Abbreviated Title: Immune Checkpoint Inhibition

NIH Protocol: 16C0135

Version Date: 04/28/2021

NCT Number: NCT02821754

Title: A Pilot Study of Combined Immune Checkpoint Inhibition in combination with ablative therapies in Subjects with Hepatocellular Carcinoma (HCC) or Biliary Tract Carcinomas (BTC)

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Investigational Agents:

Drug Name:	Tremelimumab	Durvalumab (MEDI4736)
IND Number:	123518	123518
Sponsor:	Center for Cancer Research, National Cancer Institute	Center for Cancer Research, National Cancer Institute
Manufacturer:	MedImmune, Inc.	MedImmune, Inc.
Supplier:	MedImmune, Inc.	MedImmune, Inc.

PRÉCIS

Background:

- Various tumor ablative procedures and techniques have been shown to result in immunogenic cell death and induction of a peripheral immune response. The term ablative therapies apply to trans-arterial catheter chemoembolization (TACE), radiofrequency ablation (RFA) and cryoablation (CA).
- The underlying hypothesis of this study is that the effect of immune checkpoint inhibition can be enhanced by TACE, CA and RFA in patients with advanced hepatocellular carcinoma (HCC) and biliary tract carcinomas (BTC). We have already demonstrated proof of principle as well as safety and feasibility of this approach with anti-CTLA4 therapy.
- Based on the concept of 'PDL1-mediated adaptive resistance' and the emerging role of PD1 therapy in HCC, we would like to evaluate the combination of tremelimumab and durvalumab (with ablative therapies) in HCC and BTC.

Objectives:

- To preliminarily evaluate the 6-month progression free survival (PFS) of combining tremelimumab and durvalumab in patients with advanced HCC (either alone or with cryoablation, TACE or RFA) and in patients with advanced biliary tract carcinoma (BTC) (either alone or with cryoablation or RFA).

Eligibility:

- Histologically or cytologically confirmed diagnosis of HCC or biliary tract carcinoma OR histopathological confirmation of carcinoma in the setting of clinical and radiological characteristics which, together with the pathology, are highly suggestive of a diagnosis of HCC (or biliary tract carcinoma).
- Childs-Pugh A/B7 cirrhosis only is allowed. If patient does not have cirrhosis, this limitation does not apply.
- Patients must have disease that is not amenable to potentially curative resection, radiofrequency ablation, or liver transplantation.

Design:

- We will evaluate the combination of tremelimumab and durvalumab (with ablative therapies) in cohorts A1 (HCC; Barcelona clinic liver cancer staging system (BCLC) stage C; N=10), A2 (HCC; BCLC stages B/C; N=30) and B (BTC; N=30). The patients in cohort A1 and first 10 patients in cohort B will receive tremelimumab and durvalumab only (i.e. no interventional radiologic procedures).

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; an IRB determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

- To preliminarily evaluate the 6-month progression free survival (PFS) of combining tremelimumab and durvalumab in patients with advanced HCC (either alone or with cryoablation, TACE or RFA) and in patients with advanced biliary tract carcinoma (BTC) (either alone or with cryoablation or RFA).

1.1.2 Secondary Objectives:

- To assess the safety and feasibility of combining tremelimumab and durvalumab in (Cohorts A1, A2) patients with advanced HCC (either alone or with cryoablation, TACE or RFA) and (Cohort B) in patients with advanced biliary tract carcinoma (BTC) (either alone or with cryoablation or RFA).

1.1.3 Exploratory Objectives:

- To evaluate changes in immune parameters as well as pharmacokinetics in the peripheral blood of patients with advanced HCC or BTC undergoing ablative therapies in combination with combined immune checkpoint inhibition.
- Overall survival.

1.2 BACKGROUND AND RATIONALE

1.2.1 HCC and the current therapeutic paradigm (radiofrequency ablation [RFA] trans-arterial catheter chemoembolization [TACE] and sorafenib)

Worldwide, hepatocellular carcinoma (HCC) is the fifth most common malignancy with a median survival of 6-9 months[1]. The therapeutic paradigm – including the possible

interventions and their indications – is outlined below. The approach to management has traditionally comprised loco-regional strategies: surgery (partial resection or transplantation) or interventional radiologic procedures, such as chemoembolization or ablative techniques. Recently, sorafenib has been added to this paradigm and it is the only systemic drug therapy which has demonstrated a survival benefit in modern randomized studies.

Table 1: Therapeutic paradigm for HCC

Intervention	Indication	Potentially curative
Partial Hepatectomy	Limited liver disease with good reserve	Yes
Transplantation	1 lesion <5cm or 3 < 3cm	Yes
RFA	Lesion to be ablated at least 1cm and not greater than 5cm.	Yes
TACE	Liver confined; no portal vein thrombosis	No
Sorafenib	Metastatic disease	No

The most widely used staging system in HCC is the Barcelona Clinic Liver Cancer (BCLC) Staging system, the major advantage of which is that in addition to staging patients it also directs management[2]. The BCLC staging system is shown in **Figure 1** below.

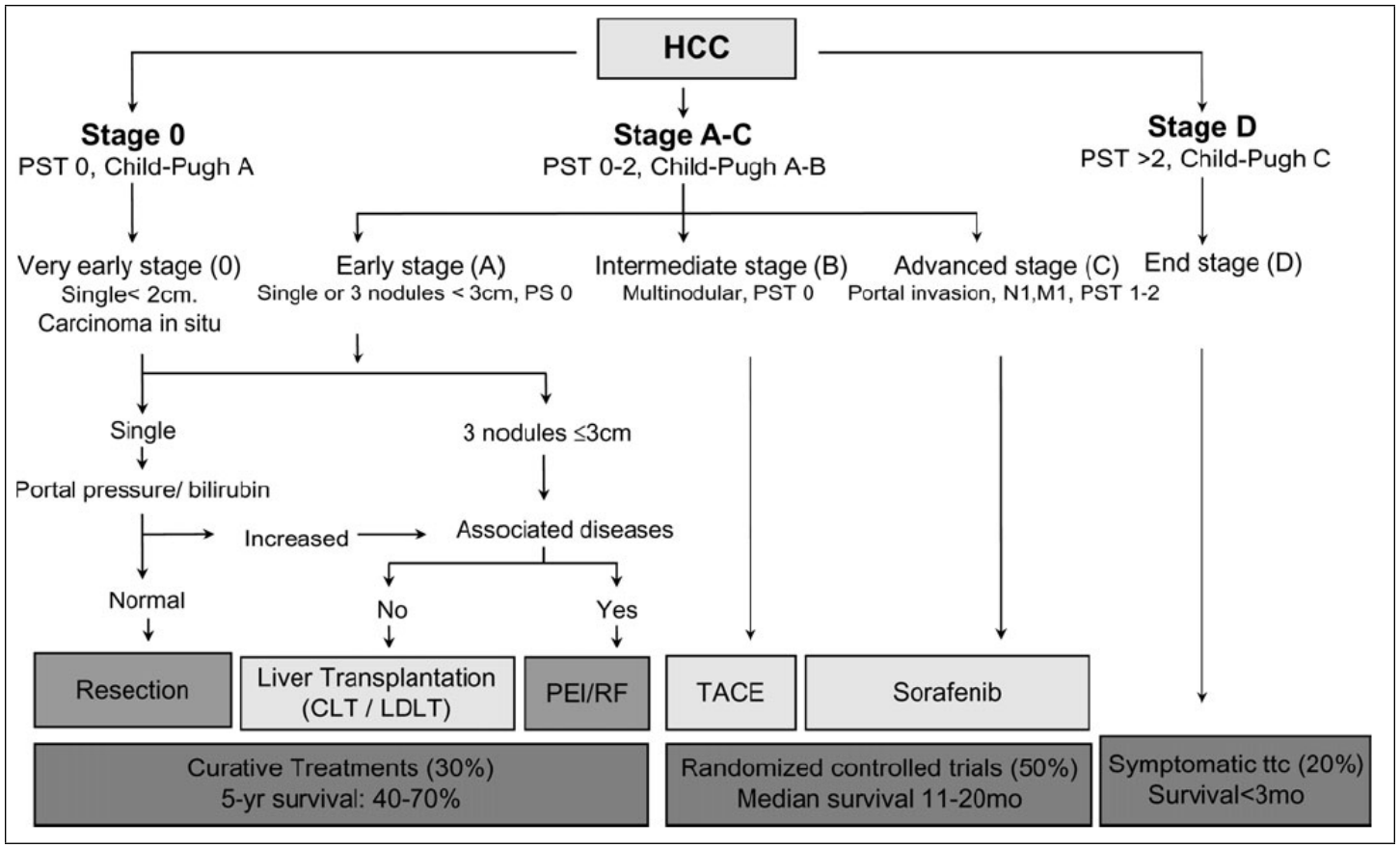

Figure 1: Barcelona Clinic Liver Cancer (BCLC) staging classification and treatment schedule.

For the proposed study, we will not include patients for whom surgical resection or transplantation is a possibility. We will also exclude patients with isolated lesions for whom RFA alone is possible, given the curative potential of that intervention. The target population will be those with advanced disease for whom the only available interventions are TACE or sorafenib.

1.2.2 Recent advances in immune-based approaches in solid tumor malignancies

The past few years have seen progress for immune-based approaches in solid tumor malignancies, with FDA approvals for these approaches in prostate cancer and lung cancer in addition to renal cell carcinoma and melanoma[3-5]. 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-PD1 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. 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[6].

Both anti-PD1 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 in inhibiting T-cell activation is represented in the schematic in **Figure 2** below. 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.

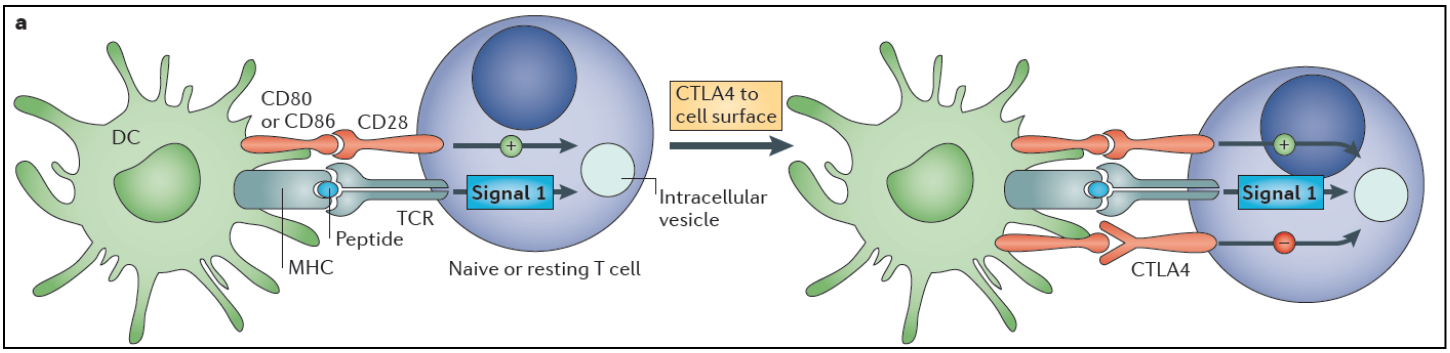

Figure 2: CTLA4-mediated immune checkpoint is induced in T cells at the time of their initial response to antigen. [7]

Whilst these studies demonstrate the potential for anti-CTLA4 (or anti PD1) 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[8]. 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 interventional procedures for HCC.

1.2.3 Immune response to interventional radiological treatments

The aim of our proposed study is to enhance the antitumor immune response which has been shown to occur following interventional radiological treatments. The attractive aspect of this approach – especially in a disease as prevalent as HCC – is that it has the potential for enhancing the effect of treatments (both RFA and TACE) which have already been approved, have demonstrated survival benefit in randomized studies and are commonly performed throughout the community. Following RFA and TACE necrotic tumor results in the release of tumor antigens which are taken up by antigen-presenting cells (mainly dendritic cells) and which activate a tumor-specific immune response[9]. Ablated tumor tissue has been shown to promote dendritic cell maturation (and resultant T-cell stimulatory properties)[10, 11]. This antigen

release is potentially significant because, although ablative procedures are very effective in eradicating visible lesions, a tumor-specific immune response may prevent recurrent disease in addition to treating distant metastases. In other words, RFA and TACE have the potential to turn a patient's tumor into an endogenous vaccine.

