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**Title:** A Pilot Study of Immune Checkpoint Inhibition (Durvalumab with or without Tremelimumab) in Combination with Radiation Therapy in Patients with Unresectable Pancreatic Cancer.

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Investigational Agents:

| Drug Name: | Tremelimumab | Durvalumab (MEDI4736) |
|---|---|---|
| IND Number: | 123518 | 123518 |
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| Manufacturer: | MedImmune, Inc. | MedImmune, Inc. |

## PRÉCIS

### Background:

- Tremelimumab is a monoclonal antibody against CTLA4. Anti-CTLA4 therapy has been shown to enhance anti-tumor immunity by blocking tumor-induced immune suppression of cytotoxic T cells.
- Durvalumab is a human monoclonal antibody directed against PD-L1. Blockage of ligation between PD-L1 and PD1 induces local immune activation and prevent anergy and exhaustion of effectors T-cells.
- Several studies have documented an increase in peripheral antitumor immunity following radiation. This effect is evidently too weak to be clinically relevant, but has the potential to be boosted by immune modulation.
- The underlying hypothesis of this study is that the effect of Immune Checkpoint inhibitor (Durvalumab with or without Tremelimumab) treatment can be enhanced by radiation in patients with advanced pancreatic carcinoma.

### Objective:

- To determine the safety, tolerability and feasibility of immune checkpoint inhibition [comprising either Durvalumab alone, or combined Durvalumab and Tremelimumab] in combination with stereotactic body radiation therapy (SBRT) in patients with unresectable pancreatic cancer.

### Eligibility:

- Histologically confirmed metastatic pancreatic cancer with primary in-situ (or locally-recurrent) with at least 1 measurable metastatic lesion by RECIST 1.1 criteria and accessible for biopsy. There is no limit to the number of prior chemotherapy regimens received.
- Patients must be $\geq$ 18 years of age and have a performance status (ECOG) $\leq$ 1
- Life expectancy of greater than 3 months.
- Acceptable organ and bone marrow function.
- Patients must not have had standard of care chemotherapy, radiotherapy, or major surgery within the last 2 weeks prior to entering the study. For recent experimental therapies, a 28 day period of time must have elapsed before commencing protocol treatment.
- No active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel disease; Wegner syndrome; Hashimoto syndrome; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc.) within the past 3 years prior to the start of treatment.
- No active or history of inflammatory bowel disease (colitis, Crohn's), irritable bowel disease, celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea. No active or history of systemic lupus erythematosus, Wegener's granulomatosis.

**Design:**

- Subjects will be assigned to 4 arms:
  - Anti-PDL1 (Durvalumab) in combination with radiation (8 Gy in 1 fraction)
  - Anti-PDL1 (Durvalumab) in combination with radiation (5 Gy in 5 fractions)
  - Anti-PDL1 (Durvalumab) and anti-CTLA4 (Tremelimumab) in combination with radiation (8 Gy in 1 fraction)
  - Anti-PDL1 (Durvalumab) and anti-CTLA4 (Tremelimumab) in combination with radiation (5 Gy in 5 fractions).

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# 1 INTRODUCTION

## 1.1 STUDY OBJECTIVES

### 1.1.1 Primary

- To determine the safety, tolerability and feasibility of immune checkpoint inhibition comprising either Durvalumab alone or combined Durvalumab and Tremelimumab in combination with stereotactic body radiation therapy (SBRT) in patients with unresectable pancreatic cancer.

### 1.1.2 Secondary

- To characterize the plasma pharmacokinetic (PK) parameters of immune checkpoint inhibition in combination with stereotactic body radiation therapy (SBRT) in patients with pancreatic cancer.
- To evaluate the 6-month overall survival rate and overall survival in patients with unresectable pancreatic cancer treated with immune checkpoint inhibition and radiation therapy relative to (1) the type of immune checkpoint inhibition and (2) quantity of radiation administered.
- To estimate overall response rate (ORR) and progression free survival (PFS) by modified immune-related Response criteria (irRC) and Response evaluation criteria in solid tumors RECIST 1.1.
- To estimate median time to progression as calculated by irRC and RECIST 1.1 in patients who progress, and duration of response in patients with unresectable pancreatic cancer during and following treatment with immune checkpoint inhibition in combination with stereotactic body radiation therapy (SBRT).
- To evaluate the 6-month, 12 month and overall survival in patients with unresectable pancreatic cancer treated with immune checkpoint inhibition and 5x5 radiation therapy (Arm C2).

### 1.1.3 Exploratory

- To measure changes in immune parameters in the peripheral blood and tumors in patients with advanced pancreatic cancer treated with immune checkpoint inhibition and radiation therapy relative to (1) the type of immune checkpoint inhibition and (2) quantity of radiation administered.

## 1.2 BACKGROUND AND RATIONALE

### 1.2.1 Pancreatic cancer and the current therapeutic paradigm

Gemcitabine was established as a cornerstone drug in pancreatic cancer in 1997 following a phase III study which demonstrated an improvement in clinical benefit - a composite measure of clinical improvement based on three factors: pain, performance status, and weight change - and

survival (a secondary endpoint in the study) compared to 5-fluorouracil (5-FU) in patients with advanced untreated pancreatic cancer. More patients treated with gemcitabine had an improvement in clinical benefit response compared to those treated with 5-FU (23.8% versus 4.8%; P = 0.0022). There were also (modest) gains in survival (median survival 5.65 versus 4.41; P = 0.0025 and 1-year survival 18% versus 2% in favor of gemcitabine). No confirmed objective tumor responses were observed. Once gemcitabine became the drug of choice in this disease, various agents were combined with it in an attempt to build on its modest efficacy. Cytotoxic combinations of gemcitabine with capecitabine and platinum agents do appear to offer a small benefit, particularly in patients with good performance status but this benefit has not been shown to be statistically significant.

The first trial to show a survival benefit for any combination therapy in pancreas cancer and which led to FDA approval of this combination in the front-line treatment of pancreas cancer in 2005 was a study by Moore et al., in which 569 patients with untreated locally advanced or metastatic pancreas cancer were randomized to receive gemcitabine with either erlotinib or placebo[1]. There was a very modest but statistically significant improvement in progression-free (HR .77, 95% CI, .64-.92; P=.004), one-year survival (23% v 17%; P=.023) and median overall survival (6.24 months v 5.91 months, HR .82, 95% CI, .69-.99; P=.038) favoring the erlotinib arm.

In 2011 the standard of care initial management for patients with good performance status changed with the publication of a phase III trial comparing gemcitabine with an intensive polychemotherapy regimen combining oxaliplatin, irinotecan and 5-FU/leucovorin (FOLFIRINOX). Although there was increased toxicity with the experimental regimen it was associated with an impressive response rate (31.6% v 9.4%) and survival advantage (11.1 v 6.8 months) compared with gemcitabine. Despite this development there remains an unmet need for effective treatments in this disease.

### 1.2.2 Radiation treatment in pancreatic cancer:

Traditionally, radiation has been employed in the management of all stages of pancreatic cancer – adjuvant, locally advanced (LAPC) and metastatic. The efficacy of radiation in each situation is a matter of controversy given an increasing awareness of the systemic biology and the efficacy data are summarized below. Nevertheless, issues related to locally recurrent or progressive disease are a very common occurrence in pancreatic cancer given its location and an important cause of morbidity. Patients who have pain related to the loco-regional extent of their disease, derive a definite palliative benefit with the use of chemoradiation[2].

The foothold of chemoradiation for LAPC – perhaps the setting in which it is most commonly used – was established on the basis of a number of small clinical trials stretching back to the 1960's. Two of these studies demonstrated a survival benefit for (5-fluorouracil based) chemoradiation compared to radiotherapy alone[3, 4]. Two other studies from the same era compared chemotherapy alone to chemoradiation. In a trial by the GITSG a benefit was demonstrated for chemoradiation plus chemotherapy compared to chemotherapy alone[5]. The chemotherapy consisted of streptozocin, mitomycin and 5-FU and the 1-year survival benefit was 41% compared to 19%. The other trial, by the Eastern Cooperative Oncology Group (ECOG), compared 5FU-chemoradiation with chemotherapy alone, failing to demonstrate a survival benefit[6]. The value of chemoradiation in LAPC has not been quantified in the modern

clinical trial era. In an attempt to address this question in the era of gemcitabine a phase III study was performed by the FFCD – SFRO (Fédération Francophone de Cancérologie Digestive - Société Française de Radiothérapie Oncologique) in France[7, 8]. In this study, the first for nearly 20 years to address this question, 119 patients (of a planned 176) were randomized to undergo induction chemoradiation (with 5-FU 300 mg/m$^2$/24 h as a continuous infusion, day 1–5 every week and cisplatin, 20 mg/m$^2$/d, day 1–5 at week 1 and 5) followed by gemcitabine, or straight to chemotherapy with gemcitabine. The study was stopped prior to its full enrollment due to an inferior survival in the chemoradiation group (median survival 8.6 v 13 months, p = 0.014). Although this study is not a definitive answer to the question of chemoradiation, it does add to the growing body of opinion that the benefit of chemoradiation in LAPC is most likely confined to a carefully selected subgroup. Recently a similar study was presented comparing gemcitabine alone (1,000 mg/m$^2$ weekly x 3 every 4 weeks for 7 cycles) to chemoradiation (RT 50.4 GY in 28 fractions plus gemcitabine 600 mg/m$^2$ weekly x 6) followed by 5 cycles of gemcitabine alone (1,000 mg/m$^2$ weekly x 3 every 4 wks.)[9]. The trial was stopped early due to slow accrual (N = 74, out of a planned 316). The median survivals were 9.2 months (95% CI 7.8 - 11.4) and 11.0 months (95% CI 8.4 - 15.5) for the two arms respectively (p=0.044).

In an interesting attempt to tease out the benefit of chemoradiation, investigators from the Groupe Coordinateur Multidisciplinaire en Oncologie (GERCOR) performed a retrospective analysis of 181 patients with locally advanced PAC who had been entered on prior prospective GERCOR studies and who had been offered chemoradiation (at the discretion of the investigator), but only if they had remained metastasis-free after a 3-month period[10]. For those patients who were metastasis-free after initial chemotherapy, there was a survival advantage if they proceeded to chemoradiation compared to those who continued with chemotherapy alone (median OS 15.0 and 11.7 months, respectively; $P$ = .0009). These data suggest that radiation may offer a survival benefit in selected patients who have disease that is proven to be localized after a test of time. This is an attractive concept as it allows patients to be selected for chemoradiation whilst receiving systemic therapy for their disease and also gives time for the logistics of the chemoradiation to be organized. The underlying principle is that patients who progress systemically prior to chemoradiation would in all likelihood not have derived a survival benefit from chemoradiation anyway and is in manner analogous to patients who develop disease progression during neoadjuvant therapy for resectable disease, who would presumably not have benefitted from surgery had it gone ahead.

The same investigators have performed a prospective phase II study based on the same concept, i.e. induction chemotherapy (with gemcitabine and oxaliplatin) for a 2-month period, followed by chemoradiation if the patient has remained metastasis-free[11]. In this study fifteen percent of patients did not go on to receive chemoradiation, which is lower than the 29% rate described in their earlier report. The authors speculate that this may have been due to the shorter period of induction (2 v 3 months) and the lower amount of chemotherapy administered. The median overall survival achieved in this study was 12.2 months which is in the upper level of the survival rate range reported for patients with LAPC. Of course, this attractive concept needs to be assessed definitively and a phase III randomized study is currently being performed by the same group.

In our proposed study, we are proposing the use of radiation in a patient population who (metastatic pancreatic cancer) who may not otherwise receive it. Given the proportion of patients

with this disease who go on to develop local symptoms we believe that this alone justifies its inclusion as part of the therapeutic regimen. Whilst the traditional RT schedule for this disease has been over a prolonged course and in combination with a chemotherapeutic (5FU or gemcitabine) as radiosensitizer, modern RT techniques allow for a hypofractionated course without chemotherapy. This will minimize the duration of RT and will make it easier to combine with anti-CTLA4 treatment. Stereotactic body radiation therapy (SBRT) has been shown to be safe and effective in locally-advanced pancreatic cancer[12].

### 1.2.3 Recent advances in immune-based approaches in solid tumor malignancies

The past two years have seen progress for immune-based approaches in solid tumor malignancies, with FDA approvals for these approaches in prostate cancer and melanoma[13-15]. In melanoma, anti-CTLA4 therapy has been shown to demonstrate a median survival benefit in two separate phases 3 studies, both of which were associated with long-term disease control in approximately one-fifth of patients. More recently, anti-PD-L1 therapy has demonstrated a similar degree of clinical activity not only in melanoma and kidney cancer but also in lung cancer, a disease type previously thought to be refractory to an immune approach[16]. Appreciation of the role in developing tumors of immune-evasion has also been evidenced by its inclusion as one of the (updated) hallmarks of cancer[17].

Both anti-PD-L1 and anti-CTLA4 therapy enhance anti-tumor immunity by blocking tumor induced immune suppression of cytotoxic T cells and therefore exaggerating the immune activation that must first occur of its own accord and is thought to be the result of tumor neo-antigens formed as a tumor progresses. The role of CTLA4 and anti-PD-L1 in inhibiting T-cell activation is represented in the schematic in **Figure 1** below.

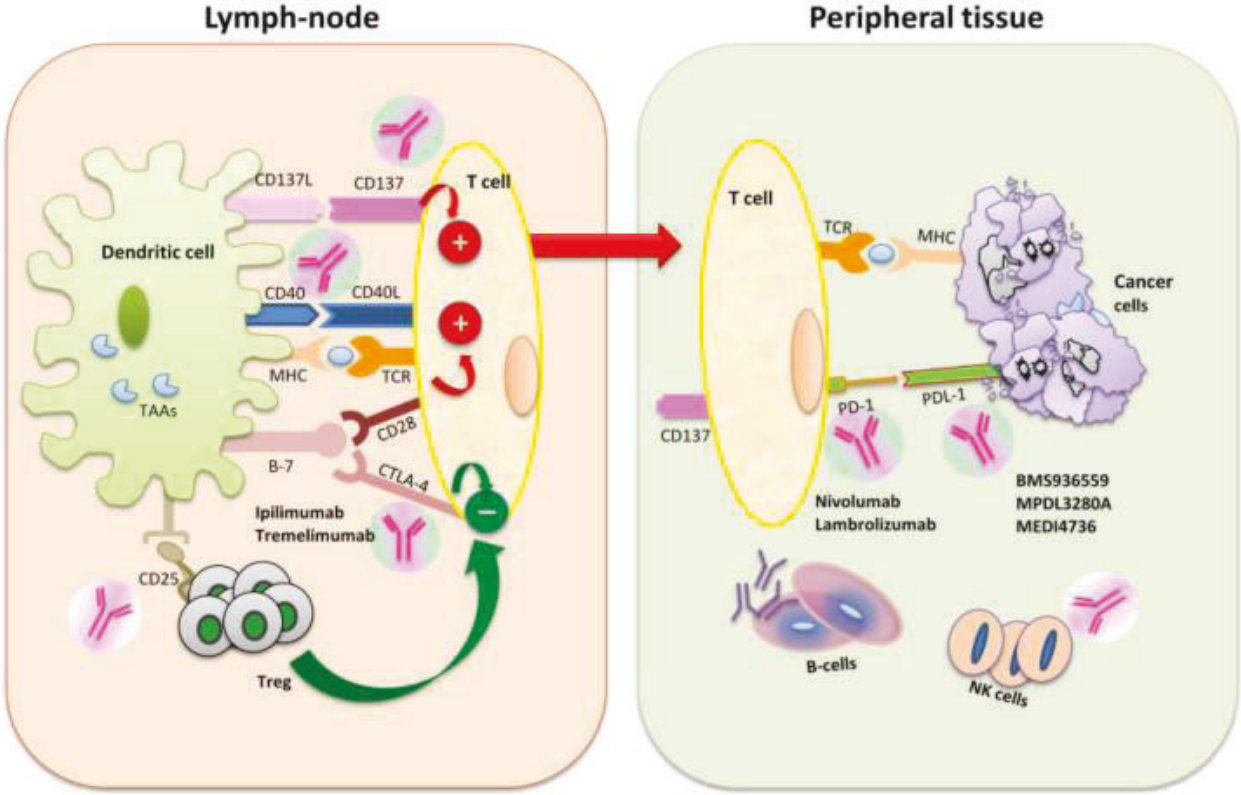


**Figure 1 CTLA-4 and PD-1/PD-L1 are negative regulators of T cell activity in lymphoid tissues and tumor microenvironment respectively. Anti-CTLA-4 antibodies, such as ipilimumab and tremelimumab, block CTLA4 and, thereby, results in activation of T-cells. Blockade with antibodies of PD-1 or PD-L1 (e.g., nivolumab and Durvalumab) augments immune response in peripheral tissues. (Gelao. Toxins 2014[18])**

CTLA4-mediated immune checkpoint is induced in T cells at the time of their initial response to antigen. The level of CTLA4 induction depends on the amplitude of the initial T cell receptor (TCR)-mediated signaling. After the TCR is triggered by antigen encounter, CTLA4 is transported to the cell surface. The stronger the stimulation through the TCR (and CD28), the greater the amount of CTLA4 that is deposited on the T cell surface. Therefore, CTLA4 functions as a signal dampener to maintain a consistent level of T cell activation in the face of widely varying concentrations and affinities of ligand for the TCR. The PD-1/PD-L1 inhibitory receptor pathway plays an important role in modulating T-cell activity in the tumor microenvironment during the effector phase of immune response. PD-1 is a surface receptor member of the B7-CD28 superfamily. The ligation of PD-1 with PD-L1 causes the negative regulation of T-cells resulting in anergy, exhaustion and death of effector T-cells. Blockade with antibodies of PD-1 or PD-L1 (e.g., nivolumab and Durvalumab) results in the continuing activation of T-cells and enhances anti-tumor immune activity.

While these studies demonstrate the potential for anti-CTLA4 or anti PD1/PD-L1 therapy to enhance the anti-tumor immune response already in process, it clearly does not work in the majority of patients. The question is whether the initial immune activation stage can be enhanced. The potential for this was intriguingly demonstrated in a recent publication by Postow et al who reported a case of the so-called abscopal effect in a patient with melanoma treated with ipilimumab and radiotherapy[19]. Temporal associations were noted between tumor shrinkage and antibody responses to the cancer-testis antigen NY-ESO-1 in addition to changes in peripheral-blood immune cells, and increases in antibody responses to other antigens after a patient being treated with anti-CTLA4 was then treated with external beam radiotherapy. The enhanced effect from anti-CTLA4 seen after radiation appears to have been due to a boost effect of tumor cell death and immune stimulation following deliverance of a tumor antigen load. It is this enhanced effect we wish to study in the context of radiation treatment for pancreatic cancer.

