SUMMARY OF PROTOCOL CHANGES

For Protocol Amendment # to: 7 **to 8**

UCCC Protocol #: UCCC-GI-21-01
AstraZeneca Protocol#: ESR-20-21010

Protocol Date: **09 April 2024**

#	Section	Change
1	**15.2 Known Risks of Durvalumab**	Known risks of durvalumab updated based on current durvalumab IB.
2	**Appendix 1 Toxicity Management**	Annex to Protocol September 2023
3	**Various**	Minor grammatical and formatting changes throughout

UCCC Protocol #: UCCC-GI-21-01
AstraZeneca Protocol#: ESR-20-21010

ClinicalTrials.gov Identifier: NCT05027425

Study Title: Durvalumab (MEDI4736) and Tremelimumab for Hepatocellular Carcinoma in Patients Listed for a Liver Transplant

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Participating Sites	University of Cincinnati Cancer Center Washington University University of Texas Southwestern

IND: 157193

Protocol Type / Version # / Version Date: **Original / Version 8/ 09 April 2024**

1. PROTOCOL SYNOPSIS

Clinical Protocol: ESR-20-21010, UCCC-GI-21-01

Study Title: Durvalumab (MEDI4736) and Tremelimumab for Hepatocellular Carcinoma in Patients Listed for a Liver Transplant

Protocol Number: ESR-20-21010

Clinical Phase: II

Study Duration: Four years to complete accrual. Survival follow up will continue for 5 years.

Investigational Product(s) and Reference Therapy:

1. Durvalumab concentrate for solution for infusion will be supplied in glass vials containing 500 mg durvalumab at a concentration of 50 mg/mL.
2. Tremelimumab concentrate for solution for infusion will be supplied in glass vials containing 25 mg tremelimumab at a concentration of 20 mg/mL.
3. Locoregional therapy will be per institutional standards of care.

Research Hypothesis:
Immunotherapy can safely downstage patients and achieve durable systemic disease control to improve clinical outcomes in HCC patients undergoing liver transplant.

Objectives:
Primary Objectives:

1. To assess the safety of immunotherapy for treatment of HCC in patients listed for a liver transplant, with respect to cellular rejection rates.

Secondary Objectives:

1. To assess the safety of immunotherapy for treatment of HCC in patients listed for a liver transplant, with respect to adverse events during treatment, and graft loss and mortality rates up to 30 days after transplant;
2. To assess the efficacy of immunotherapy for treatment of HCC in patients listed for a liver transplant, with respect to radiologic and pathologic responses, and survival outcomes.

Exploratory Objectives:

1. To assess the correlation of peripheral blood immune cell profiles with clinical outcomes
2. To assess the correlation of baseline stool sample microbiome profiles with clinical outcomes

Study Design:
ESR-20-21010 is a single-arm, open-label, Phase II, multicenter clinical trial designed to evaluate the safety and efficacy of durvalumab and tremelimumab for the treatment of hepatocellular carcinoma (HCC) patients who have cirrhosis or portal hypertension and are listed for a liver transplant.

The key eligibility requirements include HCC, Child-Pugh score of up to 7, and ECOG PS of 0 or 1.

Patients will be treated with the immunotherapy combination for up to 4 months. After a minimum 28 day gap following the final durvalamab dose, they will undergo locoregional therapy per institutional standards. Eventually, after a minimum 72-day gap from the end of immunotherapy, they will undergo liver transplant.

The primary endpoint is proportion of patients experiencing post-transplant rejection, graft loss, death, or loss to follow up (within 30 days of transplant). A total of 30 patients are to be enrolled, to allow at least 20 transplants for adequate primary endpoint analysis. An interim analysis after 10 patients will be performed to ensure safety. If there are untoward safety signals, study modification/discontinuation will be taken into consideration by the UCCC DSMB, investigators, the sponsor-investigator and AstraZeneca during the study and at interim analysis.

Number of Centers: 3

Number of Patients: 30

Study Population:

HCC patients who have cirrhosis or portal hypertension and are listed for a liver transplant.