Several studies have documented an increase in peripheral antitumor immunity following interventional radiological procedures, predominantly RFA[10, 12-15]. This has been demonstrated both in animal models and in human studies[12, 14, 15]. Ayaru et al. evaluated the immune response in HCC patients (N=10) undergoing TACE[16]. They found that AFP-specific CD4-T cell responses were significantly expanded during ($p < 0.0001$) and after embolization ($p < 0.002$). The development of higher frequencies of AFP-specific CD4 T cells after treatment were significantly associated with the induction of >50% necrosis of tumor and an improved clinical outcome ($p < 0.007$). Mizukoshi et al. measured cytotoxic T cell response to tumor associated antigens (TAA) in HCC patients undergoing treatment[17]. They measured the frequency of TAA-specific T cells before and after HCC treatment by ELISPOT assay in 12 cases who received TACE, RFA or chemotherapy. The frequency of TAA-specific T cells was found to be increased in all patients. Furthermore, incubation of T cells with CTLA-4 antibodies resulted in an increase of the number of TAA-specific T cells. Dromi et al. evaluated the influence of subtotal RFA on tumor-specific immune response in a murine urothelial carcinoma (MB49) tumor model[18]. RFA resulted in enhanced systemic antitumor T-cell immune responses and tumor regression that was associated with increased dendritic cell infiltration into the remaining viable, non-ablated tumor.

Hansler et al. assessed the specific cytotoxic T cell response in patients with malignant liver tumors (both metastatic colon cancer and HCC) which were treated with RFA. Significant tumor-specific cytotoxic T-cell stimulation was seen, with a dramatically increased tumor specific cytolytic activity of CD8(+) T cells against autologous liver and tumor lysate after RFA[12]. Hiroishi et al. analyzed tumor-specific CD8(+) T-cell responses in twenty patients with HCC undergoing loco-regional therapy (either RFA or TACE)[13]. They found that the CD8(+) T-cell response was increased and, on multivariate analysis, the magnitude of the immune response was the only significant prognostic factor for a prolonged tumor-free interval (hazard ratio 0.342, P = 0.022).

Despite this, only a few cases of spontaneous remission of metastases following RFA – the so-called abscopal effect – have been reported, presumably because this immune response by itself is too weak to be clinically significant[19-21]. A number of studies have tried to boost this anti-tumor immune response following ablation by combining with an immunomodulatory agent:

Waitz et al. provided preclinical proof-of-concept for this in a mouse model of prostate cancer using CTLA-4 blockade to augment the immune response from cryoablation[22]. The combination therapy resulted in >80% of intratumoral CD8+ T cells being antigen-specific. The effect on secondary responses was assessed by injection of the secondary tumor on the opposite flank of the mouse on Day 2 following ablation. The growth of secondary tumors was found to be unaffected by cryoablation alone, but the combination treatment (anti-CTLA4 + RFA) was sufficient to slow growth or trigger rejection. In addition, secondary tumors were highly infiltrated by $CD4^+$ T cells and $CD8^+$ T cells, and there was a significant increase in the ratio of intratumoral T effector cells to T regulatory cells, compared with either RFA or anti-CTLA4 alone. Johnson et al. sought to enhance the antitumor effect of RFA by combining it with huKS-

IL2 immunocytokine [tumor-specific monoclonal antibody fused to interleukin-2 (IL2)] in mice bearing CT26-KS colon adenocarcinoma. Mice were treated with RFA, huKS-IL2 via intratumoral injection, or combination therapy. Treatment of mice bearing subcutaneous tumors with RFA and huKS-IL2 resulted in significantly greater tumor growth suppression and enhanced survival compared with mice treated with either RFA or huKS-IL2 alone. When sub-therapeutic regimens of RFA or huKS-IL2 were used, tumors progressed in all treated mice. In contrast, the combination of RFA and immunocytokine resulted in complete tumor resolution in 50% of mice. Treatment of a tumor with RFA and intratumoral huKS-IL2 also showed antitumor effects against a distant untreated tumor. Tumor-free mice after treatment with RFA and huKS-IL2 showed immunologic memory based on their ability to reject subsequent challenges of CT26-KS and the more aggressive parental CT26 tumors. Flow cytometry analysis of tumor-reactive T cells from mice with complete tumor resolution showed that treatment with RFA and huKS-IL2 resulted in a greater proportion of cytokine-producing CD4 T cells and CD8 T cells compared with mice treated with RFA or huKS-IL2 alone. den Brok et al. evaluated combination treatment of RFA plus TLR9 stimulation in B16 tumors and showed that the combination resulted in far more potent antitumor immune responses than either treatment modality alone[23].

1.2.4 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.

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. However, in contrast to tremelimumab, there are no safety data for the use of ipilimumab in HCC.

1.2.4.1 Clinical experience of Tremelimumab

Tremelimumab has been evaluated in a number of clinical studies – and over 1000 patients – and demonstrated manageable toxicities[24, 25].

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.

1.2.4.2 Experience in Hepatitis/HCC

Tremelimumab has recently been shown to be safe in a study in HCC. Twenty-one patients with HCV-related HCC were treated with tremelimumab intravenously at a dose of 15 mg/kg every 90 days for two cycles. Toxicity was manageable with reported treatment-related adverse events among 80% of patients. Grade 3 or higher adverse events included 1 case of pruritus, 1 case of purpura, and 5 cases of elevated transaminases. There was preliminary evidence of efficacy. In an intention-to-treat analysis, investigators observed a median overall survival of 7.5 months and time to progression of 6.4 months as well as a reduction of hepatitis C virus (HCV) in the patients' blood, which was also accompanied with objective enhancements of antiviral immunity. A significant and progressive decline in serum HCV viral load was observed (median values: baseline 3.78x10e5 copies/ml vs. day 120 3.02x10e4 copies/ml, $P = .02$; vs. day 210 1.69x10e3 copies/ml, $P = .04$).

1.2.5 Durvalumab

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass. The fragment crystallizable (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[26]. 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 are expected to have less adverse events in comparison with anti-PD-1 antibodies that target effector T-cells in the tumor microenvironment.

Blockade of PD-L1 with durvalumab is 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 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.

1.2.6 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[7].

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 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.

1.2.6.1 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.

1.2.7 Rationale for Viral Hepatitis Studies and Specifically for Hepatitis B Surface Antigen and Hepatitis B Immune Monitoring

Anti-HCV specific immune responses as well as a reduction in Hepatitis C viral load have been described in in patients with chronic HCV infection and HCC treated with anti-CTLA4 therapy (decline in serum HCV viral load from median values: basal 3.78x10e5 copies/ml to median values on day 120 of 3.02x10e4 copies/ml, p=0.02; vs. day 210 1.69x10e3 copies/ml, p=0.04); in addition three patients demonstrated a complete viral response for the duration of the follow-up[27].

The antiviral effect of CTLA-4 blockade in patients with chronic HBV infection is unknown. Hepatitis e antigen (HBeAg) is a marker of viral replication and infectivity that is usually associated with and active liver disease. Hepatitis B surface antigen (HBsAg) is a protein on the surface of the hepatitis B virus. Its presence identifies patients with chronic infection. CTLA-4 blockade in cynomolgus macaques enhanced antibody response to hepatitis B surface antigen (HBsAg)[28]. Interestingly, polymorphisms of CTLA-4 have been associated with chronic hepatitis B and C infection[29, 30]. The mechanisms behind these events imply an existing link between CTLA-4 activity and hepatic viral pathogenesis that should be exploited in detail for therapeutic benefit. The population of HCC patients with chronic hepatitis B virus (HBV) infection will provide an exceptional occasion to simultaneously test the anti-tumoral, immune and antiviral effect of tremelimumab.

1.2.8 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). 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 cause delays or inconvenience to an unreasonable degree, we will forgo at investigator discretion.

1.2.9 Rational for micro biome analysis

The relationship between the gut flora and the immune system is a complex and intriguing one that needs to be dissected and characterized in the disease setting. The gut microbiota is known to affect immune responses by influencing innate and adaptive immunity, tissue repair, etc. Murine studies using mice with selective immune deficiencies have found that both innate and adaptive immune cells appear to shape the composition of the gut microbiota. Alterations in the gut microbiota composition, frequently referred to as dysbiosis, are associated with the development of allergies and inflammatory/autoimmune diseases, including inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and T1D, in humans (Microbiome and Anticancer Immunosurveillance [31].

1.2.10 Current status of 13-C-0120 and rationale for this new protocol (as of March 11, 2016).

The current status of NCI 13-C-0120 is as follows. We began enrollment on July 24th, 2013. In total, N=41 patients have been enrolled across 4 cohorts as shown (N=32 with HCC; N=9 with cholangiocarcinoma). Of the N=32 patients with HCC, N=4 have been unevaluable, having come off study treatment for either toxicity or disease progression within the first few weeks of treatment. Treatment overall has been well tolerated. No DLT was encountered at an initial mini dose escalation of 3.5mg/kg so we proceeded to the recommended tremelimumab dose of 10mg/kg. Most common toxicity was grade 1/2 pruritus. One patient developed pulmonitis and was taken off study but remained disease-free at 16m. In total n=3 patients discontinued therapy due to immune-related adverse events (pneumonitis, colitis, adrenal insufficiency) which is consistent with what would be expected from single-agent immune checkpoint experience. We have also seen evidence of efficacy with a PR rate of 23.5% and prolonged stability (>6 months) in an additional 23.5%. Given the context of HCC – generally a poorly responsive tumor type – these results are encouraging.

The field has moved on a little given the recently presented data showing highly encouraging and dramatic results for nivolumab (anti-PD1 therapy) in HCC. Based on this it is likely that nivolumab will challenge the status of sorafenib as the front-line (and only) option for this disease. Randomized trials are ongoing. Even if this occurs however, and while complete responses were seen in the nivolumab study, the majority of patients did not seem to derive benefit. The current research focus of the field is on combinations, either of two different immunotherapies or immunotherapy combined with non-immunotherapy. One of the striking things that we have seen in our own study so far is that anti-CTLA4 therapy (with tremelimumab) is capable of driving T-cell infiltration into the tumor[32]. In actual fact, based on further analysis that we have performed[33] it appears that this occurrence is a prerequisite for response to tremelimumab in HCC. However, the concept of PDL1-mediated ‘adaptive resistance’– i.e. resistance emerging due to PDL1 upregulation secondary to interferon-gamma – means that responses are destined to be short-lived. This has been our experience, with only one of our 5 PRs lasting longer than one year. Conversely, combined immune checkpoint inhibition, with the addition of anti-PD1/PDL1 therapy can overcome this and has demonstrated increased

clinical response rates in melanoma. We would therefore like to open new cohorts which combine anti-PDL1 therapy (durvalumab) with anti-CTLA4 (tremelimumab).

The combination of tremelimumab and durvalumab has been tested in a dose-escalation study performed by AstraZeneca employing dose ranges of 1-10mg/kg q4weeks (tremelimumab) and 10-20mg/kg q2-4weeks (durvalumab). 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. This is the dose level the company is bringing forward. Also, of note, PK analysis indicated only minor impact of body weight (WT) on PK of both agents so to minimize errors and for ease of use the company have moved to a fixed-dose schedule of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W).

1.2.11 Regarding research nature of the IR procedures

While RFA and cryoablation are approved, standard of care procedures for these cancer types, the intent of their use in this protocol is strictly research. The ablative procedure will be performed in a subtotal fashion (per radiologist judgement) in order to stimulate an immune response, rather than complete eradication of the lesion as per standard of care indication. The TACE however will be as per standard of care (BCLC B patients). All procedures will or may be performed under CT guidance.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histopathological confirmation of hepatocellular carcinoma (HCC) or biliary tract carcinoma (BTC) by the Laboratory of Pathology of the NCI prior to entering this study OR histopathological confirmation of carcinoma in the setting of clinical and radiological characteristics which, together with the pathology, are highly suggestive of a diagnosis of HCC (or biliary tract carcinoma). Fibrolamellar variant is also allowed. The term BTC includes intra- or extrahepatic cholangiocarcinoma, gallbladder cancer or ampullary cancer.

2.1.1.2 Patients must have disease that is not amenable to potentially curative resection, transplantation or ablation. HCC patients must have progressed on, been intolerant to, or refused prior sorafenib therapy. Patients with BTC must have received, been intolerant of or refused at least one line of chemotherapy.

2.1.1.3 Patients must have multiple tumor lesions (at least 2): one for the ablation procedure and another for evaluation located outside the proposal ablation zone.

2.1.1.4 Disease must be technically amenable to transhepatic arterial chemoembolization (TACE) (HCC patients only), radiofrequency ablation (RFA), or cryoablation. Each case will be discussed at GI tumor board with interventional radiology. Patients must have evaluable disease.