### 1.2.4 Immune response following radiation, mechanism and rationale for combination with immune checkpoint inhibition:

Several studies have documented an increase in peripheral antitumor immunity following radiation. It may even be the case that an intact immune system is critical for RT to exert its maximal antitumor effect. This was suggested by a mouse model of melanoma in which single-fraction RT slowed the growth of small tumors in immune-competent but not immune-deficient mice[20]. The same authors also showed that in an animal model of breast cancer ablative RT of a primary tumor prevented the growth of metastatic tumor colonies in the lung, an effect that was dependent on the presence of CD8+ T cells. Other animal models have likewise displayed augmentation of systemic antitumor immunity following local RT[21-23].

The underlying mechanism appears to be that RT-induced necrosis results in the exposure of tumor antigens, thereby increasing the pool of intracellular peptides for cross-presentation[24]. Radiation has been shown to augment MHC-I expression by tumors, which is critical for antigen

recognition by cognate CD8+ TCRs and which is known to be diminished in tumors as one of their escape mechanisms[25]. Tumor antigen processing and presentation on MHC-I molecules is dependent on expression of a protein called high mobility group box 1 (HMGB-1), a "danger signal" which binds toll-like receptor 4 (TLR4) on dendritic cells. In a pivotal study Apetoh et al. demonstrated that RT causes dying tumor cells to release HMGB-1[26]. Intriguingly these authors also reported that in breast cancer patients undergoing radiation and chemotherapy the presence of a polymorphism in TLR4 – and by implication a less immunogenic drug-induced cell death – was associated with an inferior prognosis. Similarly, in esophageal cancer patients preoperative chemoradiation has been shown to increase cancer-specific T cell responses and serum levels of HMGB-1, the latter of which correlated with overall survival[27].

Despite this, only a few cases of spontaneous decrease of metastases following radiation – the so-called abscopal effect – have been reported[28-30]. This is presumably because the immune response by itself is too weak to be clinically significant. A number of studies have tried to boost this anti-tumor immune response following ablation by combining with an immunomodulatory agent:

- Zeng et al. tested the combination of anti-PD-1 immunotherapy with stereotactic radiosurgery in a glioblastoma model. Improved survival was demonstrated with the combination treatment compared with either modality alone. Long-term survival was seen only in the combined treatment arm, with a fraction (15%-40%) of animals alive at day 180+ after treatment. There was also increased tumor infiltration by cytotoxic T cells and decreased regulatory T cells in the combined treatment group compared with the single modality arms[31].
- Dewan et al. evaluated RT in combination with anti-CTLA-4 antibody in two separate mouse models of breast and colorectal carcinoma[32]. The authors found that the combination of anti-CTLA4 and RT achieved enhanced tumor response at the primary site (compared to either modality alone). in addition to an abscopal effect. (Interestingly this only occurred in fractionated versus single-dose RT). The frequency of CD8+ T cells showing tumor-specific IFN-gamma production was proportional to the abscopal effect.
- Demaria et al. tested the combination of RT with CTLA-4 blockade in a breast cancer model (4T1) known to be poorly immunogenic[33]. Anti-CTLA4 alone did not have any effect on primary tumor growth or survival. RT was able to delay the growth of the primary irradiated tumor, but in the absence of anti-CTLA4 survival was similar to that of control mice. In contrast, mice treated with RT + anti-CTLA4 had a statistically significant survival advantage. The increased survival correlated with inhibition of lung metastases formation and required CD8+.

### 1.2.5 Tremelimumab

Tremelimumab (formerly CP-675,206) is a human IgG2 mAb directed against CTLA-4. Upon T cell activation, CTLA-4 expression acts to dampen immune responses by CTLA-4 relocation to the cell surface in order to modulate and eventually switch off T cell activation.

Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T cell activation. The binding of CTLA-4 to its target ligands (B7.1 [CD80] and B7.2 [CD86]) provides a negative regulatory signal, which limits T cell activation. Blockade of B7 binding to CTLA-4 by anti-

CTLA-4 antibodies also results in markedly enhanced T cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins.

Anti-CTLA-4 therapy has recently been shown to be a validated approach to cancer treatment by the approval of the mAb ipilimumab in 2011 for the treatment of patients with metastatic melanoma, based on 2 Phase III studies that demonstrated a significant improvement on OS in the first- and second-line settings. In general, tumor response rates to anti-CTLA-4 therapy are low; approximately 10%, but the durable response or stable disease seen in a proportion of patients can lead to a significant prolongation of OS. In a large, single-arm Phase II

Tremelimumab trial in patients with advanced refractory and/or relapsed melanoma, objective responses (primary endpoint) following Tremelimumab 15 mg/kg Q3M were observed in 16 of 241 (6.6%) patients (95% CI: [3.84, 10.56]). Responses were durable (present at ≥6 months from enrollment) in all 16 responders. A Phase III, open-label, randomized study comparing Tremelimumab 15 mg/kg Q3M (Arm A) to either dacarbazine or temozolomide (Arm B) in patients with advanced melanoma was terminated following a pre-specified interim futility analysis. At the time of database lock, the median OS (primary endpoint) was 12.58 months in Arm A and 10.71 months in Arm B (HR=1.1416, p=0.1272).

The efficacy data for tremelimumab are consistent with those of the related – and FDA-approved- anti-CTLA-4 antibody ipilimumab: tumor response rates are generally low (approximately 10%) but the responses observed are generally durable. The ipilimumab melanoma data clearly demonstrate that a small proportion of patients with an objective response and a small impact on PFS rates can lead to a significant prolongation of OS, and support development of this class of agent in other tumors. Although Phase II and Phase III studies of tremelimumab in metastatic melanoma failed to meet the primary endpoints of response rate and OS, respectively, the data clearly indicate activity of tremelimumab in melanoma, with response rates and median OS similar to those observed in the ipilimumab trials.

Tremelimumab has been evaluated in a number of clinical studies – and over 1000 patients – and demonstrated manageable toxicities[34, 35]. The efficacy data for Tremelimumab are consistent with those of the related anti-CTLA-4 antibody ipilimumab: tumor response rates are generally low (approximately 10%) but the responses observed are generally durable. The ipilimumab melanoma data clearly demonstrate that a small proportion of patients with an objective response and a small impact on PFS rates can lead to a significant prolongation of OS, and support development of this class of agent in other tumors. Although Phase II and Phase III studies of Tremelimumab in metastatic melanoma failed to meet the primary endpoints of response rate and OS, respectively, the data clearly indicate activity of Tremelimumab in melanoma, with response rates and median OS similar to those observed in the ipilimumab trials.

The AE profile of Tremelimumab is consistent with that of ipilimumab, and with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo, which appears to be confined to patients with melanoma). Events reported at a frequency of ≥5% and assessed by the investigator as related to treatment (listed in descending order of frequency) were diarrhea, rash, pruritus, fatigue, nausea, vomiting, anorexia, headache, abdominal pain, and colitis.

### 1.2.6 Anti-CTLA4 therapy in pancreatic cancer

A small number of studies have evaluated the strategy of anti-CTLA4 treatment in pancreatic cancer, though not in combination with radiation. Recently, Le et al evaluated ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in patients with previously treated pancreatic cancer[36]. Three patients treated with the combination had evidence of prolonged disease stabilization (31, 71, and 81 wk.) and 7 patients experienced CA19-9 declines. In 2 of these patients, disease stabilization occurred after an initial period of progression. The median overall survival (OS) (3.6 vs. 5.7 mo., hazards ratio: 0.51, P = 0.072) and 1 year OS (7 vs. 27%) favored the combination of vaccine plus anti-CTLA4. Similar to prior ipilimumab studies, 20% of patients in each arm had grade 3/4 immune-related adverse events. Among patients with OS > 4.3 months, there was an increase in the peak mesothelin-specific T cells (P = 0.014) and enhancement of the T-cell repertoire (P = 0.031) all of which suggested that checkpoint blockade in combination with GVAX has the potential for clinical benefit.

Investigators within NCI performed a phase II trial evaluating the efficacy of Ipilimumab for advanced pancreatic cancer. In that study subjects with locally advanced or metastatic pancreas adenocarcinoma with measurable disease, good performance status, and minimal comorbidities were treated with Ipilimumab (3.0 mg/kg every 3 wk.; 4 doses/course) for a maximum of 2 courses. Twenty-seven subjects were enrolled (metastatic disease: 20 and locally advanced: 7) with median age of 55 years (27 to 68 y) and good performance status (26 with Eastern Cooperative Oncology Group performance status =0 to 1). Three subjects experienced ≥ grade 3 immune-mediated adverse events (colitis:1, encephalitis:1, hypohysitis:1). There were no responders by response evaluation criteria in solid tumors criteria but one subject experienced a delayed response after initial progressive disease. In this subject, new metastases after 2 doses of Ipilimumab established progressive disease, but continued administration of the agent per protocol resulted in significant delayed regression of the primary lesion and 20 hepatic metastases. This was reflected in tumor markers normalization, and clinically significant improvement in performance status. Overall the experience in this study suggests that while single agent Ipilimumab at low, (3 mg/kg) dose was ineffective for the treatment of advanced pancreas cancer the activity hinted at in the one patient who experienced a significant delayed response suggests that this approach deserved further exploration, for example by increasing dose or combining with other immune-stimulatory approaches.

### 1.2.7 Durvalumab

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass. The fragment crystallize (Fc) domain of Durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody dependent cell mediated cytotoxicity[37]. Durvalumab inhibits binding of programmed cell death ligand 1 (PD-L1) to programmed cell death 1 (PD-1) and CD80. Programmed death ligand 1 (PD-L1) is a transmembrane immunoreceptor which controls peripheral tolerance by inhibiting effector functions of T lymphocytes trough engagement with PD-1 receptor on antigen presenting cell. Anti-PD-L1 antibodies directly target tumor cells and expected to have less adverse events in comparison with anti-PD-1 antibodies that target effector T-cells in tumor microenvironment.).

Blockade of PD-L1 with Durvalumab expected to relieve PD-L1-mediated suppression of human T-cell activation within tumors. In a xenograft model, Durvalumab inhibited human tumor growth via a T-cell-dependent mechanism. PD-L1 is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some indications. In a pancreatic cancer, the tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis. In the preclinical studies effect of Durvalumab on the growth of human pancreatic adenocarcinoma tumor cell lines in mice was investigated. Durvalumab significantly inhibited growth of the pancreatic adenocarcinoma cell line, HPAC, by up to 74% as compared to the isotype-control antibody.

In the clinical studies to date more than 220 subjects have been enrolled and treated. Currently Durvalumab investigated in 5 ongoing clinical studies (2 employing Durvalumab as monotherapy and 3 as combination therapy). The majority of the clinical data are from Study CD-ON-Durvalumab-1108, which has the greatest number of enrolled subjects. This is a Phase 1, multicenter study in adult subjects with advanced solid tumors refractory to standard therapy (N = 198 subjects). Partial efficacy data available for CD-ON-Durvalumab-1108 based on Response Evaluation Criteria in Solid Tumors (RECIST). Of the 177 subjects treated with Durvalumab 10 mg/kg Q2W, 77 have had at least one post-baseline disease assessment. Four subjects (5.2%) had a best response of PR. In addition, 36 subjects (46.8%) had stable disease.

Of the 177 subjects treated with 10 mg/kg Q2W, 121 subjects (71.8%) had at least 1 treatment-emergent AE (Table 5.3.1.3-1 of current IB edition 6.0). The most frequently reported (≥ 10% of subjects) TEAEs (all grades) were fatigue, dyspnea, nausea, constipation, and decreased appetite. The majority of these TEAEs were Grades 1 to 2 in severity and manageable by the general treatment guidelines as described in the current Durvalumab study protocols. Grade 3 or higher TEAEs were noted in 44/177 subjects (24.9%). These events occurring in more than 1 subject included dyspnea (9 subjects); dehydration (4 subjects); abdominal pain, fatigue, sepsis, increased aspartate aminotransferase, and increased gamma-glutamyltransferase (3 subjects); and hyperbilirubinemia, back pain, pulmonary embolism, respiratory failure, and hypotension (2 subjects each). The Grade 3 or higher TEAEs that were considered by the investigator to be related to Durvalumab were increased aspartate aminotransferase (2 subjects), and hypothyroidism, vomiting, fatigue, infusion-related reaction, troponin, dehydration, and arthralgia (1 subject each). Treatment-related, TEAEs were reported for 52/177 subjects (29.4%). The most frequently reported (2 or more subjects) treatment-related TEAEs (all grades) were fatigue (11.3%); nausea (5.6%); dyspnea (4.0%); diarrhea, vomiting, and pyrexia (3.4% each); myalgia (2.8%); hypothyroidism, decreased appetite, dizziness, cough, pruritus, and rash (2.3% each), abdominal pain, increased aspartate aminotransferase, and arthralgia (1.7% each); and asthenia, influenza-like illness, edema peripheral, increased alanine aminotransferase, headache, and dry skin (1.1% each). No DLTs have been reported. The SAEs reported for 3 or more subjects were dyspnea, dehydration, abdominal pain, and sepsis. Three subjects had treatment-related SAEs: arthralgia (1 subject); pleural effusion and pneumonitis (both in the same subject); and muscular weakness and “rule out cord compression” (verbatim term) (both in the same subject). For the entire study population, none of the deaths or TEAEs resulting in discontinuation of Durvalumab in this study were considered related to Durvalumab treatment.

### 1.2.8 Anti-CTLA4 in combination with anti-PD1/PD-L1.

Durvalumab and tremelimumab data: There is a sound rationale for evaluating the combination of Durvalumab and tremelimumab for the treatment of advanced malignancies. The mechanisms of activation of known activity sites for CTLA-4 and PD-L1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity[38].

The Combination therapy (dual targeting of PD-L1 and CTLA-4) has been shown in preclinical studies with a mouse model to cause tumor regression of colorectal cancer. To date, 2 clinical trials employing Durvalumab as combination therapy with tremelimumab in adults with advanced non-small cell lung cancer (NSCLC) and advanced solid tumors was initiated with preliminary efficacy data for combination still pending. Nivolumab plus ipilimumab clinical data: Results of nivolumab administered in combination with ipilimumab for stage III or IV measurable, unresectable melanoma have recently been reported. At the maximum tolerated combination dose—1mg/kg anti-PD1 plus 3 mg/kg ipilimumab every three weeks administered concurrently, 53% of patients had an objective response, all with tumor reduction of 80% or more. Adverse effects occurred in 53% of patients and were similar in quality and intensity to those observed with ipilimumab monotherapy. Sequential administration resulted in a lower response rate and lower toxicity rate. With regard to biomarkers previously associated with responses to anti-CTLA4 or anti-PD1, investigators evaluated PD-L1 expression in tumors and absolute lymphocyte counts and looked for relationships with response. In patients treated concurrently, 6/13 patients with PD-L1+ tumors responded whereas 9/22 patients with PD-L1– tumors responded (P>0.99 by Fisher's exact). Interestingly however, in the sequential group, 4/8 patients whose tumors were PD-L1+ responded 6 whereas only 1/13 who had PD-L1- tumors responded. Absolute lymphocyte counts at weeks 5-7 were not associated with response in this study.

In the ongoing Tremelimumab + Durvalumab combination study D4190C00006 in advanced NSCLC patients, preliminary AE data as of 18Feb2014 available for 7 subjects treated with Durvalumab (3 or 10 mg/kg) and tremelimumab (1 mg/kg) in this study showed that the only TEAE reported for more than 1 subject was fatigue (3 subjects). All TEAEs were Grade 1 or 2 with the exception of one Grade 3 event of increased aspartate aminotransferase. None were considered by the investigator to be related to treatment with the exception of one event of increased amylase (Grade 2), one event of increased aspartate aminotransferase (Grade 3), and one event of increased alanine aminotransferase (Grade 2), which were all deemed related to both Durvalumab and tremelimumab. No DLTs have been reported in this study.

Updated information for combination of durvalumab and tremelimumab:

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

Study D4190C00006: As of 20Feb2015, durvalumab PK (n = 55) and tremelimumab PK (n = 26) data were available from 10 cohorts (1a, 2a, 3a, 3b, 4, 4a, 5, 5a, 8, and 9) following durvalumab every 4 weeks (Q4W) or Q2W dosing in combination with tremelimumab Q4W

regimens. An approximately dose-proportional increase in PK exposure (Cmax and area under the concentration-time curve from 0 to 28 days [AUC0 28]) of both durvalumab and tremelimumab was observed over the dose range of 3 to 15 mg/kg durvalumab Q4W and 1 to 10 mg/kg tremelimumab Q4W. Exposures following multiple doses demonstrated accumulation consistent with PK parameters estimated from the first dose. It is to be noted that steady state PK parameters are based on limited numbers of subjects. The observed PK exposures of durvalumab and tremelimumab following combination were consistent with respective monotherapy data, indicating no PK interaction between these 2 agents.

As of February 20, 2015, ADA data were available from 60 subjects for durvalumab and 53 subjects for tremelimumab in Study D4190C00006. Four of 60 subjects were ADA positive for anti durvalumab antibodies post treatment. One of 53 subjects were ADA positive for anti tremelimumab antibodies post treatment. There was no clear relationship between ADA and the dose of either durvalumab or tremelimumab, and no obvious association between ADA and safety or efficacy.

