care ADLs)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IVmethylprednisolone 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-stimulatinghormone; 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 clinicallysignificant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/studyregimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/studyregimen 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 studydrug/studyregimen administration. Otherwise, discontinue study drug/studyregimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue studydrug/studyregimen (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: Durvalumab Dose Calculations

Durvalumab Dosing

The durvalumab dosing should be done depending on subject weight (if subject is < 30kg)):

1. Cohort dose: X mg/kg

2. Subject weight: Y kg

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

4. Dose to be added into infusion bag:

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

where 50 mg/mL is durvalumab nominal concentration

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

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

Number of vials = Dose (mL) / 10 (mL/vial)

Example:

1. Cohort dose: 10 mg/kg

2. Subject weight: 30 kg

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

4. Dose to be added into infusion bag:

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

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

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