2.1.1.5 ECOG performance status 0-2 (see **APPENDIX A**)

2.1.1.6 If liver cirrhosis is present, patient must have a Child-Pugh A/B7 classification (see **Appendix B**).

2.1.1.7 Age ≥18 years

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

leukocytes	≥ 3,000/mcL
absolute neutrophil count	≥ 1,000/mcL
platelets	≥ 60,000/mcL
total bilirubin	If cirrhosis present: Part of Child Pugh requirement If no cirrhosis: bilirubin should be ≤ 2 x ULN
serum albumin	If cirrhosis present: Part of Child Pugh requirement If no cirrhosis: albumin should be ≥ 2.5g/dl
Patients are eligible with ALT or AST up to 5 x ULN.	
creatinine	< 1.5x institution upper limit of normal 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 Patients must not have other invasive malignancies within the past 5 years (with the exception of non-melanoma skin cancers, non-invasive bladder cancer or localized prostate cancer for whom systemic therapy is not required).

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

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

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

sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

2.1.1.13 Body weight >30kg

2.1.2 Exclusion Criteria

2.1.2.1 Patients who have had standard of care chemotherapy, large field radiotherapy, or major surgery must wait 2 weeks prior to entering the study. For recent experimental therapies, a 28-day period of time must elapse before treatment.

2.1.2.2 Patients who have undergone prior liver transplantation are ineligible.

2.1.2.3 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.

2.1.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active systemic infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (excluding insignificant sinus bradycardia and sinus tachycardia) or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.5 History of chronic autoimmune disease (e.g., Addison's disease, multiple sclerosis, Graves' disease, Hashimoto's thyroiditis, rheumatoid arthritis, hypophysitis, etc.) with symptomatic disease within the 3 years before randomization. Note: Active vitiligo or a history of vitiligo will not be a basis for exclusion.

2.1.2.6 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.

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

2.1.2.8 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.

2.1.2.9 Currently receiving immunosuppressive doses of steroids or other immunosuppressive medications (inhaled and topical steroids are permitted)

2.1.2.10 History of sarcoidosis syndrome

2.1.2.11 Patients should not be vaccinated with live attenuated vaccines within 30 days of starting durvalumab or tremelimumab treatment.

2.1.2.12 Has a known history of Human Immunodeficiency Virus (HIV). HIV-positive patients receiving anti-retroviral therapy are excluded from this study due to the possibility of pharmacokinetic interactions between antiretroviral medications and tremelimumab. HIV positive patients not receiving antiretroviral therapy are excluded due to the possibility that tremelimumab may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events.

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

2.1.2.14 Pregnancy and breast feeding are exclusion factors. The effects of tremelimumab on the developing human fetus are unknown. Enrolled patients must agree to use adequate contraception (see section **4.1** and **4.2**) prior to study entry, the duration of study participation and 6 months after the end of the treatment. 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.

2.1.2.15 Patients with unhealed surgical wounds for more than 30 days.

2.1.3 Inclusion of Women and Minorities

Men and women of all races and ethnic groups are eligible for this trial.

2.1.4 Recruitment Strategies

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

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone or video communications with prospective subjects
- Review of existing medical records to include H&P, laboratory studies, etc.
- Review of existing MRI, x-ray, or CT images
- Review of existing photographs or videos
- Review of existing pathology specimens/reports from a specimen obtained for diagnostic purposes.

2.2.2 Screening activities performed after a consent for screening has been signed

The following activities will be performed only after the subject has signed the consent for study #01-C-0129 on which screening activities will be performed. Assessments performed at outside facilities or on another NIH protocol within the timeframes below may also be used to determine eligibility once a patient has signed the consent.

Studies should be done within 28 days prior to enrollment unless otherwise noted below.

- Complete history (including prior hormone use) and physical examination (including height, weight, vital signs, EKG, and performance status).
- CT scan of chest, abdomen and pelvis (or MRI liver (if clinically indicated) (may be done at an outside institution)
- 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 and amylase
- Gamma glutamyltransferase (if clinically indicated).
- Urinalysis
- Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy). Test to be performed within 72 hours prior to enrollment.

- Histologic confirmation (at any time point prior to enrollment). A block or unstained slides of primary or metastatic tumor tissue will be required from each participant to confirm diagnosis with analysis being performed by the Laboratory of Pathology, NIH. As stated in the inclusion criteria above, histopathological confirmation of carcinoma may be sufficient. Fibrolamellar variant is also allowed.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.3.1 Treatment Assignment Procedures (For registration purposes only):

Cohorts

Number	Name	Description
1	A1	First 10 Subjects with Advanced HCC, BCLC Stage C
2	A2	Subjects with Advanced HCC, BCLC Stage B/C
3	B	Subjects with Intra/extra-hepatic cholangiocarcinoma

Arms

Number	Name	Description
1	A1	Durvalumab + Tremelimumab
2	A2	Durvalumab + Tremelimumab + TACE
3	A3	Durvalumab + Tremelimumab + RFA
4	A4	Durvalumab + Tremelimumab + Cryo

Subjects in cohort A1 will be directly assigned to arm A1.

Subjects in cohort A2 will be directly assigned to arms A2, A3 or A4 per consultation with the interventional radiologists. The reason for this is that there are technical considerations (size and location of lesion, main portal vein occlusion etc.) which would make one procedure preferable over the other. 10 evaluable subjects will be assigned to each intervention.

The first 10 subjects in cohort B will be directly assigned to arm A1.

The remaining subjects in Cohort B will be directly assigned to arms A3 or A4 per consultation with the interventional radiologists. The reason for this is that there are technical considerations (size and location of lesion, main portal vein occlusion etc.) which would make one procedure preferable over the other. 10 evaluable subjects will be assigned to each intervention.

2.4 BASELINE EVALUATION

Baseline evaluations do not need to be repeated if performed during Screening within designated time-frame,

Within 28 days prior to first dose, unless otherwise specified:

- CT scan of chest, abdomen and pelvis (or MRI of liver if clinically indicated)
- Electrocardiogram
- Laboratory evaluation
  - Hepatitis B and/or C viral load and serology
  - HLA-A, HLA-B, HLA-C and HLA-A*02 phenotype (may be done at any time prior to treatment)
  - AMA & Liver/kidney microsomal antibody
  - ANA
  - Rectal swab (optional)
  - Serum or urine pregnancy test for female participants of childbearing age (in the absence of prior hysterectomy, within 72 hours prior to first dose)
- Research tumor biopsy.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

The proposed study is a pilot study combining tremelimumab and durvalumab treatment in patients with advanced HCC (Cohorts A1 and A2) either alone (Arm A1) or with cryoablation, TACE or RFA (Arms A2, A3, A4) and patients with advanced BTC (Cohort B) either alone (Arm A1) or with cryoablation or RFA (Arms A3, A4).

The decision on which interventional radiologic procedure to administer (i.e. RFA vs. TACE vs. cryoablation) will be made in consultation with the interventional radiologists. The reason for this is that there are technical considerations (size and location of lesion, main portal vein occlusion etc.) which would make one procedure preferable over the other.

- Transarterial chemoembolization is percutaneous procedure performed under general anesthesia or conscious sedation. (See **3.5.1** for details)
- Patients undergoing trans-arterial chemoembolization, RFA or cryoablation are pre-medicated with analgesics, antibiotics and anti-emetics per clinical standards. For details regarding each procedure please see **3.5**.

Cohort	**Population**	**Immune stimulating procedure**	**Dose level**	**Planned N**
A1	Advanced HCC, BCLC Stage C	No ablative procedure	Tremelimumab 75mg flat dose q28 days for 4 doses Durvalumab 1500mg flat dose q28 days until EOS###	**10 total**
A2	Advanced HCC, BCLC Stage B/C	Cryoablation/ RFA/TACE*	Tremelimumab 75mg flat dose q28 days for 4 doses Durvalumab 1500mg flat dose q28 days until EOS**	**30 total** 10 trem+ dur + TACE 10 trem + dur + RFA 10 trem + dur + cryo
B	Intra/extra-hepatic cholangiocarcinoma	N= 1st 10 pts: No ablative procedure RFA/ cryoablation	Tremelimumab 75mg flat dose q28 days for 4 doses Durvalumab 1500mg flat dose q28 days until EOS**	**30 total** 10 trem+ dur alone 10 trem + dur + RFA 10 trem + dur + cryo

* For BCLC stage B patients TACE may be repeated as per standard of care

** EOS = end of study treatment as defined in section **3.8.1**.

3.2 SCHEDULE

3.2.1 Cohort A1

- All 10 patients with BCLC Stage C will receive combined immune checkpoint inhibition only i.e. no interventional radiologic procedure.
- Patients 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. 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).

3.2.2 Cohort A2

The schema for Cohort A2 is shown below. For Cohort A2 (BCLC Stage B/C patients) TACE, RFA or cryoablation will be performed once only, on Day 36 (+/- 96hrs).

- Both BCLC stage B and C are eligible for cohort A2.
- Patients 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. 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).

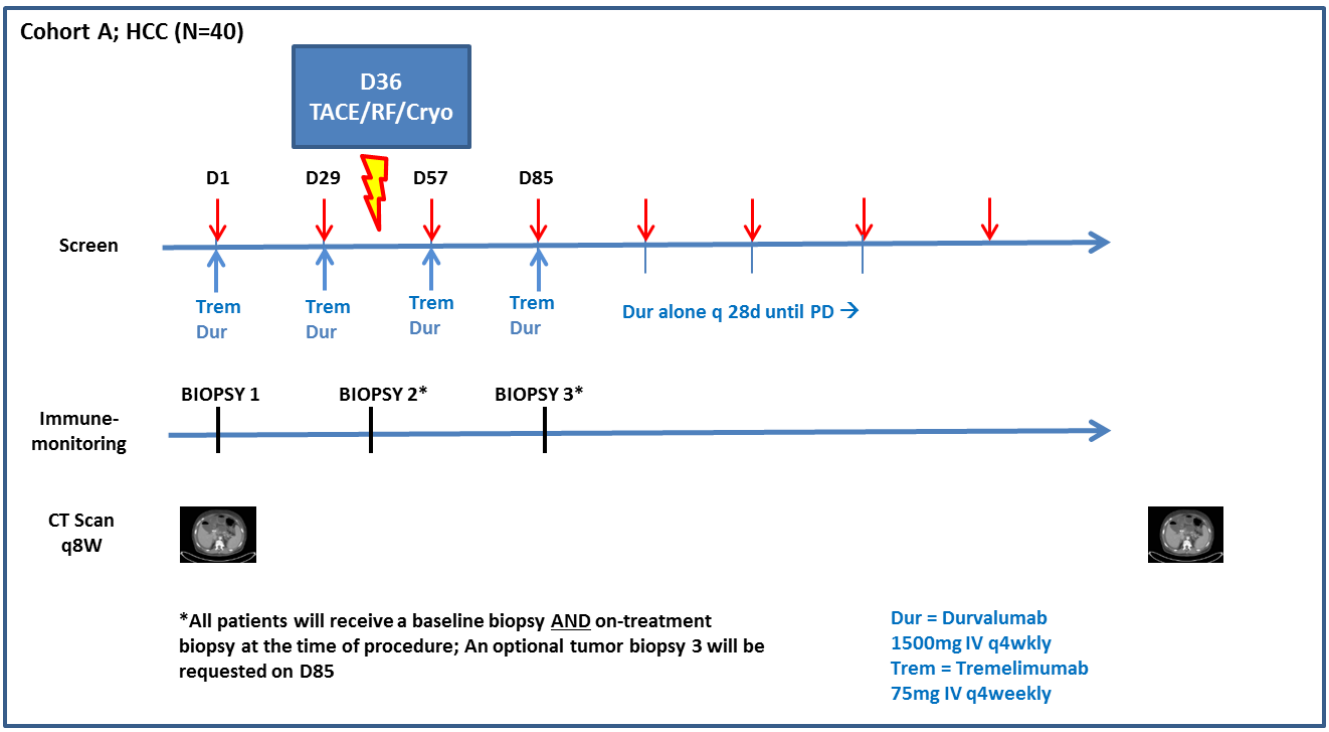

Figure 3: Schema cohort A2

3.2.3 Cohort B

The schema for Cohort B is shown below. For Cohort B (BTC patients, status post prior chemotherapy with intrahepatic disease) RFA or cryoablation will be performed once only, on Day 36 (+/- 96hrs). The first N=10 patients will not undergo an ablative procedure i.e. they will receive drug only.

- The first N=10 patients will receive combined immune checkpoint inhibition only i.e. no interventional radiologic procedure.
- Patients 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. 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).