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

In order to reduce the dosing frequency of durvalumab to align with the q4w dosing of tremelimumab, while ensuring an acceptable PK/PDx, safety, and efficacy profile, cohorts were narrowed to 15 and 20 mg/kg durvalumab q4w. PK simulations from the durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUCss; 4 weeks) was expected following both 10 mg/kg q2w and 20 mg/kg q4w durvalumab. The observed durvalumab PK data from the D4190C00006 study were well in line with the predicted monotherapy PK data developed preclinically. This demonstrates similar exposure of durvalumab 20 mg/kg q4w and 10 mg/kg q2w, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median Cmax at steady state (Cmax,ss) is expected to be higher with 20 mg/kg q4w (approximately 1.5-fold) and median trough concentration at steady state (Ctrough,ss) is expected to be higher with 10 mg/kg q2w (approximately 1.25-fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

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

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further,

the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

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

In Study D4190C00006, of all treatment cohorts, the cohort of 11 patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed strong evidence of clinical activity. This cohort had a lower number of treatment-related Grade ≥3 AEs or treatment related SAEs. No dose-limiting toxicities were reported.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

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

Additionally, of all cohorts, the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort had the fewest AEs, Grade ≥3 AEs, SAEs, and treatment discontinuations due to AEs, but still showed some evidence of clinical activity. Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

### 1.2.9 Justification for dose and schedule

#### 1.2.9.1 Tremelimumab

The proposed dose and schedule is informed by PK, safety, and efficacy data on tremelimumab. In an early small Phase II study (A3671002), 2 dosing regimens of tremelimumab were compared in subjects with melanoma: 15 mg/kg Q3M (N=45) and 10 mg/kg QM (N=44). Comparable efficacy and overall AE rates were observed in both arms; however, the rate of treatment-related CTCAE Grade 3 or 4 AEs was higher in the 10 mg/kg QM arm (27%) compared to the 15 mg/kg Q3M arm (13%). Subsequently, 2 pivotal tremelimumab studies (Phase II Study A3671008 and Phase III Study A3671009) in patients with melanoma used the regimen 15 mg/kg Q3M. Although neither study met its primary endpoint, the observed response

rate and OS clearly indicate activity of tremelimumab in melanoma. Retrospective exposure-survival analyses of these studies suggest better OS in subjects with higher tremelimumab exposure. In the Phase III trial, there was no difference in the incidence of Grade ≥3 AEs between low and high exposure groups of tremelimumab. Tremelimumab at a concentration of 30 μg/mL enhanced IL-2 release (in vitro) and showed antitumor activity (in vivo), and was consequently identified as the target concentration. PK simulations indicate that following a dose of 10 mg/kg QM for 6 months, approximately 90% of patients are expected to be above the target level of 30 μg/mL during the induction phase. In the Phase III melanoma trial with less frequent dosing of 15 mg/kg Q3M, only approximately 50% of the patients treated with tremelimumab were above the target concentration, for only half of the dosing interval. Tremelimumab at a dose of 10 mg/kg QM for 6 months followed by 10 mg/kg Q3M is expected to yield PK exposures similar to those of the related anti-CTLA-4 mAb ipilimumab at a dose of 10 mg/kg every 3-weeks followed by 10 mg/kg Q3M, the dosing regimen that was tested in the pivotal first-line melanoma trial[15]. The ipilimumab data suggest that the long-term benefits of anti-CTLA-4 therapy may be sustained with a reduced frequency of dosing in patients who are benefiting from therapy. Based on these data, we will use a tremelimumab dose of 10 mg/kg QM for 6 months of treatment. Following the first 6 months of dosing, in the absence of confirmed disease progression, the interval will be increased to Q3M. Treatment will be continued for up to one year as long as the patient continues to derive clinical benefit.

#### 1.2.9.2 Durvalumab

Preclinical toxicities studies with Durvalumab in cynomolgus monkeys, showed that repeated dosing of Durvalumab was not associated with any adverse effects. Therefore, the NOAEL(no-observed-adverse-effect) level of Durvalumab in all the general toxicity preclinical studies was considered to be 100 mg/kg, the highest dose tested in these studies. The majority of the clinical safety data for Durvalumab from Study CD-ON-Durvalumab-1108, Phase 1, first-time-in-human (FTIH), multicenter, open-label, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose (OBD), safety, PK, immunogenicity, and antitumor activity of Durvalumab in adult subjects with advanced solid tumors. A total of 198 subjects have been enrolled in Study CD-ON-Durvalumab-1108 and 177 of these subjects have received Durvalumab at 10 mg/kg Q2W (either in the dose-escalation or dose-expansion phase of the study). No DLTs have been reported. The SAEs reported for 3 or more subjects were dyspnea, dehydration, abdominal pain, and sepsis. Durvalumab PK/pharmacodynamic data were evaluated for 32 subjects in the FTIH study (4 subjects in each of the 0.1 and 0.3 mg/kg groups, 3 subjects in each of the 1 and 3 mg/kg groups, and 18 subjects in the 10 mg/kg group). Results suggest that Durvalumab exhibits nonlinear PK likely due to saturable target-mediated clearance, resulting in faster rate of Durvalumab elimination at lower doses compared with high doses. The Michaelis constant (Km) describing half maximum capacity for nonlinear clearance was ~0.4 μg/mL. Based on mean Km value, > 99% target saturation (both soluble and membrane bound) is expected at ≥ 40 μg/mL concentration of Durvalumab. Hence, this concentration was identified as target trough concentration during dose selection. Pharmacokinetic simulations indicate that following 10 mg/kg Q2W dose of Durvalumab, > 90% of subjects are expected to maintain PK exposure ≥ 40 μg/mL throughout the dosing interval. Near complete target saturation, membrane bound and soluble PD-L1 (sPD-L1) is expected at a ≥ 3.0 mg/kg Q2W dose of Durvalumab. Exposures following multiple doses (currently data available up to a maximum of 20 doses) demonstrated accumulation consistent with the half-lives estimated from

the first dose in each group. Significant target engagement, as measured by sPD-L1 suppression, was observed in all individuals following dosing.

Samples from 31 subjects were available for ADA (antidrug antibody) testing. Of these subjects, 3 (1 subject each in the 0.1, 1.0, and 3.0 mg/kg Q2W cohorts) were ADA positive following dosing. Low ADA titers of 2 and 4 were observed in ADA-positive samples in 1 subject from both the 0.1 and 1.0 mg/kg Q2W cohorts, respectively, with no obvious impact on either PK or pharmacodynamics. In 1 subject in the 3.0 mg/kg Q2W cohort, the ADA titer increased from 128 to 4096 in sequential ADA positive samples. Lower than expected PK exposure and suppression of sPD-L1 were observed in this subject likely as a consequence of this ADA response.

1.2.9.3 Tremelimumab in combination with Durvalumab

Preliminary safety data as of are available for N=7 subjects treated in the ongoing study evaluating the combination of Durvalumab and tremelimumab. Three subjects were enrolled in each of the first 2 dose cohorts. Thereafter, dose escalation proceeded simultaneously to Durvalumab 15 mg/kg with 1 mg/kg tremelimumab and Durvalumab 10 mg/kg with 3 mg/kg tremelimumab, with 1 subject enrolled in the latter cohort as of the cutoff date. The only AE reported for more than 1 subject was fatigue (3 subjects). All AEs were Grade 1 or 2 with the exception of one Grade 3 event of increased aspartate aminotransferase. One subject in this study (Durvalumab 3 mg/kg with 1 mg/kg tremelimumab) was discontinued from treatment because of an SAE of disease progression. No DLTs or deaths have been reported in this study.

The safety profile of durvalumab and tremelimumab combination therapy in the 102 subjects with advanced NSCLC in Study D4190C00006 is generally consistent with that observed across 177 subjects treated with durvalumab and tremelimumab combination therapy (not including subjects treated with blinded investigational product). As of April 15, 2015, 95 of 102 subjects (93.1%) reported at least 1 AE. All subjects in the tremelimumab 3 and 10 mg/kg dose cohorts experienced AEs; subjects in the durvalumab 20 mg/kg and tremelimumab 1 mg/kg Q4W cohort experienced the lowest AE rate (77.8%). Treatment-related AEs were reported in 74 of 102 subjects (72.6%), with events occurring in > 10% of subjects being diarrhea (27.5%), fatigue (22.5%), increased amylase and pruritus (14.7% each), rash (12.7%), colitis (11.8%), and increased lipase (10.8%). Treatment-related ≥ Grade 3 AEs reported in ≥ 5% of subjects were colitis (8.8%), diarrhea (7.8%), and increased lipase (5.9%). Five subjects reported treatment-related Grade 4 events (sepsis, increased ALT, and increased AST in 1 subject; increased amylase in 2 subjects; myasthenia gravis in 1 subject; and pericardial effusion in 1 subject) and 2 subjects had treatment-related Grade 5 events (polymyositis and an uncoded event of neuromuscular disorder [VT]); the Grade 4 event of myasthenia gravis and Grade 5 polymyositis occurred in 1 subject. There were 2 subjects (both in the durvalumab 20 mg/kg + tremelimumab 3 mg/kg Q4W cohort) with dose-limiting toxicities (DLTs): 1 subject with Grade 3 increased AST, and 1 subject with Grade 3 increased amylase and Grade 4 increased lipase. Fifty-six subjects (54.9%) reported SAEs, with events occurring in > 5% of subjects being colitis (9.8%) and diarrhea (7.8%). Thirty-six subjects (35.3%) experienced treatment-related SAEs. Twenty-seven subjects (26.5%) permanently discontinued treatment due to AEs. Treatment-related AEs resulting in discontinuation in ≥ 2 subjects were colitis (7 subjects), pneumonitis (5 subjects), diarrhea (3 subjects), and increased AST (2 subjects). Additional safety results from this study are presented in Section **1.2.8** and the durvalumab IB.

1.2.9.4 Fixed Dosing for durvalumab and tremelimumab

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

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses= 0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma)[39]. Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤ 0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimen.

Similar findings have been reported by others[40, 41],[42],[43]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters[42].

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

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

1.2.10 Rationale for study population and schedule:

RT is part of the standard treatment for advanced pancreatic cancer both in the locally advanced setting and in the context of metastatic disease where patients frequently develop symptoms from the primary tumor. The vast majority of patients with pancreatic cancer have a primary or locally recurrent tumor in-situ for which RT is an acceptable treatment. This allows for a fairly homogenous patient population and radiation schedule. Whilst the traditional RT schedule for this disease has been over a prolonged course and in combination with a chemotherapeutic (5FU or gemcitabine) as radiosensitizer, modern RT techniques allow for a hypofractionated course

without chemotherapy. This will minimize the duration of RT and will make it easier to combine with Immune Checkpoint inhibitors (Tremelimumab and Durvalumab) treatment. Stereotactic body radiation therapy (SBRT) has been shown to be safe and effective in locally-advanced pancreatic cancer[12]. Because it is unclear what the optimal schedule of Tremelimumab and Durvalumab treatment with regard to RT is, we intend to employ two separate schedules to evaluate this in an exploratory manner.

### 1.2.11 Justification for Tumor Biopsies

Whilst the preclinical data suggest important immune-regulatory effects of radiation treatment on tumors, with potential for amplification with immune checkpoint therapy, the effect on humans is really unknown. Given that this is essentially a small pilot study evaluating feasibility and safety whose next step in development – if safe and feasible as per the primary endpoint – will most likely be a larger randomized study, it is scientifically important to obtain as much information about the treatment effect. This may lead to altered and improved design of the next study. The best strategy for doing this is with tumor biopsies in order to evaluated immune cell infiltration (CD4/8 T-cells, MDSC). As pointed out by Deng et al. administration of anti–PD-L1 enhanced the efficacy of radiation through a cytotoxic T cell–dependent mechanism. Concomitant with radiation-mediated tumor regression, they observed that radiation and anti–PD-L1 synergistically reduced the local accumulation of tumor-infiltrating MDSCs, which suppress T cells and alter the tumor immune microenvironment. It would be important to replicate this observation – or disprove it – in humans and would be relevant knowledge whether the clinical data (response, PFS etc.) was either positive or negative. Given this, the historical difficulty with obtaining tissue in stroma-rich pancreatic tumors and the fact that in order for the biopsy material from any single patient to be relevant and worthwhile in the context of small patient numbers we would really require participation from all or almost all of the patients. However, if a patient has technically biopsiable disease but the interventional radiologist has concerns that pursuing the biopsy increases the risk to above average, or if pursuing the biopsy creates additional logistical complications (availability, pre-anesthesia requirements etc.) which causes delays or inconvenience to an unreasonable degree, we will forgo at investigator discretion.

#### 1.2.11.1 Details of Planned Tumor Analysis

We will attempt to perform immunohistochemically and gene analysis of all tumor biopsies. No non-tumor tissue will be analyzed. Analysis will be focused and confined to IHC and RNA characterization of specific immune cell populations - T-cell, MDSC, NK cells, macrophages- as well as markers of importance in the microenvironment such as PD-L1/2 expression.

RNA analysis will be performed as follows: RNA will be extracted and sent to Cell Processing Section at DTM for microarray analysis using a standard Affymetrix array. Genetic analysis will be on tumor tissue only. No germ line analysis is planned or will be performed without study amendment and IRB approval.

### 1.2.12 Justification for accrual increase in Arm C2 with Amendment I

The primary purpose of this amendment is to increase enrollment in treatment Arm C2 as we enrolled already 10 patients. There are two patients among 10 patients (20%) treated in Arm C2, who had been treated with current protocol over one year and obtained durable partial response

(>12 months). This outcome is inspiring given the benefit of available clinical trials involved with immune checkpoint inhibitors in pancreatic cancer has been decimal. It will be desirable to have additional patients enrolled in Arm C2 to more precisely estimate its efficacy. Thus, with Amendment I, we would like to double the accrual number of Arm C2 from 10 to a total of 20 evaluable patients to provide a more precise estimate of the treatment efficacy in this arm.

# 2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

## 2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histopathological confirmation of pancreatic adenocarcinoma prior to entering this study by the Laboratory of Pathology of the NCI prior to entering this study

2.1.1.2 Patients must have disease that is not amenable to potentially curative resection. Either primary in-situ (or locally-recurrent) tumor must be present and, in the opinion of radiation oncology, be amenable to radiation therapy as planned in the protocol or an extra pancreatic lesion which in the opinion of the radiation oncologist is amenable to radiation. Each case will be discussed at GI tumor board with multidisciplinary team.

2.1.1.3 Patients must have at least 1 measurable metastatic lesion by RECIST1.1 criteria.

2.1.1.4 There is no limit to the number of prior chemotherapy regimens received. Patients must have received at least one line of prior systemic chemotherapy for advanced unresectable and/or metastatic disease.

2.1.1.5 Age ≥18 years

2.1.1.6 Life expectancy of greater than 3 months.

2.1.1.7 ECOG performance status 0-1 (see **Appendix A**)

2.1.1.8 Patients must have normal organ and marrow function as defined below:

| | |
|---|---|
| absolute neutrophil count | > 1,000/μL |
| Platelets | ≥ 100,000/μL |
| total bilirubin | Bili should be ≤ 2 x ULN (patients with Gilbert's Syndrome must have a total bilirubin less than 3.0 mg/dL) |
| serum albumin | ≥ 2.5 g/dL |
| Patients are eligible with ALT or AST up to 3 x ULN. (up to 5 x ULN if liver metastases present) | |
| Creatinine | <2X institution upper limit of normal<br>OR |

| | |
|---|---|
| creatinine clearance | >45 mL/min/1.73 $m^2$, for patients with creatinine levels above institutional normal |

2.1.1.9 Patients must have recovered from any acute toxicity related to prior therapy, including surgery. Toxicity should be ≤ grade 1 or returned to baseline.

2.1.1.10 Patient must be able to understand and willing to sign a written informed consent document.

2.1.2 Exclusion Criteria

2.1.2.1 Malignant ascites that is clinically detectable by physical examination or is symptomatic. Evidence of radiographic ascites that is not clinically significant will not be an exclusion criterion.

2.1.2.2 Any prior Grade ≥ 3 imAE while receiving immunotherapy, including anti-CTLA4 treatment, or any unresolved imAE > Grade 1. Note: Active or history of vitiligo will not be a basis for exclusion.

2.1.2.3 Patients must not have had standard of care chemotherapy, radiotherapy, or major surgery within the last 2 weeks prior to entering the study. Note: Local surgeries for isolated lesions for palliative intent are acceptable. For recent experimental therapies, a 28-day period of time must have elapsed before commencing protocol treatment.

2.1.2.4 Patients with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

2.1.2.5 Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, current pneumonitis, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring adverse events from Durvalumab or tremelimumab, or compromise the ability of the subject to give written informed consent.

2.1.2.6 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel disease; Wegner syndrome; Hashimoto syndrome; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc.) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:

- Subjects with vitiligo or alopecia
- Requirement for intermittent use of bronchodilators or local steroid injections
- Subjects with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement, or psoriasis not requiring systemic treatment

2.1.2.7 History of primary immunodeficiency or history of active tuberculosis. Note: Latent tuberculosis will not be a basis for exclusion.

2.1.2.8 Diverticulitis (either active or history of) within the past 2 years. Note that diverticulosis is permitted.

2.1.2.9 Dementia or significantly altered mental status that would prohibit the understanding or rendering of Information and Consent and compliance with the requirements of the protocol.

2.1.2.10 True positive test results for hepatitis A (IgM positive). Subjects with a history of hepatitis A with IgG blood test are not excluded. True positive test results hepatitis B, or C infection.

2.1.2.11 Active or history of inflammatory bowel disease (colitis, Crohn's), irritable bowel disease, celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis.

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

- Intranasal, inhaled, and topical steroids
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

2.1.2.13 History of sarcoidosis syndrome.

2.1.2.14 Patients should not be vaccinated with live attenuated vaccines within 1 month of starting Tremelimumab and Durvalumab treatment. Subjects, if enrolled, should not receive live vaccine during the study and 180 days after the last dose of both drugs.

2.1.2.15 HIV-positive patients receiving anti-retroviral therapy are excluded from this study due to the possibility of pharmacokinetic interactions between antiretroviral medications and Tremelimumab or Durvalumab. HIV positive patients not receiving antiretroviral therapy are excluded due to the possibility that Tremelimumab or Durvalumab may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events.

2.1.2.16 History of hypersensitivity reaction to human or mouse antibody products.

2.1.2.17 Pregnancy and breast feeding are exclusion factors. The effects of Tremelimumab and Durvalumab on the developing human fetus are unknown. Enrolled patients must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, the duration of study participation and 180 days (female patients) or 90 days (male patients) after the end of the treatment. In addition, male patients must refrain from sperm donation for 90 days after the final dose of investigational product. Female patients must refrain from egg cell donation for 180 days after the final dose of investigational product. Should a woman become pregnant

or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

2.1.2.18 Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results.

2.1.3 Recruitment Strategies

The study will be posted on the CCR website and on clinicaltrials.gov.

## 2.2 SCREENING EVALUATION

Studies should be done within 28 days prior to enrollment.