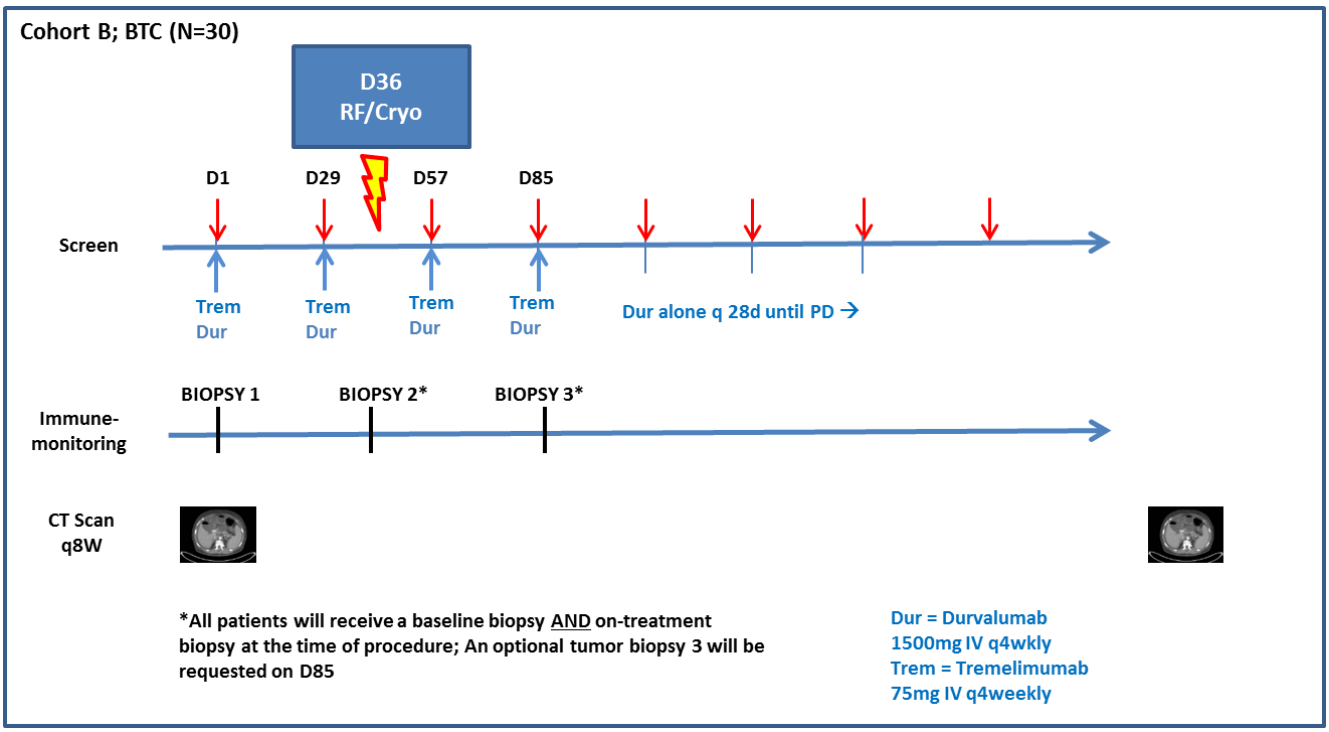

Figure 4: Schema cohort B

3.3 DRUG ADMINISTRATION

3.3.1 Tremelimumab Drug Administration

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

1) Investigational product must be administered at room temperature (25°C) by controlled infusion at a rate of 250 mL/hour 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 contents 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.

The duration of the investigational product administration will be recorded.

3.3.2 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.

3.3.3 Monitoring of Dose Administration

Vital signs will be collected before investigational product infusion and at the completion of the infusion.

In the event of a ≤ grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is one hour, however, if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature (otherwise requires new infusion preparation).

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.

3.4 DOSING DELAYS

The following broad guidelines for dose delivery schedule delays and alternations apply to both 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 7 days of planned interval to accommodate scheduling issues/logistics.

3.4.1 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[4, 34, 35]. These AEs are inflammatory in nature and can affect any organ.

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

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

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

AESIs observed with durvalumab and tremelimumab include:

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

For current list of adverse drug reactions (ADR)s for durvalumab, please, see **Appendix G**

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

3.4.2.1 Pneumonitis

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

3.4.2.2 Infusion reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to AstraZeneca and are defined, for the purpose of this protocol, as all AEs occurring from the start of IP infusion up to 48 hours after the infusion start time. For all infusion reactions, SAEs should be reported to AstraZeneca Patient safety as described in Section **7.4**.

3.4.2.3 Hypersensitivity reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti PD-L1 and anti-PD-1 therapy[34]. As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of mAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the mAbs and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness. Guidelines for the management of patients with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are provided in **Appendix F**.

3.4.2.4 Hepatic function abnormalities (hepatotoxicity)

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

Due to the fact that in HCC patients elevated transaminase and/or bilirubin levels are common and fluctuant as a result of underlying liver disease (e.g. viral hepatitis), the toxicity criteria outlined in **Appendix F** will be interpreted with the following caveats:

1) For patients with HCC with normal liver transaminases and/or bilirubin at baseline, the criteria apply as outlined in **Appendix F**. (i.e. if a grade 2 event occurs treatment will be held until resolution to grade 1)

2) For patients with HCC who have elevated liver transaminases and/or bilirubin at baseline (grade 1 or 2 i.e. still allowing for study entry), subsequent occurrences of grade 2 elevations will not result in holding of therapy.

3) Grade 3 events will be treated as per **Appendix F** irrespective of baseline levels.

3.4.2.5 Gastrointestinal disorders

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

3.4.2.6 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in **Appendix F**.

3.4.2.7 Pancreatic disorders

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

3.4.2.8 Neurotoxicity

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

3.4.2.9 Nephritis

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

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

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

3.4.2.10 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 should immediately consider 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.

3.5 SPECIFIC PROCEDURES FOR TACE, RFA AND CRYOABLATION

3.5.1 Transarterial chemoembolization

Percutaneous procedure is performed under general anesthesia or conscious sedation. Access is obtained from the common femoral artery and selective catheterization of the superior

mesenteric and celiac arteries is performed to define anatomy and hepatic arterial supply. Super selective catheterization of hepatic artery branches feeding the tumors is then performed followed by infusion of a chemotherapeutic mixture.

Trans-arterial chemoembolization will be performed with drug eluding beads (DEB). In this case, 100mg of doxorubicin are loaded into 100-250 micron beads. The DEB are mixed with contrast and infused into the hepatic artery branches supplying the tumor. Patients undergoing trans-arterial chemoembolization are pre-medicated with analgesics, antibiotics and anti-emetics per clinical standards.

3.5.2 Radiofrequency ablation

Thermal ablation is a minimally invasive image guided procedure performed under general anesthesia or conscious sedation. Radiofrequency or microwave ablations are performed; the ablation zone includes the tumor and a safety margin of surrounding tissue. Thermal ablation therapy will be administered according to the manufacturer's instructions of the device. The probe chosen varies depending on the type of thermal ablation, size of the tumor. The ablation probe will be inserted into the lesion, under image guidance. After confirmation of appropriate positioning, the lesion will be heated typically for 10-15 minutes for RFA and 5-10 minutes for microwave, according to manufacturer's guidelines. The time of ablation will depend on thermal ablation technique (RF vs. microwave) as well as the size of the ablation zone desired. The ablation time might also vary depending on proximity of critical structures, patient-specific anatomy or issues. Depending on ablation zone size, several probes might be required with several heating times to achieve complete coverage of the desired ablation zone. Balloon catheter may be used in cases where the tumor is adjacent to a hepatic vein to avoid "heat sync" where the ablation zone is cooled by the blood inflow. This catheter is typically inserted from the neck vein and is then placed into a hepatic vein. Hydrodissection may also be used in cases where the tumor is adjacent to a critical structure such as the heart or colon. These organs can sustain damage from heating, therefore a catheter is inserted into the space separating them and the tumor and fluid (dextrose 5%) is administered during the ablation.

3.5.3 Cryoablation

The freeze zone of cryoablation effects depend upon the probe size and configuration as well as the nadir of the freeze cycle (dependent upon the specific cryogen). Two cryoablation systems are commercially available and FDA cleared for human use (Endocare / Healthtronics and Galil). Both use helium and argon gases to induce lethal temperatures locally.

The systems require argon and helium gases which produce low temperatures upon phase change from gas to liquid. The cryotherapy equipment will be an argon-helium gas system using 1.6mm or 2.4 mm cryoprobes (Endocare, Inc., Irvine, CA) or 0.049 inches = 18 gauge = 1.3 mm cryoprobes (Galil). The ice-ball diameters for these probes may vary according to the tissue and blood supply, but their freeze lengths should be comparable to the RFA system (10-30 mm). Ice-ball diameters refer to the outer 0°C margin, but cytotoxic temperatures (e.g., < -20 to -40 °C) are known to occur 3-5 mm behind visualized ice margins. A 10-20 minutes' freeze, followed by a 5-10 minutes' thaw, and a 10-20 minute re-freeze produces visible ice and necrosis by rapid and slow mechanisms (dehydration and vascular stasis). The specific times depend upon the temperatures and potentially the temperatures of any remote thermometry used to asse4ss temperature at the margin of a freeze. Rapid intracellular ice formation causes irreversible cell

death. Cell membrane dysfunction occurs below -10 degrees C, leading to intracellular ice formation, disrupting organelles. During thawing, osmolar shifts cause cellular swelling and rupture. Apoptosis and vascular stasis may also play a role in cell death by freezing.

The probes are placed into the tumor(s) by ultrasound, CT or MRI guidance. Up to 8 simultaneous probes may be placed sequentially for simultaneous treatment (different from current monopolar RFA). 1 % lidocaine is applied to the subcutaneous tissues down to the organ of interest. The helium and argon gases are hooked up to the system, and the cryotherapy machine and software are relatively automatic at this point with the freeze, thaw, refreeze cycles as described above. The process is monitored with ultrasound and CT scans as clinically required for standard operating procedures described by the manufacturers.

3.5.4 Determination of the amount of subtotal ablation.

At all times, the volume to be ablated should be within that regarded as acceptable per standard of care for ablations performed for curative intent. Certainly, this would be less than 4 cm max in cross-sectional imaging. For the purposes of this protocol subtotal ablation refers to the complete treatment of a solitary lesion in the setting of multifocal disease, leaving other lesions (both intrahepatic and extrahepatic) intact and untreated. The lesion subjected to ablation is to be chosen at the discretion of the interventional radiologist based on technical factors, such as ease of access, proximity to vessels etc.

3.6 STUDY CALENDAR

Procedure	**Pre-study**	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**D1 of every subsequent cycle** [o]	**EOT** [p]	**LT FU** [r]
Day		**1**	**8**	**15**	**22**	**1**	**8 (day 36)**	**15**	**22**	**1**	**8**	**15**	**22**	**1 (day 85)**	**8**	**15**	**22**			
Tremelimumab [a]		X				X				X				X						
Durvalumab [a]		X				X				X				X				X		
RFA/TACE/ Cryoablation [b]							X													
Informed consent	X																			
Demographics	X																			
Medical history	X																			
Advance Directive [c]	X																			
Concomitant meds		X				X				X				X				X		
Adverse event evaluation		X				X				X				X				X	X	
Physical exam [d]	X	X				X				X				X				X	X	
Vital signs	X	X [e]				X [e]				X [e]				X [e]				X [e]	X	
Height	X																			
Weight	X	X				X				X				X				X		
Performance Status	X	X				X				X				X				X	X	

Procedure	**Pre-study**	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**D1 of every subsequent cycle [o]**	**EOT[p]**	**LT FU[r]**
Day		**1**	**8**	**15**	**22**	**1**	**8 (day 36)**	**15**	**22**	**1**	**8**	**15**	**22**	**1 (day 85)**	**8**	**15**	**22**			
CBC w/differential, Platelets [f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PT, INR, PTT, Fibrinogen [f]	X	X				X				X				X				X	X	
Thyroid Panel [q, h]		X				X				X				X				X		
ANA	X													X [q]						
Biochemical profile [f, g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Uric acid, amylase [f]	X	X				X				X				X				X		
Gamma glutamyltransferase [i]	X	X																X		
Serum aFP or Ca 19.9 [q]		X				X				X				X				X		
Hepatitis B and C [f, j]	X	X				X				X				X				X		
Urinalysis [f]	X	X				X				X				X				X		
Urine or serum pregnancy test	X																			

Procedure	**Pre-study**	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**D1 of every subsequent cycle[o]**	**EOT[p]**	**LT FU[r]**
Day		**1**	**8**	**15**	**22**	**1**	**8 (day 36)**	**15**	**22**	**1**	**8**	**15**	**22**	**1 (day 85)**	**8**	**15**	**22**			
HLA Phenotyping	X																			
ECG	X																			
Confirmation of dx by NCI LP	X																			
Restaging radiologic Evaluation [k]	X									X								X		
Tumor biopsy [l]	X						X							X						
Immune monitoring [q]		X				X	X [n]			X				X				X[s]		
Pharmacokinetic studies [m]		X	X [n]	X [n]		X				X									X	
Immunogenicity [t]		X				X				X				X				X[s]	X	
AMA & Liver/kidney microsomal antibody [q]	X													X						
Tumor-specific αFP responses [q]		X				X				X				X				X[s]		
CFSE		X				X				X				X				X[s]		