- Labs may be performed outside of NIH. Complete history (including prior hormone use) and physical examination (including height, weight, vital signs, EKG, and performance status).
- Laboratory Evaluation
  - Hematological profile: CBC with differential and platelet count, PT, INR, aPTT, fibrinogen.
  - Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, amylase.
  - Hepatitis A, B, C serological testing.
  - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy).
- Imaging studies
  - CT scan of chest, abdomen and pelvis
  - And/or MRI abdomen
- Histologic confirmation by laboratory of Pathology of the NCI (at any time point prior to commencement). A block or unstained slides of primary or metastatic tumor tissue will be required from each participant to confirm diagnosis.

## 2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.1 Treatment Assignment Procedures:

**Cohorts**

| Number | Name | Description |
|---|---|---|
| 1 | Cohort 1 | Subjects with unresectable pancreatic cancer |

**Arms**

| Number | Name | Description |
|---|---|---|
| 1 | A1 | Durvalumab +8 Gy in 1 fraction |
| 2 | A2 | Durvalumab +5 Gy in 5 fractions |
| 3 | B1* | Tremelimumab + 8 Gy in 1 fraction |
| 4 | B2* | Tremelimumab + 5 Gy in 5 fractions |
| 5 | C1 | Durvalumab + Tremelimumab + 8 Gy in 1 fraction |
| 6 | C2 | Durvalumab + Tremelimumab + 5 Gy in 5 fractions |

Subjects in Cohort 1 will be directly assigned to Arms A1, A2, C1, C2 as follows:

- Subjects will initially be enrolled in Arm A1 or A2. Assignment to A1 or A2 is per investigator discretion in consultation with multidisciplinary team.
- Once enrollment to arms A1 and A2 are complete, subjects will be enrolled in Arms C1 and C2, with assignment to C1 or C2 per investigator discretion in consultation with multidisciplinary team.

* With amendment A, the study design was revised, Arms B1 and B2 were removed, no subjects were assigned to B1 and B2.

## 2.4 BASELINE STUDIES

Tests done at screening do not need to be repeated on baseline if performed in designated time frame.

If laboratory tests done within 72 hours of Cycle 1 Day 1 they do not need to be repeated on Day 1.

Labs may be performed outside of NIH.

Within 28 days prior to study intervention:

- EKG
- CT scan of chest, abdomen and pelvis and/or MRI

- Tumor biopsy

Within 7 days prior to study intervention:

- Tumor marker profile: CA 19-9
- Physical exam with vital signs

Within 72 hours prior to study intervention:

- Hematological profile: CBC with differential and platelet count, PT, INR, aPTT, fibrinogen.
- Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium, uric acid, amylase.
- Thyroid function tests (TSH, T3, T4)
- ANA, AMA, Liver autoantibody panel (autoimmune hepatitis)
- Immune monitoring
- Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy).

# 3 STUDY IMPLEMENTATION

## 3.1 STUDY DESIGN

The proposed study is a pilot/phase I study of immune checkpoint inhibition in combination with short course radiation therapy in patients with unresectable pancreatic cancer.

For arms A1 and A2: Durvalumab treatment will continue until off treatment criteria are met (Section **3.6.1)** (**Figure 2**).

For arms B1 and B2: It was intended for Tremelimumab treatment to continue for a total of 12 months or until confirmed progressive disease (PD; if PD occurs before completion of the 12-month treatment period) assessed by irRC criteria. With amendment A, the study design was revised and it was decided that we would not assign subjects into these treatment arms.

For arms C1 and C2: Assignment to arms C1 and C2 will only proceed following 1) NCI IRB approval of updated safety information of ongoing combination therapy studies evaluating tremelimumab in combination with Durvalumab and 2) submission to the FDA of a revised protocol specifying the selected drug doses and dose schedule.

Patients assigned to arms C1 and C2 will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w until off treatment criteria are met (Section **3.6.1)** (see **Figure 3**). Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (i.e. 1mg/kg for tremelimumab and 20mg/kg for durvalumab). Flat weight dosing will be used for all other patients including those who are greater than 75Kg e.g. 100-110Kg. Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1 hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are

observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

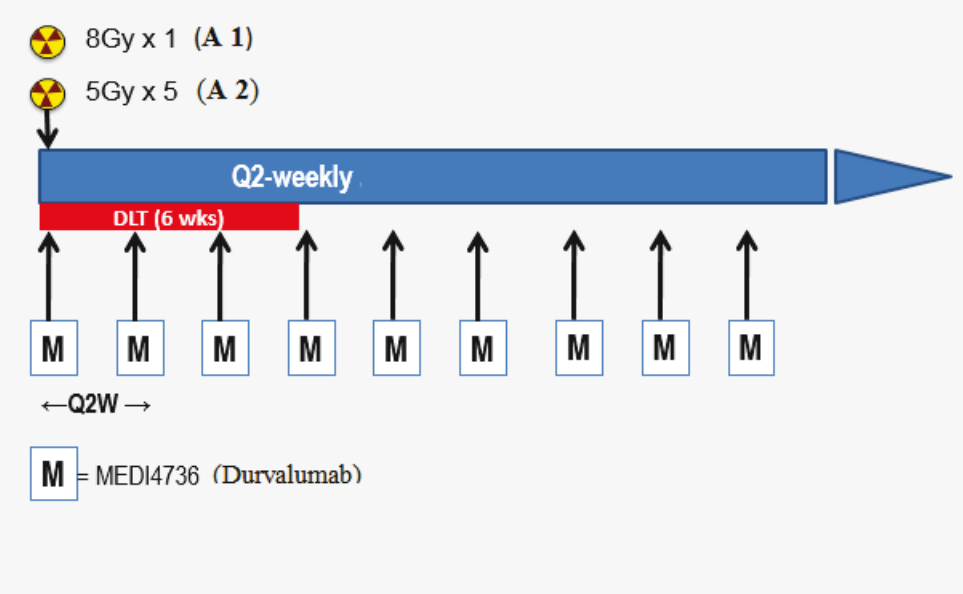
Subjects who permanently discontinue treatment will be followed. All subjects will be followed for survival. Follow up details are outlined in Section **3.5**.

- The original study design was to have 6 separate treatment arms:
    - Arms A1 and A2: anti-PDL1 (Durvalumab) in combination with radiation
    - Arms B1 and B2: anti-CTLA4 (tremelimumab) in combination with radiation (never opened)
    - Arms C1 and C2: anti-PDL1 (Durvalumab) and anti-CTLA4 (tremelimumab) in combination with radiation.
- Arms differ by the quantity of radiation.
    - Arms A1 and C1: 8Gy in 1 fraction (Total = 8Gy) Day 1.

      Arms A2 and C2: 5Gy in 5 fractions (Total = 25Gy) for 5 days which will be identified as Day -3, Day -2, Day -1, Day 0, Day 1.
- Patient allocation:
    - No randomization will occur.
    - The subjects will be assigned to arms sequentially i.e. A before C (the latter of which will require IRB approval.)
- The radiation schedule the patient receives will be decided through multidisciplinary discussion with the radiation oncologist and based on clinical factors rather than dictated purely by sequence based on when the patient happens to be seen. The reason for this is based on our experience thus far where we commonly encounter one of two specific scenarios as follows: A) If a patient has a relatively large pancreatic mass which is causing pain we would like the flexibility to administer the 5x5Gy schedule as this would at least give a good palliative dose of radiation; B) Some patients have very small pancreatic primaries which would be more suited to the lower dose of radiation. Mandatory baseline and Day 29 tumor biopsies will be obtained on all patients. However, if a patient has technically biopsiable disease but the interventional radiologist has concerns that pursuing the biopsy increases the risk to above average, or if pursuing the biopsy creates additional logistical complications (availability, pre-anesthesia requirements, etc.) which causes delays or inconvenience to an unreasonable degree, we will forgo at investigator discretion.
- Given that the primary aim of this study is to assess safety and feasibility of immune checkpoint inhibition in combination with radiation the DLT evaluation period will extend for a total of 6 weeks following completion of radiation.

### 3.1.1 Arms A1 and A2

**Figure 2: Durvalumab in combination with radiation:**




Patients with pancreatic cancer who satisfy the eligibility criteria will receive Durvalumab 10mg/kg as an intravenous infusion until off-treatment criteria are met.

| **Arm** | | **Checkpoint inhibitor** | **SBRT[a] dose/schedule** | **N** |
|---|---|---|---|---|
| **A1** | | Durvalumab 10mg/kg/q2w | 8Gy x 1# | 10 |
| **A2** | | Durvalumab 10mg/kg/q2w | 5Gy x 5# | 10 |

[a]SBRT= Stereotactic body radiation therapy.

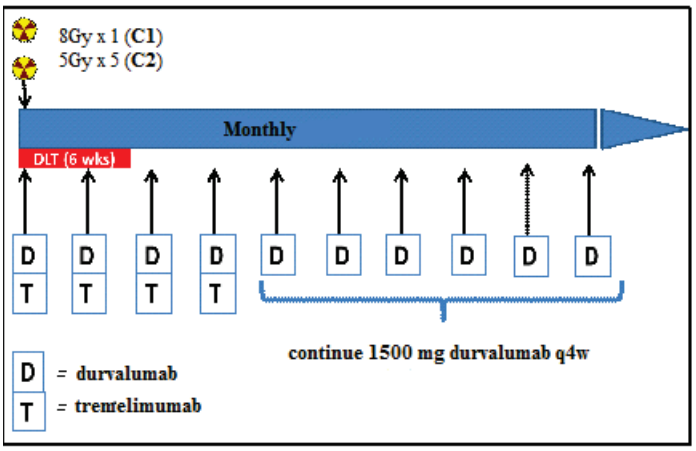
Timing of checkpoint inhibitor with regard to RT: If RT given for 1 day (Arm A1), checkpoint inhibitor given on D1, immediately post RT. If RT given for 5 days (Arm A2), checkpoint inhibitor(s) given on the last day of RT immediately post RT and this will be identified as D1.

- Initially N=10 patients will be assigned to Arm A1 as per the table. Patients in Arm A1 will undergo external beam radiation to the pancreatic mass comprising 8Gy in a single fraction on Day 1.
- The goal will be to evaluate 10 patients in A1 and then 10 in A2, provided that no more than 1 of the first 6 in A1 or A2 has a DLT, and that no more than 3 of 10 patients in either A1 or A2 has a DLT. If either of these is exceeded, then no further patients would be enrolled in arms A1 and A2.
- Patients in Arm A2 will undergo external beam radiation to the pancreatic mass comprising 25Gy in 5 fractions (5Gy per fraction) for 5 days, on Day -3, Day -2, Day -1, and Day 0, Day 1.

- Restaging CT scan (or MR) will be performed every 8 weeks. RECIST 1.1 and modified Immune-related RECIST criteria will be applied.

3.1.2 Arms C1 and C2

**Figure 3: Durvalumab and Tremelimumab in combination with radiation.**




Patients with pancreatic cancer who satisfy the eligibility criteria will receive 1500 mg durvalumab via IV infusion q4w for up to 4 doses/cycles and 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles, and then continue 1500 mg durvalumab q4w until off-treatment criteria are met (see graphic above). Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion. The duration will be approximately 1 hour for each infusion. A 1 hour observation period is required after the first infusion of durvalumab and tremelimumab. If no clinically significant infusion reactions are observed during or after the first cycle, subsequent infusion observation periods can be at the Investigator's discretion (suggested 30 minutes after each durvalumab and tremelimumab infusion).

| **Arm** | | **Checkpoint inhibitor** | **SBRT[b] dose/schedule** | **N** | **Start date** |
|---|---|---|---|---|---|
| **C1** | | Durvalumab 1500mg + Tremelimumab 75mg | 8Gy x 1# | 10 | March 2016 |
| **C2** | | Durvalumab 1500mg + Tremelimumab 75mg | 5Gy x 5# | 20 | |

[a]SBRT= Stereotactic body radiation therapy.

Timing of checkpoint inhibitor with regard to RT: If RT given for 1 day (Arm C1), checkpoint inhibitor given on D1, immediately post RT. If RT given for 5 days (Arm C2), checkpoint inhibitor(s) given on the last day of RT immediately post RT and this will be identified as D1.

- The goal will be to evaluate 10 patients in C1 and then 20 in C2, provided that no more than 1 of the first 6 in C1 or C2 has a DLT, and that no more than 3 of first 10 patients in either C1 or C2 has a DLT. If either of these is exceeded, then no further patients would be enrolled in arms C1 and C2.
- Patients in Arm C2 will undergo external beam radiation to the pancreatic mass comprising 25Gy in 5 fractions (5Gy per fraction) for 5 days, on Day -3, Day -2, Day -1, and Day 0, Day 1.
- Restaging CT scan (or MR) will be performed every 8 weeks. RECIST 1.1 and Immune-related RECIST criteria will be applied.
- The decision on which radiation schedule to be employed will be based on technical and clinical factors and after discussion with and at the discretion of the radiation oncologist.

#### 3.1.3 Protocol Stopping Rules

This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for grading systemic toxicity. For safety reasons, new subject enrollment will be temporarily halted for either of the following events.

- One occurrence of grade 5 toxicity by the NCI-CTCAE version 4.0 attributable to the treatment regimen.
- Two occurrences of grade 4 toxicity by the NCI-CTCAE version 4.0 attributable to the treatment regimen.

Discussions will be had, if applicable, with the NCI IRB and Sponsor regarding necessary amendment in order to resume enrollment.

#### 3.1.4 Re-treatment

If patient is taken off treatment for reasons other than disease progression or unacceptable toxicity, attributed to Durvalumab, but later, in the opinion of Investigator, can benefit from re-starting of Durvalumab and meets eligibility criteria, re-treatment with Durvalumab will be initiated (q4w). Screening evaluations will be repeated. No research procedures will be done during re-treatment; however, clinical assessments will be performed per study calendar.

### 3.2 DOSE LIMITING TOXICITIES

#### 3.2.1 Definition of Dose-limiting Toxicities (DLTs):

A DLT will be defined as any Grade 3 or higher treatment-related (related to any investigational product) toxicity that occurs during the DLT evaluation period, including:

3.2.1.1 Any Grade 4 immune-mediated AE (imAE)

3.2.1.2 Any Grade 3 imAE that does not downgrade to ≤ Grade 2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to ≤ Grade 1 or baseline within 14 days

3.2.1.3 Liver transaminase elevation higher than 8 × upper limit of normal (ULN) or total bilirubin higher than 5 × ULN

3.2.1.4 Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care.

3.2.2 Definition of Dose-limiting Toxicities (DLTs) excludes the following conditions:

- Grade 3 asymptomatic elevation of pancreatic enzymes which resolve to grade 1 within 28 days.
- Grade 3 rash or pruritus that downgrades to ≤ Grade 2 within 3 days after onset of the event with maximal supportive care including systemic corticosteroids or downgrade to ≤ Grade 1 or baseline (on oral prednisone 10mg/day) within 30 days.
- Grade 3 endocrinopathy that is asymptomatic, managed with or without corticosteroid therapy and/or hormone replacement and which downgrades to ≤ Grade 1 or baseline within 30 days. Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
- Dosing may continue despite concurrent vitiligo and alopecia of any AE grade
- Grade 3 pyrexia, headache, and chills that are controlled with appropriate supportive treatment and do not result in permanent treatment discontinuation
- Grade 3 nausea, vomiting, or mucositis/esophagitis that is felt to be related to the radiation and that responds to maximal supportive care within 3 days
- Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

3.2.3 Investigational Drug Administration

3.2.3.1 The first day of dosing is considered Day 1.

3.2.3.2 Tremelimumab IV infusion will be approximately 1 hour in duration Durvalumab will be approximately 1 hour in duration;

3.2.3.3 For Arms C1 and C2: Tremelimumab will be administered first. Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion.

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

1) Investigational product must be administered at room temperature (25°C) by controlled infusion at a rate of 250 mL/hr. via an infusion pump into a peripheral vein. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
2) Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.
3) The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22 or 0.2 μm in-line filters.

4) If there are no requirements to slow, interrupt, or permanently stop the infusion, the anticipated infusion time to deliver each dose (250 mL) is anticipated to be approximately 60 minutes.
5) For infusion-related reactions: The infusion rate of Durvalumab or tremelimumab may be decreased by 50% or temporarily interrupted until resolution of the event. Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. Consider premedication prior to subsequent doses.
6) When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice). The duration of the investigational product administration will be recorded.

### 3.2.4 Durvalumab Drug Administration

Each dose of Durvalumab should be administered using the following guidelines:

1) Durvalumab will be administered as an IV infusion over approximately 60 minutes.
2) When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).
3) Since the compatibility of Durvalumab with other IV medications and solutions, other than normal saline (0.9% [w/v] Sodium Chloride for Injection), is not known, the Durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered.
4) The duration of the investigational product administration will be recorded.

### 3.2.5 Tremelimumab Dose Administration:

Tremelimumab will be administered as an IV infusion (250 mL) over approximately 1 hour. When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

### 3.2.6 Monitoring of Dose Administration

Vital signs will be collected within 30 minutes before and within 30 minutes after investigational product infusion only. Patients will need to stay for one hour post the infusion to assess for any delayed reactions for the first infusion. For subsequent infusions patient will be required to stay for only 30 minutes or at the discretion of the Principal Investigator.

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis, as per local institutional guidelines.

## 3.3 DOSING DELAYS

The following broad guidelines for dose delivery schedule delays and alternations apply to both of the planned dosages of Tremelimumab and Durvalumab and are dependent on the clinical and laboratory assessment on the day of dosing. Tremelimumab and Durvalumab can be delivered within 72 hours of planned interval to accommodate scheduling issues/logistics.

### 3.3.1 Immune-mediated AEs (imAEs)

Based on the mechanism of action of Durvalumab and tremelimumab leading to T-cell activation and proliferation, there is the possibility of observing immune-mediated AEs (imAEs) during the conduct of this study. Potential imAEs may be similar to those seen with the use of ipilimumab, BMS-936558 (anti-PD-1 mAb), and BMS-936559 (anti-PD-L1 mAb) and may include immune-mediated enterocolitis, dermatitis, hepatitis (hepatotoxicity), and endocrinopathies[14, 16, 44]. These AEs are inflammatory in nature and can affect any organ. With anti-PD-LI and anti-CTLA-4 combination therapy (arms C1 and C2), the occurrence of overlapping or increasing cumulative toxicities that include imAEs, could potentially occur at higher frequencies than with Durvalumab (arms A1 and A2) monotherapy.

Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (e.g., infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy. Dosing modification and management guidelines for imAEs specified in **Appendix D**.

### 3.3.2 Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. 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.

- Liver: Immune Checkpoint inhibitors (Tremelimumab and/or Durvalumab) can result in severe and fatal inflammation of the liver most commonly manifested as elevation of transaminases and hyperbilirubinemia. Liver enzymes and liver function tests (hepatic transaminase and bilirubin levels) will be evaluated and patients assessed for signs and symptoms of hepatitis before each dose of Tremelimumab and Durvalumab. Guidelines for management of subjects with hepatic function abnormality are outlined in **Appendix D**.
- Pneumonitis Adverse events of pneumonitis are also of interest, as pneumonitis has been observed with anti-PD-1 mAbs (but not with anti-PD-L1 mAbs). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.
- Infusion Reactions. Adverse events of infusion reactions (also termed infusion-related reactions) are of special interest and are defined, for the purpose of this protocol, as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time.

- Hypersensitivity Reactions: In case of hypersensitivity reactions, the investigator should institute treatment measures deemed medically appropriate per institutional guidelines
  - Grade 1 = Transient flushing or rash; drug fever < 38°C
  - Grade 2 = Rash; flushing; urticaria; dyspnea; drug fever ≥ 38°C
  - Grade 3 = Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension; anaphylaxis
  - Grade 4 = Anaphylaxis
  - Grade 5 = Death

3.3.2.1 Autoimmunity

If a subject experience an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, hepatitis, pancreatitis, thrombocytopenia, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing and immediate consideration of endocrinology consultation. If specific auto-antibodies are present, the blood sample taken for storage at baseline can be tested for the presence of auto antibodies. Continuation of investigational product in the presence of immune-mediated events should be done by the investigator with consideration to risk-benefit analysis.

## 3.4 SPECIFIC PROCEDURES FOR STEREOTACTIC BODY RADIATION THERAPY (SBRT)

3.4.1 Radiotherapy administration

3.4.1.1 Modality, Fractionation, and Total Dose

Radiation will be delivered with megavoltage external beam radiation with beam energies of 6MV or higher. For Arms A1 and C1 treatment will be delivered in 8Gy as a single fraction. For Arms A2 and C2 treatment will be delivered in 5Gy fractions for 5 days. The decision on which radiation schedule to be employed will be based on technical and clinical factors and after discussion with and at the discretion of the radiation oncologist.

3.4.1.2 Simulation

Patients will be simulated supine with the addition of a 4D CT if appropriate. A stereotactic immobilization device with abdominal compression will be used. Oral contrast will be delivered approximately one hour prior to simulation to allow opacification of small bowel unless contraindicated. IV contrast may be delivered for the simulation if deemed necessary by the treating radiation oncologist.

3.4.1.3 Volume definitions

GTV: The gross tumor volume (GTV) will be defined as all gross disease evident on imaging and examination at the site of treatment PTV: The planning target volume will be a 3-5 mm concentric expansion on the GTV. An additional margin of up to 3 mm may be added as needed if 4D CT reveals extensive respiratory motion of the target.

3.4.1.4 Target lesions

Target lesions for radiation will be primary or recurrent pancreatic lesions. If there is no pancreatic lesion present or in the opinion of the radiation oncologist, there is a more amenable lesion outside of the pancreas, this may be designated as a target lesion.

3.4.1.5 Dose specification

The PTV doses should meet the following criteria:

1) >93% of the PTV should receive at least 93% of the prescribed dose.
2) < 5% of the PTV should receive more than 110% of the prescribed dose. Efforts will be made to reduce heterogeneity if possible.

Normal Structures The following dose goals will apply for normal tissues:

- Kidney: mean dose < 10 Gy (total kidney volume)
- Small bowel: maximum 35 Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Duodenum: maximum 35Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Stomach: 35 Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Large bowel: maximum 35Gy, mean <25Gy, V30< 5cc, V35Gy <1cc
- Liver: V30<10%
- Spinal cord: maximum 20Gy

Daily treatment delivery

Treatment will be delivered at the discretion of the radiation oncologist.

Localization will be verified with pretreatment imaging prior to every fraction. Ideally, this will include Tomotherapy localization or cone beam CT, although kV/kV imaging may be used if necessary.

### 3.5 STUDY CALENDAR

| | Screening | Baseline [n] | C1 | | | | | | | | C2 | | | | C3 | | | | D1 of every subsequent cycle | EOT [j] | FU [k] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | -3 | -2 | -1 | 0 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | | | |
| Durvalumab [a] | | | | | | | X | | X | | X | | X | | X | | X | | X | | |
| Tremelimumab [b, o] | | | | | | | X | | | | X | | | | X | | | | X | | |
| SBRT [c] Arms A1, C1 | | | | | | | X | | | | | | | | | | | | | | |
| SBRT [c] Arms A2, C2 | | | X | X | X | X | X | | | | | | | | | | | | | | |
| Informed consent | | X | | | | | | | | | | | | | | | | | | | |
| Medical history | X | | | | | | | | | | | | | | | | | | | | |
| Concomitant meds | | X | | | | | X | | | | X | | | | X | | | | X | | |
| Formal adverse event evaluation | | X | | | | | X | | | | X | | | | X | | | | X | X | |
| Physical exam | X | X | | | | | X | | | | X | | | | X | | | | X | X | |
| Vital Signs | X | X | | | | | X[i] | | X[i] | | X[i] | | X[i] | | X[i] | | X[i] | | X | X | |
| CBC [d] | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |
| Hepatitis A, B, C | X | | | | | | | | | | | | | | | | | | | | |
| PT, INR, PTT, fibrinogen [d] | X | X | | | | | X | | | | X | | X[p] | | X | | | X[p] | X | | |
| TSH, T3, T4 [d] | | X | | | | | X | | | | X | | | | X | | | | | | |
| Biochemical profile [d, e] | X | X | | | | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | |

| | Screening | Baseline [n] | C1 | | | | | | | | C2 | | | | C3 | | | | D1 of every subsequent cycle | EOT [j] | FU [k] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | -3 | -2 | -1 | 0 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | | | |
| Uric acid, amylase [d] | X | X | | | | | X | X [p] | X [p] | X [p] | X | X [p] | X [p] | X [p] | X | X [p] | X [p] | X [p] | X | X | |
| CA 19-9 | | X | | | | | X | | | | X | | | | X | | | | X | | |
| EKG | X | X | | | | | | | | | X | | | | X | | | | X | | |
| Restaging radiologic Evaluation | X | X | | | | | | | | | | | | | X | | | | X [f] | | |
| Tumor biopsy [g, o] | | X | | | | | | | | | X | | | | | | | | | | |
| Immune monitoring [o] | | X | | | | | | | | | X | | | | X | | | | X [h] | | |
| Pharmacokinetic studies [o] | | | | | | | X | X | X | | X | | | | X | | | | X [h] | X | X [m] |
| Immunogenicity (ADA) [o] | | | | | | | X | | | | X | | | | | | | | X [h] | X | X [m] |
| ANA, AMA, Liver autoantibody panel (autoimmune hepatitis) [o] | | X | | | | | | | | | | | | | | | | | X [h] | | |
| T cell activation/ICOS expression/ functional analyses / immunodiversity (PBMC) [o] | | | | | | | X | X | X | | X | | | | X | | | | X [h] | X | |

| | Screening | Baseline [n] | C1 | | | | | | | | C2 | | | | C3 | | | | D1 of every subsequent cycle | EOT [j] | FU [k] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | -3 | -2 | -1 | 0 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | 1 | 8 | 15 | 22 | | | |
| Plasma-based assays for circulating receptors/ligands e.g., PDL1[o] | | | | | | | X | X | X | | X | | | | X | | | | X [h] | X | X [m] |
| Advance Directive [l] | | X | | | | | | | | | | | | | | | | | | | |
| Serum or urine pregnancy test | X | X | | | | | | | | | | | | | | | | | | | |
| Histologic confirmation | X[o] | | | | | | | | | | | | | | | | | | | | |

[a] Subjects will receive one dose of Durvalumab on Days 1 and 15 in Arms A1 and A2 and on Day 1 only in Arms C1 and C2 until off-treatment criteria are met.

[b] Subjects will receive 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles.

[c] Hypofractionated radiation will be administered to the pancreatic primary tumor OR a lesion noted outside the pancreas per the discretion of the radiation oncologist.

[d] For all labs a '+/- 72 hr.' window applies, with the exception of those needed to determine proceeding with treatment. Labs may be performed outside of NIH.

[e] Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium.

[f] Restaging CT /MRI scan every 8 weeks (+/- 1 week) to evaluate TTP in target lesion.

[g] Mandatory baseline and post-RT tumor biopsies (D29 approx. (+/- 7 days) will be obtained on all patients.

[h] Refer to section **5** for detailed timing schema

[I] collected within 30 minutes before and within 30 minutes after investigational product infusion.

[j] End Off Treatment Visit: patients will be invited to clinical center approximately 30 days following the last dose of study drug. If patents are not able or not willing to come, they will be asked by phone for performance status, any adverse events and new cancer treatment.

[k] FU Follow Up: all study subjects will be followed for overall survival. Follow-up will be semi-annual telephone contact to assess survival status. Every attempt will be made to contact patient/subject including: contacting referring physician, contacting emergency contact patient identified on admission, checking SSDI (Social Security Death Index).

[l] Filling out of the Advance Directive will be offered, but obtaining of it is not required. For details see Section **10.3**

[m] Done at day 90 after last dose of drug, but only if patient is willing to come for a visit to NIH

n Tests done at screening do not need to be repeated on baseline if performed in designated time frame.

[O] will not be done during re-treatment

p Optional

## 3.6 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to documenting removal from off study, effort must be made to have all subjects complete a safety visit approximately 30 days following the last dose of study therapy.

### 3.6.1 Criteria for removal from protocol therapy

- Withdrawal of consent from further treatment with investigational product
- Unacceptable Toxicity as defined in section **3.2**
- Pregnancy or intent to become pregnant
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent
- Progressive Disease as defined in section **6.2.4**. NOTE: While RECIST PD will be noted and recorded the immune-related RECIST criteria will be applied to determine discontinuation of study treatment.
- Subject who has received any amount of infliximab or other tumor necrosis factor alpha inhibitor
- Intercurrent illness that prevents further administration of treatment
- Investigator discretion

### 3.6.2 Criteria for Removal from Study

- Lost to follow-up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status at that time. Subjects who refuse continuing participation in the study including telephone contact should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

- Death
- Patient voluntarily chooses to withdraw from the protocol
- Investigator discretion
- PI decision to close the study
- Completed study follow-up period

Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study. An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment (including telephone contact) regardless of the number of doses of

investigational product that was received. Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up.

### 3.6.3 Off Protocol Therapy and Off Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

# 4 CONCOMITANT MEDICATIONS/MEASURES

All routine and appropriate supportive care (including blood products) will be provided during this study, as clinically indicated, and in accordance with the standard of care practices. Clinical judgment should be utilized in the treatment of any AE experienced by the patient.

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 4.1. Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management [including palliative radiotherapy, etc.]) should be used when necessary for all subjects. Information on all concomitant medications, administered blood products, as well as interventions occurring during the study must be recorded on the patient's eCRF.

## 4.1 PROHIBITED CONCOMITANT MEDICATIONS

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The sponsor must be notified if a subject receives any of these during the study.

1. Any investigational anticancer therapy
2. Monoclonal antibodies against CTLA-4, PD-1, or PD-L1 through 90 days post last dose during the study
3. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Temporary uses of corticosteroids for concurrent illnesses (e.g., food allergies, CT contrast hypersensitivity, etc.) are acceptable.

5. Live attenuated vaccines during the study through 180 days after the last dose of both investigational products
6. Inactivated vaccinations ± 30 days around any dose of investigational product.

# 5 BIOSPECIMEN COLLECTION

## 5.1 CORRELATIVE STUDIES FOR RESEARCH/PHARMACOKINETIC STUDIES

The correlative studies which we wish to perform are outlined below and summarized in the table. All samples will be sent to Dr. Figg's lab for processing and storage until they are distributed to Dr. Greten's lab or MedImmune for sample analysis as described in the protocol. A description of each test including a brief statement of rationale and processing information is made below.

| **Test/assay** | **Volume blood (approx.)** | **Type of tube** | **Collection point (+/- 48hrs)** | **Location of specimen analysis** |
|---|---|---|---|---|
| Immune- monitoring | 120 mL (for PBMC) | EDTA | Baseline on day of biopsy, C2D1, C3D1, C4D1 | Greten Lab |
| | 5-10 mL (for serum) | EDTA | | |
| PK | 3 mL | SST | C1D1 (pre- dose and End-of Infusion (EOI)*)<br>C1D8 (local patients only)<br>C1D15 (local patients only)<br>C2D1 (pre-dose)<br>C3D1 (pre-dose)<br>C4D1 (pre-dose)<br>C7D1 (pre-dose and End-of Infusion(EOI)*)<br>C10D1 (pre-dose)<br>C13D1 (pre-dose)<br>End-of-treatment (EOT), and<br>90-days post last dose.<br>*End of infusion PK samples should be collected within approximately 15 minutes.<br>C1D1 and C7D1**:** pre- | MedImmune / Intertek Alta |

| Test/assay | Volume blood (approx.) | Type of tube | Collection point (+/- 48hrs) | Location of specimen analysis |
|---|---|---|---|---|
| | | | infusion and immediately post infusion. | |
| Immunogenicity<br>(Antidrug antibody monitoring) | 4 mL | SST | Pre-dose: C1D1, C2D1, C4D1, C7D1, C10D1, C13D1<br>End of treatment<br>90-day post last dose | Medimmune/PPD |
| ANA | 4 mL | SST | Baseline and C4D1 | CC Department of Laboratory Medicine (DLM) |
| AMA &<br>Liver/kidney microsomal antibody | 4 mL | SST | Baseline and C4D1 | CC DLM will send to Mayo Labs |
| T cell activation/ICOS expression<br>(PBMC) | 12 mL | ACD-B (6 mL collection tube) | Pre infusion C1D1, C1D8 (local patients only), C1D15 (local patients only), C2D1, C3D1, C5D1, and EOT (end of treatment) | Medimmune/ Quintiles |
| Plasma-based assays for circulating receptors/ligands e.g. PDL1 | 6 mL | EDTA | C1D1 (pre- dose and End-of Infusion (EOI)*<br>C1D8 (local patients only)<br>C1D15 (local patients only)<br>C2D1 (pre-dose)<br>C3D1 (pre-dose)<br>C4D1 (pre-dose)<br>C7D1 (pre-dose and End-of Infusion(EOI)*)<br>C10D1 (pre-dose)<br>C13D1 (pre-dose)<br>End-of-treatment (EOT), and<br>90-days post last dose.<br>*End of infusion PK | Medimmune |

| Test/assay | Volume blood (approx.) | Type of tube | Collection point (+/- 48hrs) | Location of specimen analysis |
|---|---|---|---|---|
| | | | samples should be collected within approximately 15 minutes.<br>C1D1 and C7D1**:** pre-infusion and immediately post infusion. | |
| Mandatory tumor biopsy | NA | NA | Baseline + C2D1 | Pathology |

## 5.2 NCI CORRELATIVE STUDIES

### 5.2.1 Immune monitoring (all arms)

We will analyze PBMC for quantitative and functional changes of effector cells as well as analyze sera for cytokines and chemokines. The effect on (i) CD4 T cell number and activity, (ii) CD8 T cell number and activity, (iii) NK cell number and activity, (iv) Treg number, (vi) MDSC: frequency + functional assay, (vii) selected cytokines in serum.

Patients will undergo blood sampling (c.120mls blood) on the time points outlined in the table (+/- 48 hrs.). Blood will initially be sent to the Figg's Blood Processing Core (BPC) for barcoding and processing (Section **5.4.1**). On certain occasions, the blood may also be brought to the Greten lab for processing and analysis. PBMC will be isolated by Ficoll density centrifugation. Aliquots of 1 x $10^7$ PBMC/tube will be individually frozen – after initial handling and processing at the Figg laboratory.

### 5.2.2 Liver autoantibody panel for autoimmune hepatitis (AIH)

The AIH Diagnostic Panel includes tests for actin (smooth muscle) antibody, antinuclear antibodies (ANAs), and liver/kidney microsome antibody (LKM-1). ANAs and actin antibody are associated with type 1 AIH, the most common form in the United States, while LKM-1 antibody is associated with type 2 AIH, more commonly found in Europe and in some South American countries. The panel also includes mitochondrial antibody, which can help differentiate AIH from PBC. Given that autoimmune hepatitis is a potential complication of immune checkpoint inhibition we will perform this panel of autoimmune antibodies to investigate this. Samples will be collected at baseline and on D85 approximately. These antibody titers are exploratory and will not be used to guide therapy in the absence of clinical correlation.

### 5.2.3 Mandatory tumor biopsy

An image guided tumor biopsy will be attempted (if feasible) at baseline and (approx.) D29 (+/- 7 days) for analysis of immune infiltration. Tumor Tissue will be processed by the Department of

Pathology, NCI, NIH (Dr. David Kleiner). Two core biopsies will be the attempted. For each specimen obtained the core will be divided in two parts for Surgical Pathology and frozen preservation. If for some reason only one core is able to be obtained, the core will be divided, with half submitted to Surgical Pathology and half used for PD studies.

1) Formalin-fixed.
    i. The half fixed in 10% formalin will be submitted to Surgical Pathology, CCR/NCI (Bldg. 10, 2N212).
    ii. The specimens will have routine H&E stains made as well as 5 additional unstained sections.
2) Frozen-preservation
    i. Two 1.5 ml cryogenic vials (obtained from Greten lab) will be labeled with the patient's name, accession number (HP#) and date using a waterproof sharpie.
    ii. The isotherm flask (Greten lab) will be filled with liquid nitrogen on the morning of the procedure and will be available together with the cryogenic vials for pick up from there when radiology.
    iii. Once the biopsy is ready, the half-core to be cryopreserved will be transferred into an empty 1.5-mL cryogenic vial with the use of sterile, pre-chilled (in dry ice) disposable tweezers.
    iv. The vial with specimen will be immediately dropped into liquid nitrogen contained in an isotherm flask.
    v. The frozen half will be transferred in the isotherm flask to the protocol-specified location for that particular analysis.

#### 5.2.4 Details of Planned Tumor Analysis

We will attempt to perform immunohistochemically and gene analysis of all tumor biopsies. IHC analysis will include characterization of immune cell populations - T-cell, MDSC, NK cells, macrophages- as well as markers of importance in the microenvironment such as PD-L1/2 expression.

RNA analysis will be performed as follows: RNA will be extracted and sent to Cell Processing Section at DTM for microarray analysis using a standard Affymetrix array. Genetic analysis will be on tumor tissue only. No germ line analysis is planned or will be performed without study amendment and IRB approval.