Procedure	**Pre-study**	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**D1 of every subsequent cycle[o]**	**EOT[p]**	**LT FU[r]**
Day		**1**	**8**	**15**	**22**	**1**	**8 (day 36)**	**15**	**22**	**1**	**8**	**15**	**22**	**1 (day 85)**	**8**	**15**	**22**			
proliferation T cells [q]																				
MDSC functional assay [q]		X				X				X				X				X[s]		
T cell activation/ICOS expression (PBMC) [t]		X	X[n]	X[n]		X				X				X				X[s]		
Plasma-based assays for circulating receptors/ligands e.g. PDL1[t]		X				X	X[n]			X	X[n]			X				X[s]		
Rectal swab (optional)	X					X								X						
Phone call or e-mail																			X	X

a. Tremelimumab: flat dose of 75 mg q4wk (+/- 7 days) for 4 doses only. Durvalumab: flat dose of 1500 mg q4wk (+/- 7 days).
b. RFA/TACE/cryoablation on day 36 +/- 96 hrs.
c. Filling out of the Advance Directive Form will be offered but obtaining of it is not required. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. For details see Section **12.4**.

d. Full physical examination at screening; targeted physical examination at other time points
e. within 30 minutes before and within 30 minutes after infusion.
f. If pre-study laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. 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.
g. Biochemical profile: electrolytes, BUN, creatinine, AST, ALT, total and direct bilirubin, calcium, phosphorus, albumin, magnesium.
h. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
i. Screening, Day 1 and during the study, but only if clinically indicated
j. For viral hepatitis patients: For Hepatitis B: HBV viral load; Anti-HBc Antibody, Anti-HBe Antibody, HBeAg and quantitative HepB Ag, HBV specific immune response. For Hepatitis C: HCV viral load, anti-HCV Antibody titre.
k. Restaging CT of chest, abdomen and pelvis (or MRI of liver if clinically indicated) scan every 8 weeks to evaluate TTP in target lesion. Post cycle 6 restaging will occur every 12 weeks until confirmed PD. However, depending on the study design and/or comparator arm, the timing of scans may change from every 8 weeks.
l. All patients will receive a baseline mandatory biopsy. Optional biopsies will be requested on D36 and D85. Those receiving ablative therapy will have a biopsy on D36 during the ablative therapy procedure.
m. Pre-infusion and within approximately 15 minutes post infusion.
n. For local patients only.
o. Patients will continue 1500 mg durvalumab q4w until end of study treatment as defined in section **3.8.1**.
p. The end off-treatment visits will occur if patient is agreeable to coming back and physically able to return for the visits. These visits will occur approximately 60 and 90 days post the last dose of study drug. Patients declined to come, will be contacted by phone or e-mail to evaluate their status.
q. '+/- 72 hr' window applies.
r. Long time follow up. All subjects will be followed for survival by phone call or e-mail every 6 months
s. Every 12 weeks until PD
t. Pre-infusion

3.7 COST AND COMPENSATION

3.7.1 Costs

NIH does not bill health insurance companies or participants for any research or related clinical care that participants receive at the NIH Clinical Center. If some tests and procedures performed outside the NIH Clinical Center, participants may have to pay for these costs if they are not covered by insurance company. Medicines that are not part of the study treatment will not be provided or paid for by the NIH Clinical Center.

3.7.2 Compensation

Participants will not be compensated on this study.

3.7.3 Reimbursement

The NCI will cover the costs of some expenses associated with protocol participation. Some of these costs may be paid directly by the NIH and some may be reimbursed to the participant/guardian as appropriate. The amount and form of these payments are determined by the NCI Travel and Lodging Reimbursement Policy

3.8 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

Prior to removal from study, effort must be made to have all subjects complete a safety visits approximately 60 and 90 days following the last dose of study therapy.

3.8.1 Criteria for Removal from Protocol Therapy

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

- Pregnancy or intent to become pregnant
- Any AE that meets criteria for discontinuation as defined in section **3.4**.
- Patient decides to withdraw from the study
- Adverse event related to durvalumab or tremelimumab, with the exception of toxicities that do not meet the criteria for discontinuation as defined in section **3.4** if applicable
- Grade ≥ 3 infusion reaction
- Initiation of alternative anticancer therapy including another investigational agent
- Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab + tremelimumab
- Investigator discretion

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

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section **7**, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. Subjects who decline to return to the site for evaluations will be offered follow-up

by phone every 3 months as an alternative. All subjects will be followed for survival by phone call or e-mail every 6 months.

3.8.2 Off-Study Criteria

- Participant requests to be withdrawn from study
- Lost to follow-up
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- Investigator discretion
- Death
- PI decision to end the study

3.8.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 1 month and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

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.

Information on all concomitant medications, administered blood products, as well as interventions occurring during the study must be recorded on the patient's eCRF.

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

4.1 FEMALE PATIENT OF CHILD-BEARING POTENTIAL

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 2 highly effective method of contraception (**Table 2**) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab

+ tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

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

4.2 MALE PATIENTS WITH A FEMALE PARTNER OF CHILDBEARING POTENTIAL

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (**Table 2**). Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

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

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

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in **Table 2**. Note that some contraception methods are not considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 2 Highly Effective Methods of Contraception (< 1% failure rate)

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

4.3 BLOOD DONATION

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

4.4 CONCOMITANT TREATMENT(S)

The Principal Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Section 3.4 for guidance on management of IP-related toxicities.

4.5 PERMITTED CONCOMITANT MEDICATIONS

Table 3: Supportive Medications

Supportive medication/class of drug	Usage
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all patients.

Supportive medication/class of drug	Usage
Inactivated viruses, such as those in the influenza vaccine	Permitted

4.6 EXCLUDED CONCOMITANT MEDICATIONS

Table 4: Prohibited Concomitant Medications

Prohibited medication/class of drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding <<10 mg/day>> of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly. (Use of immunosuppressive medications for the management of IP-related AEs, <<premedication for patients receiving XX>>, or in patients with contrast allergies is acceptable). In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)

Prohibited medication/class of drug	Usage
EGFR TKIs	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Should be used with caution in the 90 days post last dose of durvalumab.	Should not be given through 30 days after the last dose of IP (including SoC)

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. A description of each test including a brief statement of rationale and processing information is made below.

Table 5: Sample Collection Table

Test/assay	Sample size (approx.)	Type of tube	Collection point	Location of specimen analysis
Immune-monitoring	120 ml (for PBMC)	EDTA	See Study Calendar **3.6**	Figg Lab
	5-10 ml (for serum)	EDTA		
PK	3 ml	SST	See Study Calendar 3.6	MedImmune *
Immunogenicity	4 ml	SST	See Study Calendar **3.6**	Medimmune *
Antinuclear antibody (ANA)	4 ml	SST	See Study Calendar **3.6**	CC Department of Laboratory Medicine (DLM)
Antimitochondrial antibody (AMA) & Liver/kidney microsomal antibody	4 ml	SST	See Study Calendar **3.6**	CC DLM will send to Mayo Labs
Tumor-specific responses (e.g. αFP)	20 ml	EDTA	See Study Calendar **3.6**	Greten Lab
CFSE-	5 ml	EDTA	See Study Calendar **3.6**	Greten Lab

Test/assay	Sample size (approx.)	Type of tube	Collection point	Location of specimen analysis
proliferation T cells				
MDSC functional assay	20 ml	EDTA	See Study Calendar **3.6**	Greten Lab
Hepatitis B & C viral load	8 ml	SST	See Study Calendar **3.6**	CC Department of Transfusion Medicine
T-cell activation/ICOS expression (PBMC)	10 ml	EDTA	See Study Calendar **3.6**	Medimmune *
Plasma-based assays for circulating receptors/ligands e.g. PDL1	6 ml	EDTA	See Study Calendar **3.6**	Medimmune*
Tumor biopsy	NA	N/A	See Study Calendar **3.6**	Laboratory of Pathology
Whole genome shotgun sequencing of microbial DNA	Rectal Swab	N/A	See Study Calendar **3.6**	Greten lab

* Coded linked samples without key will be sent for performing of experiments

5.2 NCI CORRELATIVE STUDIES

5.2.1 Immune monitoring (All cohorts)

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, and (viii) the detection of HCC-associated antigens using ELISPOT assay.

Patients will undergo blood sampling (c.120mls blood) on the time points outlined in the Study Calendar **3.6**. Blood will initially be sent to the Figg laboratory 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)

AIH is a chronic disorder characterized by progressive hepatocellular loss and cell-mediated immunologic attack. Histologic inflammation is present and is usually accompanied by fibrosis, which can progress to cirrhosis and liver failure. AIH accounts for 11% to 23% of chronic liver disease in North America and about 6% of liver transplants in the United States.

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 Hepatitis serology and viral load

As mentioned in the background section the phase II study of tremelimumab in HCC showed significant anti-HCV immune response with progressive decline in serum HCV viral load (median values: basal 3.78x10e5 copies/ml vs. day 120 3.02x10e4 copies/ml, p=0.02; vs. day 210 1.69x10e3 copies/ml, p=0.04). Therefore, for all viral hepatitis patients we will measure viral load and antibody titers at baseline and every 30 days. For patients with chronic HBV infection, in addition to the studies already described, we plan to:

- determine HBsAg concentrations in serum
- determine HBeAg (in HBeAg positive patients)
- determine HBsAg fractions (small, middle, large HBsAg)
- determine HBV specific T cell responses

These studies will be performed on samples obtained according to Study Calendar **3.6**. Samples with be processed by CC Department of Laboratory medicine. For HBsAg and Hepatitis B specific immune response, samples will be processed by the Department of Gastroenterology, Hannover Medical School, Germany.

The NCI Thoracic and GI Oncology Branch will release coded serum samples collected in conventional “CryoTubes” in association with this protocol to:

Heiner Wedemeyer
Department of Gastroenterology
Hannover Medical School
Carl Neuberg Strasse 1
30625 Hannover
Germany

for HBsAg and Hepatitis B specific immune response, as will be specified in NCI Material Transfer Agreement #38376-14.

Specimens will be labeled with the study identifier only and will be shipped to the address above, either on dry ice or at ambient temperatures as required by the type of sample to be analyzed.

5.2.4 Tumor-specific αFP responses

Frequency of AFP-specific $CD4^+$ T cells will be analyzed using the interferon (IFN)-[gamma] cytokine secretion assay as previously described[36]. In brief, PBMCs will be resuspended in medium cultured in duplicate with the following peptides: $AFP_{137-145}$ (PLFQVPEPV), $AFP_{249-258}$ (KVNFTEIQKL), and $AFP_{364-373}$ (QLAVSVILRV) or an irrelevant control peptide (SIINFEKL). Recombinant interleukin-2 (25 IU/mL) will be added on day 2 of culture. After 7 days, PBMCs will be re-stimulated with the same peptide and incubated for 5 hours at 37°C and IFN-[gamma] secretion by $CD4^+$ T cells analyzed by IFN-[gamma] capture assay. Live gating on $CD4^+$ T cells will be performed until up to 100,000 events were acquired. Only AFP responses >0.1% of $CD4^+$ T cells will be considered positive.

5.2.5 MDSC functional assay

Freshly isolated PBMC will be labeled with CSFE and stimulated with CD2/CD3/CD28 beads in the presence/absence of L-NMMA and NorNOHA. In control experiments CD14 depleted PBMC will be stimulated under the same conditions. Proliferative response of T cells will be assessed by FACS analysis.

5.2.6 Rectal Swab Collection, Storage and Analysis (optional)

Rectal swabs may be collected at the clinic at the indicated time points with standard sterile swabs. Rectal swabs would be obtained using standard clinical methods (inserted <1 inch beyond anal sphincter, rotated gently, and removed). Samples will be stored for future studies, including whole genome shotgun sequencing of microbial DNA.

Samples will be delivered to Dr. Figg's Blood Processing Core (BPC), Section **Error! Reference source not found.**

Upon receiving the samples, they will be kept frozen until analysis.

Microbial DNA will be isolated and DNA sequencing of the microbiome will be performed.

Samples sequenced to study microbial communities will contain human DNA sequences. However, bioinformatics analyses of the sequences will remove sequences containing significant alignment to publicly available human DNA sequences. These data will be coded and stored at the NIH Intramural Sequencing Center (NISC) per standard protocols for intramural sequencing. The resulting sequences will be analyzed. Publicly available human DNA sequences likely do not include all possible DNA sequences and could result in fragments of human DNA sequences being incorporated into the microbial DNA analysis.