### 5.3 MEDIMMUNE PLANNED STUDIES

All samples will be processed and cryopreserved in the Figg laboratory. Transfer in batch to Medimmune/vendor facilities for further analysis will occur at a later date. Please also see **Appendix B**.

### 5.3.1 Pharmacokinetics

The time points for PK sampling are described in the table in section 5 above. A validated enzyme-linked immunosorbent assay (ELISA) will be used for the quantitative determination of Tremelimumab and Durvalumab in human serum.

Samples will be collected: Day 1 (pre-dose and End of infusion), Day 8 (pre-dose), Day 15 (pre-dose in case of q 2weeks regimen), Day 29 (pre-dose), Day 57 (pre-dose), Day 85(pre-dose), Day 169 (pre-doe and End of Infusion), Day 253 (pre-dose), Day 337 (pre-dose), End of treatment and 90 day post last dose.

### 5.3.2 Immunogenicity

The time points for the assessment of anti-Tremelimumab and anti-Durvalumab antibodies are described in the table in section 5 above. A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the detection of anti-drug antibodies against Tremelimumab and Durvalumab in human serum.

Samples will be collected Pre-dose Day 1, Day 29, Day 85, Day 169, Day 253, Day 337. Additional samples will be collected End of treatment, 90-day post last dose.

### 5.3.3 T CELL Activation/ICOS expression

The number and subsets of T cells as well as other immune cells will be evaluated in PBMC by flow cytometry. The activation status of T cells will also be assessed in the same study. Whole blood samples will be collected pre-infusion at D1, D8, D15 (in case of q2 regimen), D29, D57, D113 and EOT. Samples will be processed to PBMC and stored frozen until time of analysis. Additionally, absolute lymphocyte counts at baseline and in response to Tremelimumab and Durvalumab treatment will be evaluated for any relationship with treatment outcome. Isolated PBMCs may be used for additional functional analysis or assessment of the diversity of the immune cell repertoire

### 5.3.4 Plasma-based assays for circulating receptors/ligands e.g. PDL1

Plasma samples are to be collected at the time points listed directly into plastic 6 ml lavender vacutainer tube with EDTA as anticoagulant. 2-3 ml of obtained plasma are to be aliquoted (1 ml each) and frozen. Samples may be analyzed for circulating levels of soluble factors such as CRP, cytokines, and chemokines. They may include but are not limited to soluble CTLA-4, soluble PD-L1, soluble B7.1/B7.2, soluble IL-6R, vascular endothelial growth factor, fibroblast growth factor, IL-1 IL-2, IL-4, IL-6, IL-8, IL-10, cancer biomarkers (alpha fetoprotein, carcinoembryonic antigen, cancer antigen 125, prostate specific antigen, soluble mesothelin-related protein [SMRP]), granzyme B, IFN, C-X-C motif chemokine 10 (CXCL10), suppressor of cytokine signaling 3 (SOCS3), a proliferation inducing ligand, B-cell activating factor, insulin-like growth factor (IGF)-1, IGF-2, and autoantibodies to host and tumor antigens and explore their association with Tremelimumab and Durvalumab treatment and clinical outcome.

Samples will be collected: Day 1 (pre-dose and End of infusion), Day 8 (pre-dose), Day 15 (pre-dose in case of q 2weeks regimen), Day 29 (pre-dose), Day 57 (pre-dose), Day 85(pre-dose), Day 169 (pre-dose and End of Infusion), Day 253 (pre-dose), Day 337 (pre-dose), End of treatment and 90 day post last dose.

## 5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through a Clinical Trial Data Management system. Should a CRIS screen not be available, the CRIS downtime procedures will be followed. All samples will be sent to Dr. Figg's lab for processing and storage until they are distributed to Dr. Greten's lab or MedImmune for sample analysis as described in the protocol.

### 5.4.1 Samples Managed by Dr. Figg's Blood Processing Core (BPC)

#### 5.4.1.1 BPC contact information

Please e-mail Julie Barnes at Julie.barnes@nih.gov and Paula Carter pcartera@mail.nih.gov at least 24 hours before transporting samples (the Friday before is preferred).

For sample pickup, page 102-11964.

For immediate help, call 240-760-6180 (main blood processing core number) or, if no answer, 240-760-6190 (main clinical pharmacology lab number).

For questions regarding sample processing, contact Julie Barnes by e-mail or at 240-760-6044.

#### 5.4.1.2 Sample Data Collection

All samples sent to the Blood Processing Core (BPC) will be barcoded, with data entered and stored in the LABrador (aka LabSamples) utilized by the BPC. This is a secure program, with access to LABrador limited to defined Figg lab personnel, who are issued individual user accounts. Installation of LABrador is limited to computers specified by Dr. Figg. These computers all have a password restricted login screen. All Figg lab personnel with access to patient information annually complete the NIH online Protection of Human Subjects course.

LABrador creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without LABrador access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. Patient demographics associated with the clinical center patient number are provided in the system. For each sample, there are notes associated with the processing method (delay in sample processing, storage conditions on the ward, etc.).

#### 5.4.1.3 Sample Storage

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80°C according to stability requirements. These freezers are located onsite in the BPC and offsite at NCI Frederick Central Repository Services in Frederick, MD. Visitors to the laboratory are required to be accompanied by laboratory staff at all times.

Access to stored clinical samples is restricted. Samples will be stored until requested by a researcher named on the protocol. All requests are monitored and tracked in LABrador. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol) and that any unused samples must be returned to the BPC. It is the responsibility of the NCI Principal Investigator to ensure that the samples requested are being used in a manner consistent with IRB approval.

### 5.4.2 Procedures for Storage of Tissue Specimens in the Laboratory of Pathology

Tissues designated for clinical diagnostics are transported to the Laboratory of Pathology (LP) where they are examined grossly and relevant portions are fixed, embedded in paraffin and sectioned and stained for diagnostic interpretation. Unutilized excess tissue that is not embedded in paraffin is stored in formalin for up to three months, in accordance with College of American Pathologists/Joint Commission on Accreditation of Healthcare Organizations (CAP/JCAHO) guidelines, and then discarded. Following completion of the diagnostic workup, the slides and tissue blocks are stored indefinitely in the LP's clinical archives. All specimens are catalogued and retrieved utilizing the clinical laboratory information systems, in accordance with CAP/JCAHO regulations. The use of any stored specimens for research purposes is only allowed when the appropriate IRB approval has been obtained. In some cases, this approval has been obtained via the original protocol on which the patient was enrolled.

### 5.4.3 Protocol Completion/Sample Destruction

All specimens obtained in the protocol are used as defined in the protocol. Any specimens that are remaining at the completion of the protocol will be stored in the conditions described in Section **5.4.1.3**. The study will remain open so long as sample or data analysis continues. Samples from consenting subjects will be stored until they are no longer of scientific value or if a subject withdraws consent for their continued use, at which time they will be destroyed. The PI will report any loss or destruction of samples to the NCI IRB as soon as he is made aware of such loss. If the patient withdraws consent the participant's data will be excluded from future distributions, but data that have already been distributed for approved research use will not be able to be retrieved.

- The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by a researcher. Freezer problems, lost samples or other problems associated with samples will also be reported to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

# 6 DATA COLLECTION AND EVALUATION

## 6.1 DATA COLLECTION

The NCI investigators will be responsible for the collection, maintenance, and quality control of the study data. Clinical data will be entered into the NCI C3D electronic database at least once every two weeks when patients are enrolled on the trial. Protocol-specific eCRFs will be developed for this trial in C3D. All data will be kept secure. The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant. The ICOS/activation PBMC data should be transferred from Quintiles to the Biomarker Data Mining System at MedImmune. All analysis done at MedImmune should be shared with NCI.

All adverse events, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Patients will be followed for adverse events for at least 30 days, after removal from study treatment or until off-study, whichever comes first.

An abnormal laboratory value will be recorded in the database as an AE **only** if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

**End of study procedures:** Data will be stored according to HHS and, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

**Loss or destruction of data:** Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

## 6.2 DATA SHARING PLANS

### 6.2.1 Human Data Sharing Plan

I will share de-identified human data generated in this research for future research

- in a NIH-funded or approved public repository clinicaltrials.gov
- in BTRIS
- in publication and/or public presentations

at the time of publication or shortly thereafter.

## 6.3 RESPONSE CRITERIA

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4-8 weeks following initial documentation of objective response.

Before stopping the treatment, progressive disease should be confirmed by imaging preferably 6 weeks after progression has been diagnosed according to RECIST 1.1. Treatment may be continued despite progression according to RECIST 1.1 if modified irRC do not match the criteria for progression and there are no new tumor-related symptoms or worsening of existing symptoms.

Confirmation of progression will not be done if in the opinion of Investigator patient has better option with another treatment.

**Response Evaluation Criteria in Solid Tumors (RECIST)**: 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)[45]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria. To assess response, the tumor burden at baseline will be estimated also and used for comparison with subsequent measurements. The treatment may continue immune checkpoint inhibitors (Tremelimumab and/or Durvalumab) and the Subject may remain on study according to the investigator's decision in case of progressive disease according to RECIST 1.1. For this situation, modified Immune-Related response criteria (irRC) based on RECIST 1.1 in all subjects without worsening of existing symptoms or developing new tumor-related symptoms at the time of progression will be used. Modified Immune-related response criteria will be primarily used as guidance for further clinical care.

**Modified immune-related response criteria (irRC):** This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.
For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 6 weeks after initial imaging (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%

### 6.3.1 Definitions

#### 6.3.1.1 Evaluable for toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Tremelimumab and Durvalumab.

#### 6.3.1.2 Evaluable for objective response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

### 6.3.2 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:

- By chest x-ray: ≥20 mm;

- By CT scan:
    - Scan slice thickness 5 mm or under as ≥10 mm with CT scan
    - Scan slice thickness >5 mm: double the slice thickness
- With calipers on clinical exam: ≥10 mm.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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 of diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum of 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.

### 6.3.3 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.

#### 6.3.3.1 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.

#### 6.3.3.2 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.

#### 6.3.3.3 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.

#### 6.3.3.4 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.

#### 6.3.3.5 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.

#### 6.3.3.6 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.

### 6.3.4 Response Criteria

#### 6.3.4.1 Evaluation of Target Lesions

Revised Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

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 of 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). NOTE: While RECIST PD will be noted and recorded the immune-related RECIST criteria will be applied to determine discontinuation of study treatment.

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.

#### 6.3.4.2 Evaluation of Non-Target Lesions

Revised Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

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).

6.3.4.3 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.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|---|---|---|---|---|
| lesions may be accepted as disease progression.<br>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 | | |

6.3.5 Duration of Response

6.3.5.1 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.

6.3.5.2 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.

## 6.4 MODIFIED IMMUNE-RELATED RESPONSE CRITERIA (IRRC)

Modified immune-related response criteria (irRC) will also be employed in this study. This new classification is based on the recent learning from clinical studies with cancer immunotherapies that even if some new lesions appear at the beginning of a treatment or if the total tumor burden does not increase substantially, tumor regressions or stabilizations might still occur later. The irRC were created using bi-dimensional measurements (as previously widely used in the World Health Organization criteria). For this trial, the concepts of the irRC are combined with RECIST 1.1 to come up with the modified irRC.

6.4.1 The modified irRC based on RECIST 1.1:

New non-measurable lesions: Do not define progression but precludes (irCR).

New measurable lesions: Incorporated into tumor burden.

Overall irCR: Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm.

Overall irPR: Sum of the longest diameters of target and new measurable lesions decreases ≥30%.

Overall irSD: Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir).

Overall irPD: Sum of the longest diameters of target and new measurable lesions increases ≥20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented.

Please refer to **Appendix C**.

### 6.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

## 7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

### 7.1 DEFINITIONS

#### 7.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

#### 7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

#### 7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the

pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### 7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

### 7.1.5 Serious Adverse Event

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

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

### 7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

### 7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

### 7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

### 7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

### 7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

(b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggest that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

## 7.2 NCI-IRB AND CLINICAL DIRECTOR REPORTING

### 7.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

### 7.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

    **NOTE**: Grade 1 events are not required to be reported.

### 7.2.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

## 7.3 IND SPONSOR REPORTING CRITERIA

During the first 30 days after the subject receives investigational agent/intervention, the investigator must immediately report to the sponsor, using the mandatory MedWatch form 3500a or equivalent, any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. For serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention, only report those that have an attribution of at least possibly related to the agent/intervention.

Required timing for reporting per the above guideline:

- Deaths (except death due to progressive disease) must be reported via email within 24 hours. A complete report must be submitted within one business day.
- Other serious adverse events including deaths due to progressive disease must be reported within one business day

Events will be submitted to the Center for Cancer Research (CCR) at: CCRsafety@mail.nih.gov and to the CCR PI and study coordinator.

### 7.3.1 Reporting Pregnancy

#### 7.3.1.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the study treatment should be discontinued immediately and the pregnancy reported to the Sponsor. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agents (s) should be documented in box B5 of the MedWatch form "Describe Event or Problem".

Pregnancy itself is not regarded as an SAE. However, as patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, the CCR is requesting that pregnancy should be reported in an expedited manner as **Grade 3** "***Pregnancy, puerperium and perinatal conditions - Other (pregnancy)***" under the ***Pregnancy, puerperium and perinatal conditions*** SOC.

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.

If any pregnancy occurs in the course of the study, then the investigator should inform the Sponsor within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative will work with the investigator to ensure that all relevant information is provided to the Sponsor 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.

#### 7.3.1.2 Paternal exposure

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

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 of investigational drug after the last dose should, if possible, be followed up and documented.

## 7.4 SAFETY REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

All events listed below must be reported in the defined timelines to CCRsafety@mail.nih.gov.

The CCR Office of Regulatory Affairs will send all reports to the manufacturer as described below.

### 7.4.1 Reporting of serious adverse events

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

The investigator and/or sponsor must inform the FDA, via a MedWatch or equivalent, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca.

A copy of the MedWatch report must be send 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 above timepoints.

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

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-16-11987) (AstraZeneca only)

* 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.

### 7.4.2 Overdose

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

The investigator will use clinical judgment to treat any overdose.

If the overdose results in an AE or SAE, these should be reported as such.

### 7.4.3 Hepatic function abnormality

Hepatic function abnormality in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

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

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

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

### 7.4.4 Reporting Removal from Protocol Therapy and Off Study

The study drug manufacturer should be notified of any ongoing AE that may delay treatment or necessitate permanent discontinuation of treatment.

## 7.5 DATA AND SAFETY MONITORING PLAN

### 7.5.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about radiation dose and schedule will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

### 7.5.2 Sponsor Monitoring Plan

As a sponsor for clinical trials, FDA regulations require the CCR to maintain a monitoring program. The CCR's program allows for confirmation of: study data, specifically data that could affect the interpretation of primary study endpoints; adherence to the protocol, regulations, and SOPs; and human subjects protection. This is done through independent verification of study data with source documentation focusing on:

- Informed consent process
- Eligibility confirmation
- Drug administration and accountability
- Adverse events monitoring
- Response assessment.

The monitoring program also extends to multi-site research when the CCR is the coordinating center.

This trial will be monitored by personnel employed by a CCR contractor. Monitors are qualified by training and experience to monitor the progress of clinical trials. Personnel monitoring this study will not be affiliated in any way with the trial conduct.

## 8 STATISTICAL CONSIDERATIONS

The primary objective of this trial is to conduct a pilot study of immune checkpoint inhibition in combination with Stereotactic Body Radiation Therapy (SBRT) in patients with advanced pancreatic cancer. As such, the main goal is to determine the safety of the proposed combinations of checkpoint inhibitors and SBRT as well as to evaluate if there may be any evidence of acceptable efficacy for any of the treatment combinations as well as whether one approach may be considered preferable over the others for use in future trials.

With an amendment A the decision has been made to not proceed with Arms B1 and B2 and move directly from Arms A1 and A2 to Arms C1 and C2. Unfortunately, we have not seen any evidence of clinical activity as of yet. At the time of study design we did not have any supportive safety data for the combination of tremelimumab and durvalumab and that is why a staggered approach was conceived. We now have safety data for the combination of durvalumab and tremelimumab and the company has a recommended dose and schedule for the combination of these agents which they are moving forward across all their studies. We originally thought that Arms B1 and B2 (Tremelimumab 10mg/kg + SBRT) would provide some safety data to inform Arms C1 and C2, but this is no longer the case as the recommended dosing of Tremelimumab for Arms C1 and C2 is 10mg/kg (i.e., 10% of the dose in Arms B1 and B2).

With amendment I, an additional secondary objective has been added to more precisely estimate the survival in patients enrolled in Arm C2.

Safety will be evaluated as follows: the trial will be conducted in a sequential manner with patients enrolled in the following order: A1, A2, C1, and C2. The goal will be to evaluate 10 patients in A1 and then 10 in A2, provided that no more than 1 of the first 6 in A1 or A2 has a DLT, and that no more than 3 of 10 patients in either A1 or A2 has a DLT. If either of these is exceeded, then no further patients would be enrolled in that particular arm. The same rules apply to C1 and C2, but with all 10 in C1 and the first 10 in C2. Thus, if no safety concerns arise (0-1 of the first 6; 0-3 of 10 have a DLT in each of the 4 arms), then a total of 50 evaluable patients will be enrolled. To allow for a moderate number (30-40%) of inevaluable patients – based on disease progression – we will set the accrual ceiling at 70 patients.

Among the initial patients enrolled in C2, there were two patients who have survived to approximately one year and beyond. It will be desirable to have additional patients enrolled in this arm to more precisely estimate its survival. Thus, in amendment I, the accrual to arm C2 will be expanded to a total of 20 evaluable patients to provide a more precise estimate of the patients' survival in that arm. The survival of the 20 patients will be determined by a Kaplan-Meier curve with 95% two-sided confidence intervals reported primarily at the median, and secondarily at 6 and 12 months. In addition, as a secondary analysis, the survival of the initial 10 patients treated on that arm will be reported separately from that of the second 10 patients treated on that arm, and the results will be informally compared to establish the degree of similarity of survival in the earlier and later treated patients.

The median survival in second-line studies in this patient population is approximately 4 months. An important efficacy endpoint will be reached if a given patient is able to survive for 6 months or longer.

The fraction of such patients will also be evaluated in the following manner, for purposes of making decisions about future directions, in addition to the new secondary endpoint focusing on C2, which demonstrated some survival advantage based on the first 10 patients:

### 8.1 CROSS-ARM COMPARISON

Evaluation will be performed in combination of arms: A1+A2 and C1+C2. Within each of arm combinations A1+A2 and C1+C2, the 20 total patients who are treated in the combination of arms (A1+A2) and the total of 30 who are treated in the combination of arms (C1+C2) will be evaluated as a single group and the following objective will be evaluated: For the combination of A1+A2 (n=20), if 3 or more patients out of 20 are able to survive to 6 months, this would be a desirable goal, since the probability of observing 3 or more surviving to 6 months is 7.5% if the true underlying probability of surviving 6 months is 5% and the probability is 90.9% if the true underlying probability of surviving 6 months is 25%. Thus, 3 or more surviving 6 months or longer is a meaningful goal in a combination of arms of 20 patients. For the combination of C1+C2 (n=30), if 4 or more patients out of 30 can survive to 6 months, this would be a desirable goal, since the probability of observing 4 or more surviving to 6 months is 6.1% if the true underlying probability of surviving 6 months is 5% and the probability is 96.3% if the true underlying probability of surviving 6 months is 25%. Thus, 4 or more surviving 6 months or longer is a meaningful goal in a combination of arms of 30 patients. Given that there are 2 combination of treatment arms to be evaluated (A1+A2 and C1+C2), the one with the greatest fraction of 6-month survivors, provided that the surviving number is 3 or more of 20 patients in A1+A2 or 4 or more of 30 patients in C1+C2, will be considered for further evaluation. The

numbers of patients in each combination of arms who live to or beyond 6 months who receive 1 day of SBRT or receive 5 days of SBRT will also be reported and compared informally, and will help guide future decisions.

### 8.2 DURATION OF RADIATION

In addition, the 20 patients who receive 1 day of SBRT and the 30 patients who receive 5 days of SBRT will be evaluated via a selection design, although with the caveat that lack of randomization and uneven numbers of patients should be considered when interpreting the results. The 20 or 30-patient SBRT combination of arms with the greatest fraction of survivors to 6 months would be preferentially chosen for further study. If there are 20-30 patients in the two groups and assuming the true rates are 15% and 25% in the two groups, the probability of correct selection is at least 78%.. Given that the two groups of 20 or 30 patients each have subsets of 10 (or 20) patients treated homogeneously, this would also need to be explored within the arms.

Secondary endpoints include evaluation of clinical endpoints such as response rate, duration of response, progression free survival, and overall survival. These will be estimated using confidence intervals for response rates, descriptive statistic for duration of response and Kaplan-Meier curves for PFS and OS. PK parameters will be obtained and results will be estimated and described using standard exploratory and descriptive statistical techniques. Any statistical comparisons which may be undertaken will be done using non-parametric tests, without formal correction for multiple comparisons, but interpreted in the context of the secondary nature of the tests and the number of such tests performed.

### 8.3 ANALYSIS OF IMMUNOGENICITY

Only subjects who receive at least one dose of both Durvalumab and/or tremelimumab, and provide the baseline and at least one post-treatment sample, will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-Durvalumab or anti-tremelimumab antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-Durvalumab or anti-tremelimumab antibodies. The impact of ADAs on PK will also be assessed if data allow. Samples confirmed positive for ADAs may also be evaluated for neutralizing antibody activity.

### 8.4 ANALYSIS OF PHARMACOKINETICS

Only subjects who receive at least one dose of Durvalumab and/or tremelimumab, and provide the baseline and at least one post-treatment sample, will be evaluated. Individual Durvalumab and tremelimumab concentrations will be tabulated by dose arm along with descriptive statistics. The PK of Durvalumab and tremelimumab will be assessed using parameters including Cmax, trough concentration (Cmin), time to peak concentration (Tmax) and AUC after the first dose. Durvalumab and tremelimumab steady-state PK parameters including peak concentration (Cmax,ss), trough concentration (Cmin,ss), and time to peak concentration (Tmax,ss) will be estimated. Accumulation to steady state will be assessed as the ratio of Cmax,ss:Cmax and Cmin,ss:Cmin. All PK parameters will be estimated by non-compartmental analysis. Descriptive statistics of non-compartmental PK parameters will be provided.

# 9 COLLABORATIVE AGREEMENTS

## 9.1 AGREEMENT TYPE

A CRADA, 02908, is in place between MedImmune, Inc. and CCR, NCI.

# 10 HUMAN SUBJECTS PROTECTIONS

## 10.1 RATIONALE FOR SUBJECT SELECTION

Subjects treated on this study, will be individuals with advanced pancreatic adenocarcinoma, which is not amenable to potentially curative resection. Individuals of any sex, race or ethnic group will be eligible for this study. Eligibility assessment will be based solely on the patient's medical status. Recruitment of patients onto this study will be through standard CCR mechanisms. No special recruitment efforts will be conducted.

## 10.2 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have pancreatic adenocarcinoma, and because of unknown toxicities in pediatric patients.

## 10.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **10.5**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in NIH Policy 87-4 and NIH HRPP SOP 14E for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

## 10.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS FOR ALL PARTICIPANTS

### 10.4.1 Risks of exposure to ionizing radiation

This research study involves exposure to radiation from 2 CT guided biopsies**.** This radiation exposure is not required for medical care and is for research purposes only. The amount of radiation received in this study is 1.6 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. More information about radiation is available in the pamphlet, An Introduction to Radiation for NIH Research Subjects.

### 10.4.2 Risk of baseline biopsy

All care will be taken to minimize risks that may be incurred by tumor sampling. However, there are procedure-related risks (such as bleeding, infection and visceral injury) that will be explained fully during informed consent.

### 10.4.3 Other risks/benefits

The potential benefit to a patient that goes onto study is a reduction in the bulk of their tumor which may or may not have favorable impact on symptoms and/or survival. Potential risks include the possible occurrence of any of a range of side effects which are listed in the Consent Document. The procedure for protecting against or minimizing risks will be to medically evaluate patients on a regular basis as described.

## 10.5 RISKS/BENEFITS ANALYSIS

For patients with pancreatic adenocarcinoma cancer, median survival is in the range between 6 and 10 months. It is possible that treatment on this protocol may reduce tumor burden or lessen symptoms caused by the cancer. While treatment on this protocol may not individually benefit subjects. The knowledge gained from this study may help others in the future who have pancreatic adenocarcinoma. Potential risks include the possible occurrence of any of a range of side effects listed. If patients suffer any physical injury as a result of the biopsies, immediate medical treatment is available at the NIH's Clinical Center in Bethesda, Maryland. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

## 10.6 CONSENT PROCESS AND DOCUMENTATION

Patients will meet with an associate or principal investigator on the trial in the GI oncology Clinic, during the initial evaluation for this study. During that meeting, the investigator will inform patients of the purpose, alternatives, treatment plan, research objectives and follow-up of this trial. The investigator will then provide a copy of the IRB-approved informed consent document that is included in this protocol. The patient will be allowed to take as much time as he wishes, in deciding whether or not he wishes to participate. If a prolonged period of time expires during the decision making process (several weeks, as an example), it may be necessary to reassess the patient for protocol eligibility.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on the study.

### 10.6.1 Reconsent via Telephone

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature-- -will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator.

10.6.2 Informed Consent of non-English Speaking Subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12, 45 CFR 46.117 (b) (2), and 21 CFR 50.27 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

# 11 PHARMACEUTICAL INFORMATION

## 11.1 TREMELIMUMAB

11.1.1 Source

Tremelimumab will be supplied by Medimmune, Inc.

11.1.2 Formulation and Preparation

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

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

Tremelimumab is supplied as a sterile IV solution, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL

accounting to 400 mg/vial) of Tremelimumab, in an isotonic solution at pH 5.5. Vials containing Tremelimumab must be stored in the refrigerator at 2-8C. The 20 mg/mL solution will be diluted into a saline bag for IV infusion.

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

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

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

### 11.1.3 Stability and Storage

Tremelimumab must be stored in the refrigerator at 2-8$^0$C. The 20 mg/mL solution will be diluted into a saline bag for IV infusion. Vials containing Tremelimumab may be gently inverted for mixing, but should not be shaken.

### 11.1.4 Administration procedures

Tremelimumab will be administered as an IV infusion (250 mL) over approximately 1 hour. When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

### 11.1.5 Dose Calculation

The subject's weight (in kilograms) must be measured prior to each dosing for dose calculation. Measurements can be taken in street clothes without shoes and a calibrated scale must be used for all measurements.

The dose will be calculated at each dosing visit using the following formula:

Tremelimumab:

The tremelimumab dose will be calculated using the following formula:

Arms A1 and A2 only: By weight: Dose (mL) = [subject weight (kg) × dose (mg/kg)]/ 20 (mg/mL) where 20 mg/mL is tremelimumab concentration.

The corresponding volume of tremelimumab 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.

Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

Arms C1 and C2: Following amendment B, Tremelimumab will be dosed at a flat dose of 75 mg via IV infusion q4w for up to 4 doses/cycles). Flat weight dosing will be used for all other patients including those who are greater than 75Kg e.g. 100-110Kg.

## 11.2 DURVALUMAB

### 11.2.1 Source

Durvalumab will be supplied by Meddimmune, Inc.

### 11.2.2 Formulation and Preparation

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass.

| **Investigational Product** | **Manufacturer** | **Concentration and Formulation as Supplied** |
|---|---|---|
| Durvalumab | MedImmune | Formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, pH 6.0. |

Durvalumab is supplied is supplied as a white to off-white lyophilized powder in clear 10R glass vials closed with an elastomeric stopper and a flip-off cap overseal. Each vial contains 200 mg (nominal) of active investigational product.

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

- IV infusion bags of 0.9% sodium chloride injection.
- IV infusion lines. All DEHP-containing or DEHP-free lines are acceptable.
- Catheters/infusion sets made of polyurethane or fluoropolymer with silicone and stainless steel and/or PVC components.

11.2.3 Stability

| | | | |
|---|---|---|---|
| Manufacturer | MedImmune | | |
| Expiration/Retest Date | *Expiration/retest dates are documented on the Certificate of* | | |
| Container Description | *Type:* | *Material:* | *Size:* |
| Formulation | Lyophilized powder containing 200 mg Durvalumab. When reconstituted with 4 mL of WFI, the solution contains 50 mg/mL Durvalumab, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) | | |
| Active Ingredient Content | *Mass/Weight:* | *Volume:* | *Concentration:* |
| Storage Conditions | +2°C to +8°C | | |
| Stability after reconstitution | 24h at +2-8°C and 6h at +25°C/ambient | | |
| Labeling | Product name, lot number, route of administration, and storage conditions | | |

If Durvalumab administration has to be delayed, temporally interrupted or the infusion rate decreased, the total time between reconstitution and completion of the infusion should not exceed 6 hours at room temperature or Total in-use storage time from reconstitution of Durvalumab to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8 C. If administration time exceeds these limits, a new dose must be prepared from new vials. Durvalumab does not contain preservatives and any unused portion must be discarded.

11.2.4 Storage

Unopened vials of Durvalumab lyophilized Drug Product must be stored at 2°C to 8°C (36°F to 46°F).

Protect from light.

11.2.5 Administration procedures

Durvalumab is to be administered as an IV solution of 10 mg/kg over approximately 1 hour.

When an IV bag is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

Since the compatibility of Durvalumab with other IV medications and solutions, other than normal saline (0.9% [w/v] sodium chloride for injection), is not known, the Durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of Durvalumab administration must be recorded in the source documents.

For arms C1 and C2 Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion.

11.2.5.1 Dose Calculation

*11.2.5.1.1 Arms A1 and A2 only*

The subject's weight (in kilograms) must be measured prior to each dosing for dose calculation. Measurements can be taken in street clothes without shoes and a calibrated scale must be used for all measurements.

The dose of MEDI 4736 will be calculated at each dosing visit using the following formula:

By weight: Dose (mL) = [subject weight (kg) × dose (mg/kg)]/ 50 (mg/mL) where 50 mg/mL is Durvalumab concentration after reconstitution.

The corresponding volume of tremelimumab 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.

Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

*11.2.5.1.2 Arms C1 and C2*

Following amendment B, MEDI 4736 (now called Durvalumab) will be dosed at a flat dose of 1500 mg via IV infusion q4w for up to 4 doses/cycles (in combination with 75 mg tremelimumab via IV infusion q4w for up to 4 doses/cycles), and then continue 1500 mg durvalumab q4w (see **Figure 3**). Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (i.e. 1mg/kg for tremelimumab and 20mg/kg for durvalumab). Flat weight dosing will be used for all other patients including those who are greater than 75Kg e.g. 100-110Kg.

11.2.6 Durvalumab Dose Preparation Steps

11.2.6.1 Durvalumab is formulated at 50 mg/mL in 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80 and is supplied as a lyophilized powder in 10R vials

11.2.6.2 Durvalumab should be reconstituted using aseptic techniques with 4.0 mL sterile water for injection (WFI) with the liquid added gently to the side of the vial to minimize product foaming, to give a final concentration of 50 mg/mL. The reconstituted solution will be diluted with 0.9% (w/v) saline for IV infusion using syringes or bags.

11.2.6.3 In arms C1 and C2 Durvalumab infusion will start approximately 1 hour after the end of tremelimumab infusion using a 0.2-µm in-line filter.

11.2.6.4 Flush the IV line with a volume of normal 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.

## 11.3 INVESTIGATIONAL PRODUCT PREPARATION STEPS

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

1) Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose.
2) All investigational product vials should be equilibrated to room temperature for 30 minutes prior to dose preparation.
3) To prepare the IV bag, first, calculate the dose volume of investigational product required. Second, remove the volume of 0.9% sodium chloride IV solution equivalent to the calculated dose volume of investigational product from the IV bag.
4) Lastly, add the calculated dose volume of investigational product to the IV bag. Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.
5) Example: A subject weighing 85 kg will require 42.5 mL (3 vials) of investigational product. Remove 42.5 mL of saline from the commercial IV bag. Add the 42.5 mL of investigational product to the IV bag and gently mix by inverting up and down.
6) Labels will be prepared in accordance with Good Manufacturing Practice (GMP).

## 11.4 INVESTIGATIONAL PRODUCT INSPECTION

Each vial selected for dose preparation should be inspected.

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (**11.5.1)** for further instructions.

During the inspection if the solution is not clear or any turbidity, discoloration or particulates are observed, notify your site monitor and store the vial(s) in QUARANTINE at refrigerated (2-8ºC) temperature for drug accountability and potential future inspection.

Notify the IXRS that the unusable vials are damaged. The IXRS will indicate the replacement vials. Select appropriate replacement vials for the preparation of the subject's dose, and perform the same inspection on the newly selected vials. For accountability, record the total number of vials removed from site inventory. Used vials should be held for accountability purposes at ambient storage temperature.

## 11.5 INVESTIGATIONAL PRODUCT ACCOUNTABILITY

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune.

### 11.5.1 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the Product

Complaint Department. During the investigation of the product complaint, all investigational products must be stored at labeled conditions unless otherwise instructed.

Product defects may be related to component, product, or packaging and labeling issues. The list below includes, but is not limited to, descriptions of product complaints that should be reported.

**Component Issue:** Defect in container or dosing mechanism of the investigational product. The component defect may be damaged, missing, or broken. Component examples include vials, stoppers, caps, spray barrels, spray nozzles, or plungers.

**Product Issue:** Defect in the product itself. The product appearance has visual imperfections such as foreign particles, crystallization, discoloration, turbidity, insufficient volume, or anything that does not apply to the product description.

**Packaging/Labeling Issue:** Defect in the packaging or labeling of the product. The packaging or labeling defects may be damaged or unreadable, or the label may be missing.

When reporting a product complaint, site staff must be prepared to provide the following information:

1) Customer information: reporter name, address, contact number, and date of complaint

2) Product information: product name, packaging kit number or lot number, expiry date, and clinical protocol number

3) Complaint information: complaint issue category and description

MedImmune contact information for reporting product complaints:

Email: productcomplaints@medimmune.com

Phone: +1-301-398-2105 +1-877-MEDI-411 (+1-877-633-4411)

Fax: +1-301-398-8800

Mail: MedImmune, LLC Attn: Product Complaint Department One MedImmune Way, Gaithersburg, MD USA 20878

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# 13 APPENDICES

## 13.1 APPENDIX A: PERFORMANCE STATUS CRITERIA

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## 13.2 APPENDIX B: MEDIMMUNE SAMPLE PREPARATION PROCEDURES SERUM- SST TUBE

1. Draw maximum volume of blood into gold top SST tube (s). Record time of collection.
2. Gently invert 5 times.
3. Allow the blood to clot for 30 minutes at room temperature.
4. Centrifuge within 2 hours of collection at 1100 -1300 g for 15 minutes.
5. Transfer serum into labeled cryovials.
6. Immediately freeze the cryovials upright at -20ºC or colder.
7. Store at -20ºC or colder until shipment on dry ice.

Plasma- $K_2$ EDTA Tube

1. Draw maximum volume of blood into lavender top $K_2$ EDTA tube(s). Record time of collection
2. Gently invert 8 to 10 times.
3. Centrifuge within 2 hours of collection at 1100 -1300 g for 10 minutes.
4. Transfer plasma into labeled cryovials.
5. Immediately freeze the cryovials upright at -20ºC or colder.
6. Store at -20ºC or colder until shipment on dry ice.

Tube Label should include:

1. Patient Identifier
2. Sample ID (Serum 1, Cycle 1, Day 1etc.)
3. Sample type (plasma, serum)
4. Sample volume
5. Collection time
6. Barcode (if this system is available)

## 13.3 APPENDIX C: MODIFIED IMMUNE-RELATED RESPONSE CRITERIA (IRRC)

For modified irRC, only target and measurable lesions are taken into account. In contrast to the RECIST 1.1 criteria, the modified irRC criteria (a) require confirmation of both progression and response by imaging at 6 weeks after initial imaging and (b) do not necessarily score the appearance of new lesions as progressive disease if the sum of lesion diameters of target lesions (minimum of 10 mm per lesion, maximum of 5 target lesions, maximum of 2 per organ) and measurable new lesions does not increase by ≥ 20%.
The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline, during the trial, and at the end of trial visit. All measurements should be recorded in metric notation. The modified irRC based on RECIST 1.1 are displayed below.

Modified immune-related response criteria are defined as follows:

New measurable lesions: Incorporated into tumor burden.