5.2.7 Tumor Biopsies

A tumor biopsy will be performed at baseline for analysis of immune infiltration and at a subsequent timepoints D36 and D85 if the patient is willing and the procedure can be performed safely. The biopsies may be performed under ultra sound or CT guidance. Patients receiving ablative therapy will have a biopsy on D36 during the ablative therapy procedure. 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 when radiology pages the contact person to collect the specimens.
    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.

5.3 MEDIMMUNE PLANNED STUDIES

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

5.3.1 Pharmacokinetics

The time points for PK sampling are described in the Study Calendar **3.6**. A validated enzyme-linked immunosorbent assay (ELISA) will be used for the quantitative determination of tremelimumab in human serum.

5.3.2 Immunogenicity

The time points for the assessment of anti-tremelimumab antibodies are described in the Study Calendar **3.6**. A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the detection of anti-drug antibodies against tremelimumab in human serum.

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 as specified in Study Calendar **3.6**. Samples will be processed to PBMC and stored frozen until time of analysis. Additionally, absolute lymphocyte count at

baseline and in response to tremelimumab treatment will be evaluated for any relationship with treatment outcome.

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 in Study Calendar **3.6** 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 treatment and clinical outcome.

5.4 SAMPLE STORAGE, TRACKING AND DISPOSITION

Samples will be ordered in CRIS and tracked through 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, Dr. Altan-Bonnet's lab or MedImmune for sample analysis as described in the protocol. Samples will not be sent outside NIH without appropriate approvals and/or agreements, if required.

All samples will be barcoded, with data entered and stored in the secure database Labmatrix. These databases create a unique barcode ID for every sample and sample box, which cannot be traced back to patients without database 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.).

Barcoded samples are stored in barcoded boxes in a locked freezer at either -20 or -80^{0}C according to stability requirements.

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 database. 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. 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.

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

Please e-mail NCIBloodcore@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) or pager number# 11964.

For questions regarding sample processing, contact NCIBloodcore@mail.nih.gov.

5.4.2 Dr Greten Lab Contact information

Contact information:

Sophie Wang

Building 10 Rm 3B44

Phone: 240-858-3218

E-mail: sophie.wang@nih.gov

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 sections above. 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.

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 record any loss or unanticipated destruction of samples as a deviation. Reports will be done per the requirements of section **7.2**.

6 DATA COLLECTION AND EVALUATION

6.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (C3D) and Labmatrix 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. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

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.

Document AEs from the first study intervention, Study Day 1 of Cycle 1 through 90 days after the subject received the last study drug administration. Beyond 90 days after the last intervention, only adverse events which are serious and related to the study intervention need to be recorded.

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.

Data collection required by MedImmune described in **Appendix E**

End of study procedures: Data will be stored according to HHS, FDA, and NIH Intramural Records Retention Schedule regulations 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, this will be reported expeditiously per requirements in section **7.2.1**.

6.2 DATA SHARING PLANS

6.2.1 Human Data Sharing Plan

I will share coded, linked human data generated in this research for future research in a NIH-funded or approved public repository (clinicaltrials.gov, dbGaP), in BTRIS, with approved outside collaborators under appropriate agreements, in publication and/or public presentations at the time of publication or shortly thereafter.

6.2.2 Genomic Data Sharing Plan

Unlinked genomic data will be deposited in public genomic databases such as dbGaP in compliance with the NIH Genomic Data Sharing Policy

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.

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)[37]. 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.

6.3.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with tremelimumab and durvalumab.

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.)

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

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 ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

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.

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

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

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

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published[38] [39] [40]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer[41].

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.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.3.4 Response Criteria

6.3.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum 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).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

6.3.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

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

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

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**

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

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

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

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*

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

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. Please refer to **Appendix C** for further details.

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 NIH REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 DEFINITIONS

Please refer to definitions provided in Policy 801: Reporting Research Events found here.

7.2 OHSRP OFFICE OF COMPLIANCE AND TRAINING / IRB REPORTING

7.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here. Note: Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported per these policies.

7.2.2 IRB Requirements for PI Reporting at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

7.3 NCI CLINICAL DIRECTOR REPORTING

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

7.4 NIH REQUIRED DATA AND SAFETY MONITORING PLAN

7.4.1 Principal Investigator/Research Team

The clinical research team will meet on a weekly basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable 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. Events meeting requirements for expedited reporting as described in section **7.2.1** will be submitted within the appropriate timelines.

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.

8 SPONSOR PROTOCOL/SAFETY REPORTING

8.1 DEFINITIONS

8.1.1 Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this

treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH E6 (R2))

8.1.2 Serious Adverse Event (SAE)

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 event (see section **8.1.3**)
- Inpatient hospitalization or prolongation of existing hospitalization
    - A hospitalization/admission that is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study), a planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered a serious adverse event.
    - A hospitalization/admission that is solely driven by non-medical reasons (e.g., hospitalization for patient or subject convenience) is not considered a serious adverse event.
    - Emergency room visits or stays in observation units that do not result in admission to the hospital would not be considered a serious adverse event. The reason for seeking medical care should be evaluated for meeting one of the other serious criteria
- 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.

8.1.3 Life-threatening

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (21CFR312.32)

8.1.4 Severity

The severity of each Adverse Event will be assessed utilizing the CTCAE version 4.0.

8.1.5 Relationship to Study Product

All AEs will have their relationship to study product assessed using the terms: related or not related.

- Related – There is a reasonable possibility that the study product caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study product and the adverse event.
- Not Related – There is not a reasonable possibility that the administration of the study product caused the event.

8.1.6 Adverse Events of Special Interest (AESI)

See Section **3.4.2.**

8.2 ASSESSMENT OF SAFETY EVENTS

AE information collected will include event description, date of onset, assessment of severity and relationship to study product and alternate etiology (if not related to study product), date of resolution of the event, seriousness and outcome. The assessment of severity and relationship to the study product will be done only by those with the training and authority to make a diagnosis and listed on the Form FDA 1572 as the site principal investigator or sub-investigator. AEs occurring during the collection and reporting period will be documented appropriately regardless of relationship. AEs will be followed through resolution.

SAEs will be:

- Assessed for severity and relationship to study product and alternate etiology (if not related to study product) by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.
- Recorded on the appropriate SAE report form, the medical record and captured in the clinical database.
- Followed through resolution by a licensed study physician listed on the Form FDA 1572 as the site principal investigator or sub-investigator.

For timeframe of recording adverse events, please refer to section **6.1**. All serious adverse events recorded from the time of first investigational product administration must be reported to the sponsor with the exception of any listed in section **8.4**.

8.3 REPORTING OF SERIOUS ADVERSE EVENTS

Any AE that meets protocol-defined serious criteria or meets the definition of Adverse Event of Special Interest that require expedited reporting must be submitted immediately (within 24 hours of awareness) to OSRO Safety using the CCR SAE report form.

All SAE reporting must include the elements described in section **8.2**.

SAE reports will be submitted to the Center for Cancer Research (CCR) at: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. CCR SAE report form and instructions can be found at: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

Following the assessment of the SAE by OSRO, other supporting documentation of the event may be requested by the OSRO Safety and should be provided as soon as possible.

8.4 WAIVER OF EXPEDITED REPORTING TO CCR

As death due to disease progression is part of the study objectives (OS) and captured as an endpoint in this study, death due to disease progression will not be reported in expedited manner to the Sponsor. However, if there is evidence suggesting a causal relationship between the study drug and the event, report the event in an expedited manner according to section **8.3.**

Hospitalization that is deemed to be due to disease progression, and not attributable to the intervention will not be reported as an SAE. The event, and the assessment that it was caused by disease progression will be documented in the medical records. The causality assessment of hospitalization will be re-evaluated any time when new information is received. If the causality assessment changes from disease progression to related to the study intervention, SAE report will be sent to the Sponsor in an expedited manner according to section **8.3**. If there is any uncertainty whether the intervention is a contributing factor to the event, the event should be reported as AE or SAE as appropriate.

8.5 REPORTING CRITERIA TO THE PHARMACEUTICAL COLLABORATORS

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

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

8.5.1 Expedited Adverse Event Reporting Criteria to the IND Manufacturer

All safety reports and annual reports that are submitted to the FDA will be submitted to AstraZeneca.

A copy of the MedWatch report or equivalent form must be faxed to AstraZeneca at the time the event is reported to the FDA.

A cover page should accompany the MedWatch form or equivalent 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-16-11932)

* 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

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 + 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.

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

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

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

8.5.2 Other events requiring reporting

8.5.2.1 Overdose

Any overdose of a study subject with durvalumab + tremelimumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section **8.5.1** for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section **16.5**). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section **16.5**). There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

8.5.2.2 Hepatic function abnormality

Hepatic function abnormality (as defined in Section **3.4.2**.) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section **7.4** for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

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

8.6 REPORTING PREGNANCY

All required pregnancy reports/follow-up to OSRO will be submitted to: OSROSafety@mail.nih.gov and to the CCR PI and study coordinator. Forms and instructions can be found here: https://ccrod.cancer.gov/confluence/display/CCRCRO/Forms+and+Instructions

8.6.1 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 no later than 24 hours of when the Investigator becomes aware of it. The Investigator should notify the Sponsor no later than 24 hours of when the outcome of the Pregnancy become known,

Pregnancy itself is not regarded as an SAE. However, congenital abnormalities or birth defects and spontaneous miscarriages that meet serious criteria (see section **8.1.2)** should be reported as SAEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented.

8.6.2 Paternal exposure

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

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab+ tremelimumab combined therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period after the last dose should, if possible, be followed up and documented.

8.7 REGULATORY REPORTING FOR STUDIES CONDUCTED UNDER CCR-SPONSORED IND

Following notification from the investigator, CCR, the IND sponsor, will report any suspected adverse reaction that is both serious and unexpected. CCR will report an AE as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the study product and the adverse event. CCR will notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks from clinical trials or any other source, as soon as possible, in accordance to 21 CFR Part 312.32.

All serious events will be reported to the FDA at least annually in a summary format.

9 CLINICAL MONITORING

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 and secondary study endpoints; adherence to the protocol,

regulations, ICH E6, 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.

10 STATISTICAL CONSIDERATIONS

The primary objective of this pilot trial is to preliminarily evaluate the efficacy of combining tremelimumab and durvalumab in patients with advanced HCC, either alone or with cryoablation, TACE, or RFA, and in patients with advanced biliary tract carcinoma (BTC), either alone or with cryoablation, or RFA.

Cohorts A1 and A2 will enroll patients with advanced HCC, BCLC stage B/C and cohort B will enroll patients with intra/extra-hepatic cholangiocarcinoma. Cohort A1 will have 1 treatment Arm 1 (one without any ablative procedure) and Cohort A2 will have 3 separate treatment arms of 10 patients apiece (one a piece with TACE, RFA, or cryoablation). Cohort B will have 3 separate treatment arms of 10 patients apiece (one without any ablative procedure, one with RFA, and one with cryoablation). The initial 10 patients in cohorts A1 and B, the treatment arms without ablative procedure, must have satisfactory safety and feasibility outcomes in order to permit the treatment arms with ablation to open. This will likely mean that 7 or more of 10 are able to result in complete treatment for the patients. For this pilot, the assignment to specific method of ablation will be done by the multidisciplinary tumor board and thus will not be done randomly. As such, the results must be treated as preliminary and exploratory, requiring independent confirmation of any potentially positive findings.

As each of these 7 treatment arms of 10 patients will be considered a small pilot, each will have same statistical objective, and each of these arms will be evaluated for efficacy as follows. For both HCC and BTC there is no standard second-line therapy in the advanced setting. Based on historical data of investigational agents for both these diseases and stage (i.e. post-sorafenib HCC and post-gem/cis BTC) the 6-month PFS would be not greater than 10-15%[42, 43]. In each treatment arm of 10 patients in cohorts A1, A2 and B, the trial will have 82% power to rule out 15% as the proportion stable at 6 month in favor of 50% being stable at 6 months, with each evaluation assuming that a one-sided 0.10 significance level exact binomial test would be performed. If there are 3 patients in 10 who are able to have stable disease at a 6 month evaluation, then the lower one-sided 90% confidence bound for 3/10 is 11.6% (the two sided 80% confidence interval extends from 11.6% to 55.2%). Similarly, with 4 in 10 with stable disease at 6 months, the lower one-sided 90% confidence bound for 4/10 is 18.8% (the two sided

80% confidence interval extends from 18.8% to 64.6%). Thus, in Cohorts A1, A2 or B, 3 or 4 patients out of 10 attaining stable disease at 6 months in any of the 7 treatment arms would tentatively rule out 10-15% as the fraction who would do so, with 90% one sided confidence. The results from the ablation treatment arms of cohort A2 (using TACE, RFA, or cryoablation) may also have their results combined in an exploratory fashion to report their overall efficacy. Similarly, the results from the ablation treatment arms of cohort B (using RFA or cryoablation) may also have their results combined in an exploratory fashion to report their overall efficacy.

Should positive findings be identified in any of the treatment arm of cohorts A1, A2 or cohort B, then after this pilot phase has been concluded, subsequent, more definitive evaluation may be conducted in the appropriate sub-cohorts using larger numbers of patients, as defined by amendments (or separate protocols if warranted) used to describe the expansion cohorts.

It is expected that up to 2 patients per month may be able to enroll onto this trial. Cohort A1 will require 10 evaluable patients, Cohort A2 may require up to 30 evaluable patients and cohort B may require up to 30 evaluable patients. The accrual ceiling for the protocol will be set at 90 patients to allow for a small number of inevaluable patients to be enrolled. Thus, it is expected that 24-36 months may be needed to accrue all patients onto this trial.

To address safety and feasibility of combining tremelimumab and durvalumab in (Cohorts A1 and A2) patients with advanced HCC (either alone or with cryoablation, TACE or RFA) and (Cohort B) in patients with advanced biliary tract carcinoma (BTC) (either alone or with cryoablation or RFA), adverse events will be tabulated by grade per CTCAE 4 and analyzed and reported descriptively.

11 COLLABORATIVE AGREEMENTS

11.1 COOPERATIVE RESEARCH AND DEVELOPMENT AGREEMENT (CRADA)

A CRADA is in place with MedImmune, Inc. (02853) for supply of the investigational agents.

11.2 MATERIAL TRANSFER AGREEMENTS (MTA)

MTA # 38376-14 with Hannover Medical School is in place for the transfer of samples to collaborators as described in section **5.2.3**.

12 HUMAN SUBJECTS PROTECTIONS

12.1 ETHICAL CONDUCT OF THE STUDY

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

12.2 RATIONALE FOR SUBJECT SELECTION

Subjects treated on this study, will be individuals with advanced hepatocellular carcinoma (HCC) or biliary tract carcinoma, which has recurred (or persisted) after appropriate standard treatment. Individuals of any 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.

12.3 PARTICIPATION OF CHILDREN

Individuals under the age of 18 will not be eligible to participate in this study because they are unlikely to have hepatocellular or biliary tract carcinoma, and because of unknown toxicities in pediatric patients.

12.4 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 **12.5.3**), 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 to assess ongoing capacity of the subjects and to identify a LAR, as needed.

Please see section **12.6.1** for consent procedure.

12.5 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS FOR ALL PARTICIPANTS

12.5.1 Known potential risks

The primary risk to patients participating in this research study is from the toxicity of durvalumab and tremelimumab.

12.5.1.1 Durvalumab:

More than 10% participants may have:

- Diarrhea,
- Rash/dry itchy skin,
- Liver problems: Increases in liver enzymes, inflammation of the liver (hepatitis); however, this is uncommon.
- Fatigue
- Nausea
- Vomiting
- Abdominal pain
- Accumulation of fluid causing swelling
- Upper respiratory tract infections
- Decreased appetite
- Shortness of breath
- Cough

- Fever

From 1 to 10% participants may have:

- Inflammation in the lungs (pneumonitis). Preliminary data suggested that there may be the tendency of higher frequency and severity in Japanese patients compared with non-Japanese patients.
- Low thyroid (Hypothyroidism). The condition can be treated with replacement thyroid hormone.
- High thyroid (Hyperthyroidism). Depending on the severity of the symptoms, treatment may include just monitoring the symptoms, treating the symptoms themselves and/or giving medicine to block the thyroid hormone.
- Kidney problems: an increase of creatinine levels in a blood test. Uncommonly a patient may experience nephritis which is an inflammation of the kidneys that stops the kidneys from working properly.
- Nervous system problems: symptoms can include unusual weakness of legs, arms, or face, numbness or tingling in hands or feet. In rare situations there is the potential for the inflammation of the nervous system to be severe and cause damage to the nerve cells or breakdown in the communication between nerves and muscles.
- Infusion Related Reactions.
- Inflammation of the intestine (colitis).
- A hoarse voice
- Painful urination
- Night sweats
- Pneumonia
- Oral thrush
- Dental and oral soft tissue infection
- Pain in muscles and joints
- Influenza.

Less than 1% people may have:

- Inflammation of the pancreas (pancreatitis).
- Allergic reactions.
- Problems with adrenal glands (Adrenal Insufficiency). These complications may be permanent and may require hormone replacement.
- Problems with the pituitary gland (hypopituitarism). These complications may be permanent and may require hormone replacement.
- Inflammation of the muscles or associated tissues, such as blood vessels that supply the

muscles (Myositis/polymyositis).

- Type 1 Diabetes mellitus. Type 1 diabetes will require replacement of insulin through injection.
- Problems with the pituitary gland (hypopituitarism). These complications may be permanent and may require hormone replacement.
- Inflammation of the heart muscle (myocarditis).
- Inflammation of the membrane surrounding the heart.
- Growths of tiny collections of inflammatory cells in different parts of the body.
- Inflammation of the middle layer of the eye and other events involving the eye (e.g. inflammation of the cornea and optic nerves).
- Inflammation of the brain or the membranes that cover the brain and spinal cord.
- Hardening and tightening of the skin and connective tissues and loss of skin color.
- Pemphigoid and hematological events (e.g., abnormal breakdown of the red blood cells and low levels of platelets).
- Inflammation of the blood vessels and rheumatological events (inflammatory disorder causing muscle pain and stiffness and autoimmune arthritis).

12.5.1.2 Tremelimumab

The following are side effects that have been associated with Tremelimumab:

- Diarrhea
- Rash
- Pruritus (itching)
- Fatigue
- Nausea
- Vomiting
- Anorexia
- Headache
- Abdominal Pain
- Muscle pain
- Auto-immune changes to the pituitary gland leading to hormonal changes.
- Inflammation of the part of the intestine (colitis).
- Inflammation in the lungs (pneumonitis).
- Kidney problems: an increase of creatinine levels in a blood test.

- Inflammation of the pancreas (pancreatitis).
- Inflammation of the liver (hepatitis). In extreme cases this may result in liver failure and death.
- A skin rash related to the treatment and this can also result in severe and life-threatening symptoms.
- Problems related to tremelimumab infusion
- A serious allergic reaction (anaphylaxis)

There is a remote chance that participants may develop new allergies to previously exposed substances, other than durvalumab or tremelimumab. For example, it is possible that people could develop an allergy to shellfish or IV contrast while taking durvalumab or tremelimumab. These allergies may be severe and life threatening.

All care will be taken to minimize study treatment side effects, but they can be unpredictable in nature and severity. Patients will be examined and evaluated prior to enrollment. All evaluations to monitor the treatment of patients will be recorded in the patient chart.

12.5.1.3 Risks of RFA

Subjects in Arm 3 additionally will have one protocol required RFA procedure. The risks from RFA include bleeding, injury to the normal liver tissue, re-growth of the tumor and infection.

12.5.1.4 Risks of cryoablation

Subjects in Arm 4 additionally will have one protocol required Cryo procedure. The risks from cryoablation procedure include bleeding, injury to the normal liver tissue, re-growth of the tumor and nerve damage.

12.5.1.5 Risk of optional 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.

12.5.1.6 Risks of sedation

Potential side effects of sedation include headache, nausea and drowsiness. These side effects usually go away quickly.

12.5.1.7 Risks of general anesthesia

Risks of general anesthesia include temporary confusion and memory loss, although this is more common in the elderly, dizziness, difficulty passing urine, bruising or soreness from the IV drip, nausea and vomiting, shivering and feeling cold, sore throat due to the breathing tube

12.5.1.8 Risks of exposure to ionizing radiation

The study will involve radiation from the following sources:

- Up to 6 CT scans per year for disease assessment (all subjects)
- Up to 3 CT scans for the collection of one mandatory and 2 optional biopsies (Arm A1 only)

- One TACE procedure (Arm A2 only)
- Up to 1 CT scan to guide RFA
- Up to 1 CT scan to guide cryo

Subjects in Arm 1 may have up to 6 CT scans and 3 CT guided biopsies and be exposed to approximately 9 rem per year. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 0.9 out of 100 (0.9%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

Subjects in Arm 2 may have up to 6 CT scans, 2 CT guided biopsies and one protocol required TACE procedure. The actual dose of a TACE is highly variable, depending on the patient. Based on literature reviews one average TACE is about 8 rem. So, subjects in Arm 2 may be exposed to total amount of radiation 16.2 rem. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study for participants in Arm 2 is 1.6 out of 100 (1.6%) and of getting a fatal cancer is 0.8 out of 100 (0.8%).

Subjects in Arm 3 and 4 may have up to 6 CT scans, 2 CT guided biopsies, 1 CT guided RFA or cryo and be exposed to approximately 9 rem per year. This amount is more than would be expected from everyday background radiation. Being exposed to excess radiation can increase the risk of cancer. The risk of getting cancer from the radiation exposure in this study is 0.9 out of 100 (0.9%) and of getting a fatal cancer is 0.5 out of 100 (0.5%).

12.5.1.9 Risks of CT Scans

In addition to the radiation risks discussed above, CT scans may include the risks of an allergic reaction to the contrast. Participants might experience hives, itching, headache, difficulty breathing, increased heartrate and swelling.

12.5.1.10 Risk of losing data

This includes the risk that data obtained during this study can be released to members of the public, insurers, employers, or law enforcement agencies. Although there are no plans to release results to the patients, family members or health care providers, this risk will be included in the informed consent document.

12.5.1.11 Blood Collection Risks

Risks of blood draws include pain and bruising in the area where the needle is placed, lightheadedness, and rarely, fainting. When large amounts of blood are collected, low red blood cell count (anemia) can develop.

12.5.1.12 Risks of EKG

Risks include some minor skin irritation from the electrodes

12.5.1.13 Urinalysis

There are no physical risks of urinalysis

12.5.2 Known potential 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..

12.5.3 Risks/Benefits Analysis

For patients with hepatocellular carcinoma and biliary cancer, median survival is in the range of 6 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 hepatocellular carcinoma. 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.

The risks and benefits of participation for adults who become unable to consent, are no different than those described for patients who are less vulnerable.

12.6 CONSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant or consent designee(s) (e.g., legally authorized representative [LAR] for reconsent purposes if participant is an adult unable to consent) for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms used in compliance with local policy, including M20-1) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee(s), when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed.

For optional biopsies for research in the protocol, the patient will consent at the time of the procedure. If the patient refuses the optional biopsy at that time, the refusal will be documented in the medical record and in the research record.

12.6.1 Consent Process for Adults Who Lack Capacity to Consent to Research Participation

For participants addressed in section **12.4**, an LAR will be identified consistent with Policy 403 and informed consent obtained from the LAR, as described in Section **12.6**.

13 REGULATORY AND OPERATIONAL CONSIDERATIONS

13.1 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, associate investigators, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and as applicable, Food and Drug Administration (FDA).

13.2 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

13.3 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have

a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NCI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

13.4 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), and/or regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be archived at the NIH Clinical Center.

To further protect the privacy of study participants, a Certificate of Confidentiality has been issued by the National Institutes of Health (NIH). This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

14 PHARMACEUTICAL INFORMATION

14.1 TREMELIMUMAB

14.1.1 Source

Tremelimumab will be supplied by AstraZeneca/MedImmune, Inc.

14.1.2 Formulation and Preparation

Tremelimumab is a human IgG2 anti-CTLA-4 mAb that is being developed as an immunotherapeutic agent for various cancers.

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Tremelimumab	MedImmune	Tremelimumab will be supplied by AstraZeneca either as a 400-mg or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

The 20 mg/mL solution will be diluted into a saline bag for IV infusion. Vials containing tremelimumab may be gently inverted for mixing but should not be shaken.

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

- IV infusion bags of 0.9% sodium chloride injection (250 mL size). Saline bags must be latex-free and can be made of polyvinyl chloride (PVC) or 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.

14.1.3 Administration Procedures

Tremelimumab is to be administered as an IV solution of 10 mg/kg at a rate of 250 mL/hr, followed by observation for 60 minutes.

14.1.4 Dose Calculation

Note: The dosing for tremelimumab will be a flat dosing of 75 mg.

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

The number of vials required for dose preparation is the next greatest whole number of vials from the following formula: Number of vials = Dose (mL) ÷ 20 (mL/vial)

14.1.5 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 (**14.1.8**) 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.

14.1.6 Dose Preparation Steps

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

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

1) 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. 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.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP).

14.1.7 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.

14.1.8 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

14.2 DURVALUMAB

14.2.1 Source

Durvalumab will be supplied by AstraZeneca/MedImmune Inc.