New non-measurable lesions: Do not define progression but precludes (irCR).

| | |
|---|---|
| Overall irCR: | Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to 10 mm. |
| Overall irPR: | Sum of the longest diameters of target and new measurable lesions decreases ≥ 30%. |
| Overall irSD: | Sum of the longest diameters of target and new measurable lesions neither irCR, irPR, (compared to baseline) or irPD (compared to nadir). |
| Overall irPD: | Sum of the longest diameters of target and new measurable lesions increases ≥ 20% (compared to nadir), confirmed by a repeat, consecutive observations at least 4 weeks (normally it should be done at 6 weeks) from the date first documented. |

**Overall Responses Derived from Changes in Index, Non-Index, and New Lesions**

| Measurable Response | Non-Measurable Response | | Overall Response Using Modified irRC |
|---|---|---|---|
| **Index and New, Measurable Lesions (Tumor Burden)[1]** | **Non-Index Lesions** | **New, Non-Measurable Lesions** | |
| Decrease 100% | Absent | Absent | irCR[2] |
| Decrease 100% | Stable | Any | irPR[2] |
| Decrease 100% | Unequivocal progression | Any | irPR[2] |
| Decrease ≥ 30% | Absent / Stable | Any | irPR[2] |
| Decrease ≥ 30% | Unequivocal progression | Any | irPR[2] |
| Decrease < 30% to increase < 20% | Absent / Stable | Any | irSD |
| Decrease < 30% to increase < 20% | Unequivocal progression | Any | irSD |
| Increase ≥ 20% | Any | Any | irPD |

[1] Decreases assessed relative to baseline
[2] Assuming that the response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 weeks apart (normally it should be done 6 weeks apart).

## 13.4 APPENDIX D: DOSING MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED, INFUSION-RELATED, AND NON-IMMUNE–MEDIATED REACTIONS (MEDI4736 MONOTHERAPY OR COMBINATION THERAPY WITH TREMELIMUMAB OR TREMELIMUMAB MONOTHERAPY) 1 NOVEMBER 2017 VERSION

### General Considerations

| Dose Modifications | Toxicity Management |
|---|---|
| Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.<br>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:<br>• 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<br>• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing<br>**Grade 1** No dose modification<br>**Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.<br>If toxicity worsens, then treat as Grade 3 or Grade 4.<br>Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper.<br>Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:<br>1. The event stabilizes and is controlled.<br>2. The patient is clinically stable as per Investigator or treating physician's clinical judgement.<br>3. Doses of prednisone are at ≤10 mg/day or equivalent. | It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table:<br>– 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.<br>– 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.<br>– Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.<br>– 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.<br>– Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation.<br>– If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to |

## General Considerations

| Dose Modifications | Toxicity Management |
|---|---|
| **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.<br>**Grade 4** Permanently discontinue study drug/study regimen.<br>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.<br>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<br>Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus). | 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).<br>– 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.<br>– With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring.<br>– 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 | – All recommendations for specialist consultation should occur with a |

| Pediatric Considerations | |
|---|---|
| **Dose Modifications** | **Toxicity Management** |
| 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 | pediatric specialist in the specialty recommended.<br>– 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.<br>– 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.<br>– For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist.<br>– 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:**<br>– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below.<br>– Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan. |
| | **Grade 1**<br>(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):**<br>– 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.<br>– Consider Pulmonary and Infectious disease consult. |
| | **Grade 2**<br>(symptomatic; medical intervention indicated; limiting instrumental ADL) | Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.<br>• If toxicity worsens, then treat as Grade 3 or Grade 4.<br>• If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/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):**<br>– Monitor symptoms daily and consider hospitalization.<br>– Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent).<br>– Reimage as clinically indicated.<br>– 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<br>– If still no improvement within 3 to 5 days despite IV |

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| | | 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.<br>– 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]<br>– Consider pulmonary and infectious disease consult.<br>– Consider, as necessary, discussing with study physician. |
| **Grade 3 or 4**<br>(Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated)<br><br>(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):**<br>– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.<br>– Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician.<br>– Hospitalize the patient.<br>– Supportive care (e.g., oxygen).<br>– 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.<br>– 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 |

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| | | | 2B recommendation]).[a] |
| **Diarrhea/Colitis** | **Any Grade** | **General Guidance** | **For Any Grade:**<br>– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus).<br>– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc.<br>– Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event.<br>– Use analgesics carefully; they can mask symptoms of perforation and peritonitis. |
| | **Grade 1**<br>(Diarrhea: stool frequency of <4 over baseline per day)<br>(Colitis: asymptomatic; clinical or diagnostic observations only) | No dose modifications. | **For Grade 1:**<br>– Monitor closely for worsening symptoms.<br>– Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment. |
| | **Grade 2**<br>(Diarrhea: stool frequency of 4 to 6 over baseline per day)<br>(Colitis: abdominal pain; mucus or blood in | Hold study drug/study regimen until resolution to Grade ≤1<br>• If toxicity worsens, then treat as Grade 3 or Grade 4.<br>• If toxicity improves to Grade ≤1, then study drug/study regimen can be | **For Grade 2:**<br>– Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide.<br>– Promptly start prednisone 1 to 2 mg/kg/day PO or IV |

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| stool) | resumed after completion of steroid taper. | equivalent.<br>– If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.<br>– If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.<br>– Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days.<br>– 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**<br>(Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences)<br>(Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; | **Grade 3**<br>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.<br><br>**Grade 4**<br>Permanently discontinue study drug/study regimen. | **For Grade 3 or 4:**<br>– Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent.<br>– Monitor stool frequency and volume and maintain hydration.<br>– Urgent GI consult and imaging and/or colonoscopy as appropriate.<br>– If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general |

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| | Grade 4 colitis: life-threatening consequences, urgent intervention indicated) | | guidance before using infliximab.<br>– 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)**<br>Infliximab should not be used for management of immune-related hepatitis.<br><br>**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:**<br>– Monitor and evaluate liver function test: AST, ALT, ALP, and TB.<br>– Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications). |
| | **Grade 1**<br>(AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN) | • No dose modifications.<br>• If it worsens, then treat as Grade 2 event. | **For Grade 1:**<br>– Continue LFT monitoring per protocol. |
| | **Grade 2**<br>(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.<br>• If toxicity worsens, then treat as Grade 3 or Grade 4.<br>• If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. | **For Grade 2:**<br>– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved.<br>– If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician.<br>– If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.<br>– 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.<br>– If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start |

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| | | immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**<br>– 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**<br>(Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN)<br>(Grade 4: AST or ALT >20×ULN and/or TB >10×ULN) | **For Grade 3:**<br>For elevations in transaminases ≤8 × ULN, or elevations in bilirubin ≤5 × ULN:<br>• Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline<br>• Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper.<br>• Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days<br>For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen.<br>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 | **For Grade 3 or 4:**<br>– Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.<br>– If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**<br>– Perform hepatology consult, abdominal workup, and imaging as appropriate.<br>– 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] |

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| | | findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]<br><br>**For Grade 4:**<br>Permanently discontinue study drug/study regimen. | |
| **Hepatitis (elevated LFTs)**<br>Infliximab should not be used for management of immune-related hepatitis.<br><br>**THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients**<br><br>See instructions at bottom of shaded area if transaminase rise is not isolated but (at any | **Any Grade** | **General Guidance** | **For Any Grade:**<br>– Monitor and evaluate liver function test: AST, ALT, ALP, and TB.<br>– Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]).<br>– For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg<br>– For HCV+ patients: evaluate quantitative HCV viral load<br>– 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<br>– Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold<br>– For HCV+ with HBcAB+: Evaluate for both HBV and HCV as |

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| time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation** | | | above |
| | **Grade 1**<br>(Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline) | • No dose modifications.<br>• If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event.<br>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**<br>(Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline)<br><br>(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.<br>• If toxicity worsens, then treat as Grade 3 or Grade 4.<br>If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. | **For Grade 2:**<br>– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved.<br>– Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion.<br>– Consider, as necessary, discussing with study physician.<br>– 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.<br>– 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.<br>– 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 |

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|---|---|---|
| | | (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** |
| **Grade 3**<br>(Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline)<br><br>(Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline) | • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline<br>• Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper.<br>• Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days<br>Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b] | **For Grade 3:**<br>– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved.<br>– Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy.<br>– Consider, as necessary, discussing with study physician.<br>– If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent.<br>– If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**<br>– 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**<br>(Isolated AST or ALT >20×ULN, whether | Permanently discontinue study drug/study regimen. | **For Grade 4:**<br>**Same as above**<br>**(except would recommend obtaining liver biopsy early)** |

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| | normal or elevated at baseline) | | |
| **If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR):**<br>- **Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise**<br>- **Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise**<br>- **Grade 3-4: Permanently discontinue study drug/study regimen** | | | |
| **Nephritis or renal dysfunction**<br>(elevated serum creatinine) | **Any Grade** | **General Guidance** | **For Any Grade:**<br>– Consult with nephrologist.<br>– Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria).<br>– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections).<br>– Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event. |
| | **Grade 1**<br>(Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN) | No dose modifications. | **For Grade 1:**<br>– Monitor serum creatinine weekly and any accompanying symptoms.<br>• If creatinine returns to baseline, resume its regular monitoring per study protocol.<br>• If creatinine worsens, depending on the severity, treat |

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| | | as Grade 2, 3, or 4.<br>– Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. |
| **Grade 2**<br>(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.<br>• If toxicity worsens, then treat as Grade 3 or 4.<br>• If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper. | **For Grade 2:**<br>– Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.<br>– Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted.<br>– Consult nephrologist and consider renal biopsy if clinically indicated.<br>– If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.<br>– 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.<br>– 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]<br>– When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol. |
| **Grade 3 or 4**<br>(Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; | Permanently discontinue study drug/study regimen. | **For Grade 3 or 4:**<br>– Carefully monitor serum creatinine on daily basis.<br>– Consult nephrologist and consider renal biopsy if clinically indicated.<br>– Promptly start prednisone 1 to 2 mg/kg/day PO or IV |

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| | Grade 4: serum creatinine >6.0 × ULN) | | equivalent.<br>– 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.<br>– 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**<br>(excluding bullous skin formations) | **Any Grade**<br>(refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash) | **General Guidance** | **For Any Grade:**<br>– Monitor for signs and symptoms of dermatitis (rash and pruritus).<br>– IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED.** |
| | **Grade 1** | No dose modifications. | **For Grade 1:**<br>– 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.<br>• If toxicity worsens, then treat as Grade 3.<br>• If toxicity improves to Grade ≤1 or | **For Grade 2:**<br>– Obtain dermatology consult.<br>– Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).<br>– Consider moderate-strength topical steroid. |

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| | | baseline, then resume drug/study regimen after completion of steroid taper. | – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, 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.<br>– Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs. |
| | **Grade 3 or 4** | **For Grade 3:**<br>Hold study drug/study regimen until resolution to Grade ≤1 or baseline.<br>If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen.<br>**For Grade 4:**<br>Permanently discontinue study drug/study regimen. | **For Grade 3 or 4:**<br>– Consult dermatology.<br>– Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent.<br>– Consider hospitalization.<br>– Monitor extent of rash [Rule of Nines].<br>– Consider skin biopsy (preferably more than 1) as clinically feasible.<br>– Once 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]<br>– Consider, as necessary, discussing with study physician. |
| **Endocrinopathy**<br>(e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, | **Any Grade**<br>(depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the | **General Guidance** | **For Any Grade:**<br>– Consider consulting an endocrinologist for endocrine events.<br>– Consider, as necessary, discussing with study physician.<br>– Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior |

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| hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section) | CTC grade/severity) | | changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.<br>– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections).<br>– 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).<br>– 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.<br>– 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):**<br>– Monitor patient with appropriate endocrine function tests.<br>– 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).<br>– 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. |

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| **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.<br>• If toxicity worsens, then treat as Grade 3 or Grade 4.<br>Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.<br>Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions:<br>1. The event stabilizes and is controlled.<br>2. The patient is clinically stable as per investigator or treating physician's clinical judgement.<br>3. Doses of prednisone are ≤10 mg/day or equivalent. | **For Grade 2 (including those with symptomatic endocrinopathy):**<br>– Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan.<br>– 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).<br>– Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.<br>– Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids.<br>– 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]<br>– 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. | **For Grade 3 or 4:**<br>– Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. |

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| | | Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.<br>Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions:<br>1. The event stabilizes and is controlled.<br>2. The patient is clinically stable as per investigator or treating physician's clinical judgement.<br>3. Doses of prednisone are ≤10 mg/day or equivalent. | – 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).<br>– For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity.<br>– Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.<br>– Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids.<br>– 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**<br>(to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre) | **Any Grade**<br>(depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity) | **General Guidance** | **For Any Grade:**<br>– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications).<br>– Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness).<br>– Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). |

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| | | | – Perform symptomatic treatment with neurological consult as appropriate.<br>– |
| | **Grade 1** | No dose modifications. | **For Grade 1:**<br>– See "Any Grade" recommendations above. |
| | **Grade 2** | For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1.<br>For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1.<br>If toxicity worsens, then treat as Grade 3 or 4.<br>Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper. | **For Grade 2:**<br>– Consider, as necessary, discussing with the study physician.<br>– Obtain neurology consult.<br>– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).<br>– Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent.<br>– 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:**<br>Hold study drug/study regimen dose until resolution to Grade ≤1.<br>Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days.<br>**For Grade 4:**<br>Permanently discontinue study drug/study regimen. | **For Grade 3 or 4:**<br>– Consider, as necessary, discussing with study physician.<br>– Obtain neurology consult.<br>– Consider hospitalization.<br>– Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.<br>– If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG).<br>– Once stable, gradually taper steroids over ≥28 days. |
| **Peripheral neuromotor** | **Any Grade** | **General Guidance** | **For Any Grade:** |

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| **syndromes**<br>(such as Guillain-Barre and myasthenia gravis) | | – 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.<br>– 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.<br>– Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.<br>– 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:**<br>– Consider, as necessary, discussing with the study physician.<br>– Care should be taken to monitor patients for sentinel symptoms |

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| | | of a potential decompensation as described above.<br>– Obtain a neurology consult. |
| **Grade 2** | Hold study drug/study regimen dose until resolution to Grade ≤1.<br>Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. | **For Grade 2:**<br>– Consider, as necessary, discussing with the study physician.<br>– Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.<br>– Obtain a neurology consult<br>– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).<br>*MYASTHENIA GRAVIS:*<br>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.<br>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.<br>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.<br>*GUILLAIN-BARRE:*<br>o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. |

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| | | | ○ 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:**<br>Hold study drug/study regimen dose until resolution to Grade ≤1.<br>Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.<br>**For Grade 4:**<br>Permanently discontinue study drug/study regimen. | **For Grade 3 or 4 (severe or life-threatening events):**<br>– Consider, as necessary, discussing with study physician.<br>– Recommend hospitalization.<br>– Monitor symptoms and obtain neurological consult.<br>*MYASTHENIA GRAVIS:*<br>○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.<br>○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.<br>○ 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.<br>*GUILLAIN-BARRE:*<br>○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.<br>○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG. |
| **Myocarditis** | **Any Grade** | **General Guidance** | **For Any Grade:** |

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| | Discontinue drug permanently if biopsy-proven immune-mediated myocarditis. | – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function.<br>– Consider, as necessary, discussing with the study physician.<br>– 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.<br>– 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.<br>– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) |
| **Grade 1**<br>(asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities) | No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0. | **For Grade 1 (no definitive findings):**<br>- 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.<br>- Consider using steroids if clinical suspicion is high. |
| **Grade 2, 3 or 4** | - If Grade 2 -- Hold study drug/study | **For Grade 2-4:** |

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| | (Grade 2: Symptoms with mild to moderate activity or exertion)<br><br>(Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated)<br><br>(Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) | 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.<br>If Grade 3-4, permanently discontinue study drug/study regimen. | – Monitor symptoms daily, hospitalize.<br>– Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy.<br>– Supportive care (e.g., oxygen).<br>– 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.<br>– 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:**<br>– 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.<br>– If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic |

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| | | 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.<br>– Consider, as necessary, discussing with the study physician.<br>– 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.<br>Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). |
| **Grade 1**<br>(mild pain) | - No dose modifications. | **For Grade 1:**<br>– Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated.<br>– Consider Neurology consult.<br>– Consider, as necessary, discussing with the study physician. |
| **Grade 2**<br>(moderate pain associated with weakness; pain limiting instrumental activities | Hold study drug/study regimen dose until resolution to Grade ≤1.<br>- Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or | **For Grade 2:**<br>– Monitor symptoms daily and consider hospitalization.<br>– Obtain Neurology consult, and initiate evaluation.<br>– Consider, as necessary, discussing with the study physician. |

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| | of daily living [ADLs]) | if there are signs of respiratory insufficiency. | – 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<br>– 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<br>– 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.<br>– 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**<br>(pain associated with severe weakness; limiting self-care ADLs) | **For Grade 3:**<br>Hold study drug/study regimen dose until resolution to Grade ≤1.<br>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.<br><br>**For Grade 4:**<br>- Permanently discontinue study | **For Grade 3 or 4 (severe or life-threatening events):**<br>– Monitor symptoms closely; recommend hospitalization.<br>– Obtain Neurology consult, and complete full evaluation.<br>– Consider, as necessary, discussing with the study physician.<br>– Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.<br>– 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 |

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| | drug/study regimen. | (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.<br>– Consider whether patient may require IV IG, plasmapheresis.<br>– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] |

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

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

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

## Infusion-Related Reactions

| Severity Grade of the Event (NCI CTCAE version 4.03) | Dose Modifications | Toxicity Management |
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| **Any Grade** | General Guidance | **For Any Grade:**<br>– Manage per institutional standard at the discretion of investigator.<br>– Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia). |
| **Grade 1 or 2** | **For Grade 1:**<br>The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event.<br>**For Grade 2:**<br>The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event.<br>Subsequent infusions may be given at 50% of the initial infusion rate. | **For Grade 1 or 2:**<br>– Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator.<br>– Consider premedication per institutional standard prior to subsequent doses.<br>– Steroids should not be used for routine premedication of Grade ≤2 infusion reactions. |
| **Grade 3 or 4** | **For Grade 3 or 4:**<br>Permanently discontinue study drug/study regimen. | **For Grade 3 or 4:**<br>– 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 |
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| **Any Grade** | Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant. | Treat accordingly, as per institutional standard. |
| **Grade 1** | No dose modifications. | Treat accordingly, as per institutional standard. |
| **Grade 2** | Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. | Treat accordingly, as per institutional standard. |
| **Grade 3** | Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.<br>For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen. | Treat accordingly, as per institutional standard. |
| **Grade 4** | Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.). | Treat accordingly, as per institutional standard. |

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.