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

14.2.3 Stability

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

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

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

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Remove 30.0 mL of IV solution from the IV bag prior to addition of durvalumab. Next, 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

For patients <30kg, Calculate the dose volume of durvalumab and tremelimumab and number of vials needed for the subject to achieve the accurate dose.

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

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

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

Protect from light.

14.2.4 Dose Calculation

Note: The dosing for durvalumab will be a flat dosing of 1500mg.

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

The number of vials required for dose preparation is the next greatest whole number of vials from the following formula: Number of vials = Dose (mL) ÷ 20 (mL/vial)

14.2.5 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) Labels will be prepared in accordance with Good Manufacturing Practice (GMP).

14.2.6 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 (**14.2.8**) 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.

14.2.7 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.

14.2.8 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

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

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16 APPENDICES

16.1 Appendix A -PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale

Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
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).
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.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

16.2 APPENDIX B - CHILD-PUGH CLASSIFICATION SYSTEM

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/liter)	2-3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (35 g/liter)	2.8-3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy. A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease). These grades correlate with one- and two-year patient survival: grade A - 100 and 85 percent; grade B - 80 and 60 percent; and grade C - 45 and 35 percent.

16.3 APPENDIX C: 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 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).

16.4 APPENDIX D - 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)

16.5 APPENDIX E - DATA COLLECTION ELEMENTS REQUIRED BY MANUFACTURER

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

The following variables will be collected for each AE:

- AE (CTCAE version 4.0)
- The date and time when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab or tremelimumab (yes or no)
- Action taken with regard to durvalumab + tremelimumab/ combination agent
- Outcome

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

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

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

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

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

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

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

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

16.6 APPENDIX F: DOSING MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES (TMG) FOR IMMUNE-MEDIATED, INFUSION-RELATED, AND NON-IMMUNE–MEDIATED REACTIONS (DURVALUMAB MONOTHERAPY OR IN COMBINATION WITH OTHER PRODUCTS) 14 OCTOBER 2020

<table>
<tr><th colspan="2">General Considerations regarding Immune-Mediated Reactions</th></tr>
<tr><th>Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td>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 v5.0.

In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:
• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks of the start of the immune-mediated adverse event (imAE)
• Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing

Grade 1 No dose modification

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

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

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

Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:
1. The event stabilizes and is controlled.
2. The patient is clinically stable as per Investigator or treating physician’s clinical judgement.
3. Doses of prednisone are at ≤10 mg/day or equivalent.</td><td>It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table:
– It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines.
– Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow.
– Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.
– For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
– Some events with high likelihood for morbidity and/or mortality – e.g., 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.
– If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of</td></tr>
</table>

Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

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

Specific Immune-Mediated Reactions			
Adverse Events	**Severity Grade of the Event (NCI CTCAE version 5.0)**	**Dose Modifications**	**Toxicity Management**
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan. – Consider Pulmonary and Infectious Disease Consults
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider Chest CT with contrast and repeat in 3-4 weeks.

		upon treating physician's clinical judgment and after completion of steroid taper.	– If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 2 to 3 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 IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] – Consider Pulmonary and Infectious Disease consults. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider) . Caution: rule out sepsis and refer to infliximab label for general guidance before using

			infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). - When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. - PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only;	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide and other supportive care measures. – If symptoms persist consider checking lactoferrin; if positive treat as

	intervention not indicated)		Grade 2 below. If negative and no infection, continue Grade 1 management .
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider . **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day;	**Grade 3** - For patients treated with PD-1 or PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration.

	limiting self care ADL; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, fever; ileus; peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: life-threatening consequences; urgent intervention indicated)	after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. - Permanently discontinue study drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade large intestine perforation/Intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	– Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressant agents (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider)). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay . – 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).[a]

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline	• No dose modifications. • If it worsens, then treat as Grade 2.	– Continue LFT monitoring per protocol.

	abnormal; and/or TB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)		
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	• Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0×	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN: • Hold study drug/study regimen dose until resolution to Grade≤1 • Resume study drug/study regimen if elevations downgrade to Grade≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 within 14 days.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP

	baseline if baseline abnormal) **Grade 4** (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)	• For elevations in transaminases >8×ULN or elevations in bilirubin >5×ULN, permanently discontinue study drug/study regimen. • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3×ULN + bilirubin >2×ULN without initial findings of cholestasis [i.e., elevated alkaline P04] and in the absence of any alternative cause).	treatment (refer to current NCCN guidelines for treatment of cancer-related infections).

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if

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**			– HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations, 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**	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose untilresolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. • If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT	• Hold study drug/study regimen dose	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until

	>8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	until resolution to AST or ALT ≤5.0×ULN • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.	elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen	**Same as above** **(except would recommend obtaining liver biopsy early)**
	If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase riseFor example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**		
Nephritis or renal dysfunction (elevated serum	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and

creatinine)			creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria, recent IV contrast, medications, fluid status). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

	Grade 1 (serum creatinine >ULN to 1.5×ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
	Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup . – 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).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with an immunosuppressive in consultation with a nephrologist . – 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).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – Hold study drug if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or other severe cutaneous adverse reaction (SCAR) is suspected – Permanently discontinue study drugs if SJS, TEN or SCAR is confirmed**.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	• For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea

		Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event is persistent for >1 week or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. If toxicity worsens, then treat as Grade 4. **For Grade 4 (or life-threatening):** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (or life-threatening):** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis,	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel

hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)			habits, polydipsia, polyuria, hypotension, photophobia, visual field cuts and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. – 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).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis. – 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).
Amylase/Lipase increased		Dose Modifications (General Guidance): none Dose Modifications (Grade 1): No dose modifications Dose Modifications (Grade 2, 3 or 4): In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	For Any Grade −For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. −If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. −Assess for signs/symptoms of pancreatitis −Consider appropriate diagnostic testing (e.g, abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT)

Acute Pancreatitis		Dose Modifications (General Guidance): none Dose Modifications (Grade 1): No dose modifications Dose Modifications (Grade 2): Hold study drug/study regimen dose until resolution to Grade ≤1. Consider resumption of study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase in consultation with relevant pancreatic specialist Dose Modification (Grade 3 or 4): Permanently discontinue study drug/study regimen	For Any Grade -Consider gastroenterology referral For Grade 1: -IV hydration -Manage per amylase/lipase increased (asymptomatic) For Grade 2,3 or 4: -Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent -IV hydration

Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate.

	Grade 1	No dose modifications.	**For Grade 1:** − See "Any Grade" recommendations above. Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days .	**For Grade 2:** − Consider, as necessary, discussing with the study physician. − Obtain Neurology consult. − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). − Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 2 to 3 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 other immunosuppressive depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Consider, as necessary, discussing with study physician. − Obtain Neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG or other immunosuppressive depending on the specific imAE). Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor	**Any Grade**	**General Guidance**	**For Any Grade:** − The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably

syndromes (such as Guillain-Barre and myasthenia gravis)			experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 1 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. Obtain a Neurology consult.
	Grade 2 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate

	intervention indicated; limiting age-appropriate instrumental ADL)	instability.	medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* – Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. o Avoid medications that can worsen myasthenia gravis *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4 (Grade 3 GB: severe symptoms; limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-threatening; hospitalization or	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:**	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* – Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. – If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:*

	prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	Permanently discontinue study drug/study regimen.	– It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. – Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

	Grade 1	No dose modifications required unless	**For Grade 1 (no definitive findings):**

	(asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	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.	- Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; inter-vention indicated; new onset of symptoms*) (Grade 4: Life-threatening conse-quences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) * Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 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 IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure. – 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).[a]

Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium

			– swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over

			– ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Other Immune Mediated Reactions		Dose Modifications (Any Grade): *Note it is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines Dose Modifications (Grade 1): No dose modifications Dose Modifications (Grade 2): Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. If toxicity worsens, then treat as Grade 3 or Grade 4. Study	Any Grade - Thorough evaluation to rule out any alternative etiology (e.g. disease progression, concomitant medications and infections) - Consultation with relevant specialist - Treat accordingly, as per institutional standard Grade 1 - Monitor as clinically indicated Grade 2,3,4 - Treat accordingly as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN,

		drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Dose Modification (Grade 3): Hold study drug/study regimen Dose Modification (Grade 4): Discontinue study drug/study regimen	ESMO)

[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 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. – Consider premedication per institutional standard prior to subsequent doses. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, 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 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

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

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

16.7 APPENDIX G: FREQUENCY OF ADRS FOR DURVALUMAB MONOTHERAPY FROM POOLED DATA ACROSS MULTIPLE TUMOUR TYPES (N=3006)

SOC	PT/medical concept MedDRA (v21.1)	CIOMS frequency indicator [a]/ overall frequency all CTC grades	All CTCAE Grades n (%)	Grade 3 or 4 n (%)
Respiratory, thoracic, and mediastinal disorders	Cough/productive cough	Very common	646 (21.5)	11 (0.4)
	Pneumonitis [c]	Common	114 (3.8)	26 (0.9)
	Dysphonia	Common	93 (3.1)	2 (<0.1)
	ILD	Uncommon	18 (0.6)	4 (0.1)
Hepatobiliary disorders	ALT increased/AST increased [b, c]	Common	244 (8.1)	69 (2.3)
	Hepatitis [b, c]	Uncommon	25 (0.8)	12 (0.4)
Gastrointestinal disorders	Diarrhoea	Very common	491 (16.3)	19 (0.6)
	Abdominal pain [b]	Very common	383 (12.7)	53 (1.8)
	Colitis [b]	Uncommon	28 (0.9)	10 (0.3)
Endocrine disorders	Hypothyroidism [b]	Very common	305 (10.1)	5 (0.2)
	Hyperthyroidism [b]	Common	137 (4.6)	0
	Thyroiditis [b]	Uncommon	23 (0.8)	2 (<0.1)
	Adrenal insufficiency	Uncommon	18 (0.6)	3 (<0.1)
	Type 1 diabetes mellitus	Rare	1 (<0.1)	1 (<0.1)
	Hypophysitis/Hypopituitarism	Rare	2 (<0.1)	2 (<0.1)
	Diabetes insipidus	Rare	1 (<0.1)	1 (<0.1)
Renal and urinary disorders	Blood creatinine increased	Common	105 (3.5)	3 (<0.1)
	Dysuria	Common	39 (1.3)	0
	Nephritis [b]	Uncommon	9 (0.3)	2 (<0.1)

SOC	PT/medical concept MedDRA (v21.1)	CIOMS frequency indicator [a]/ overall frequency all CTC grades	All CTCAE Grades n (%)	Grade 3 or 4 n (%)
Skin and subcutaneous tissue disorders	Rash [b]	Very common	480 (16.0)	18 (0.6)
	Pruritus [b]	Very common	325 (10.8)	1 (<0.1)
	Night sweats	Common	47 (1.6)	1 (<0.1)
	Dermatitis	Uncommon	22 (0.7)	2 (<0.1)
	Pemphigoid [b]	Rare	3 (<0.1)	0
Cardiac disorders	Myocarditis	Rare	1 (<0.1)	1 (<0.1)
General disorders and administration site conditions	Pyrexia	Very common	414 (13.8)	10 (0.3)
	Oedema peripheral [b]	Common	291 (9.7)	9 (0.3)
Infections and infestations	Upper respiratory tract infections [b]	Very common	407 (13.5)	6 (0.2)
	Pneumonia [b,c]	Common	269 (8.9)	106 (3.5)
	Oral candidiasis	Common	64 (2.1)	0
	Dental and oral soft tissue infections [b]	Common	50 (1.7)	1 (<0.1)
	Influenza	Common	47 (1.6)	2 (<0.1)
Musculoskeletal and connective tissue disorders	Myalgia	Common	178 (5.9)	2 (<0.1)
	Myositis	Uncommon	6 (0.2)	1 (<0.1)
	Polymyositis [d]	Not determined	-	-
Nervous system disorders	Myasthenia gravis [e]	Not determined	-	-
Injury, poisoning, and procedural complications	Infusion related reaction [b]	Common	49 (1.6)	5 (0.2)
Blood and lymphatic system disorders	Immune thrombocytopenia [c]	Rare	2 (<0.1)	1 (<0.1)

b Denotes a medical concept.

c Fatal events have been reported.

d Polymyositis (fatal) was observed in a patient treated with durvalumab from an ongoing AstraZeneca-sponsored clinical study outside of the pooled dataset.

e Reported frequency from AstraZeneca-sponsored clinical studies outside of the pooled dataset is rare, with no events at Grade >2.

ADR = adverse drug reaction; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CIOMS = Council for International Organisations of Medical Sciences; CTC = Common Toxicity Criteria; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut-off; ILD = interstitial lung disease; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients; PT = preferred term; SOC = system organ class