Inclusion Criteria:

1. Hepatocellular carcinoma, diagnosed either by biopsy or by combination of cirrhosis and imaging criteria (contrast-enhanced CT or MRI)
2. Tumor confined to liver (no evidence of extrahepatic disease), with no macrovascular invasion
3. Patient evaluated by institutional Liver Transplant team and deemed eligible for transplant
4. Measurable disease by RECIST 1.1
5. No prior therapy for HCC
6. Adult patient (Age ≥18)
7. ECOG = 0 or 1 Child-Pugh Score = 5, 6, or 7
8. Creatinine < 1.5 ULN
9. Body weight >30 kg

Exclusion Criteria:

1. Extrahepatic disease
2. Variceal bleeding during 3 months prior to registration
3. Any other active cancer except: (a) Malignancy treated with curative intent and with no known active disease ≥5 years prior to the scheduled first dose of study treatment and of low potential risk for recurrence. (b) Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease. (c) Adequately treated carcinoma in situ without evidence of disease.
4. Any other autoimmune disease deemed a risk in the setting of immunotherapy per treating physician's judgment
5. Any other illness or patient condition deemed a medical or logistical barrier for protocol therapy per treating physician's judgment

Investigational Products, Dose, and Mode of Administration:

Tremelimumab 300 mg via IV infusion x 1 dose on day 1, plus durvalumab 1500 mg via IV infusion Q4W starting on day 1, for up to a maximum of 4 months (5 doses of durvalumab). If a patient's weight falls to 30kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between the investigator and study physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W).

Other Treatments:

After a minimum of a 28-day gap following the final durvalamab dose, patients will undergo locoregional therapy to their tumor(s) per institutional standards. Eventually, after a minimum of a 72-day gap from the end of immunotherapy, they will undergo liver transplant.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

During treatment, toxicities will be assessed per CTCAE v5 at each treatment visit. Laboratory evaluations will include complete blood counts, comprehensive metabolic panels, and thyroid function assessments. Symptoms will be evaluated using standard of care patient discussions. The primary endpoint is safety-based: patients with post-transplant "treatment failure", defined as rejection, graft loss, death, or loss to follow up (within 30 days of transplant). This will be evaluated by at least weekly assessment of engrafted liver function tests.

Efficacy Assessments:

Radiologic response will be assessed after immunotherapy completion – prior to locoregional therapy initiation. Using both RECIST 1.1 and/or mRECIST. Pathologic response will be assessed in the explanted liver. Recurrence-free survival and overall survival will be assessed for five years.

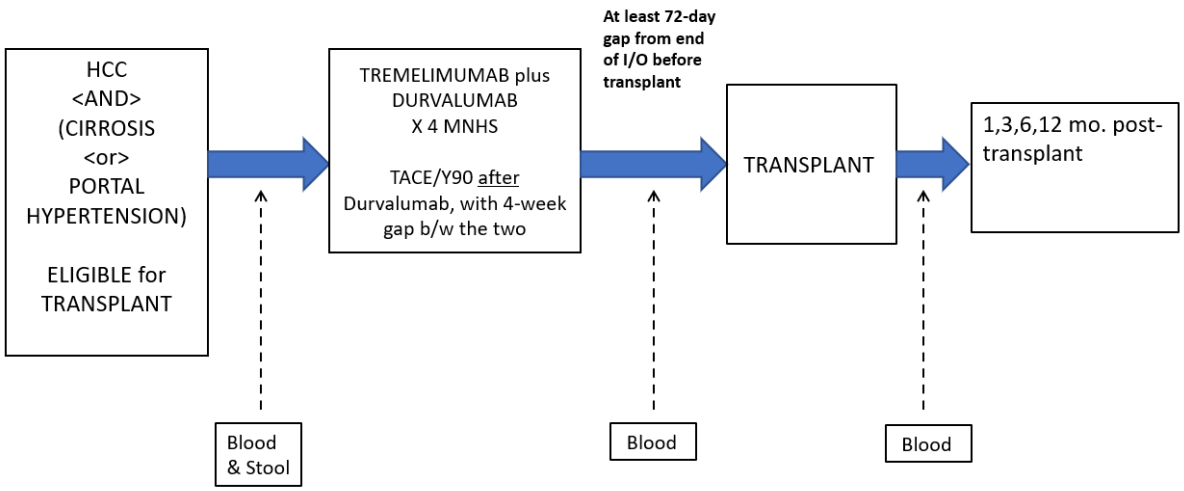
Sample Size Determination, Statistical Methods and Data Analysis:

The primary endpoint of safety is a binary endpoint, and will be assessed in patients undergoing liver transplant. Historically, 10-20% of patients are expected to experience acute cellular rejection within 30 days of transplant. We propose that an observed proportion of 20% treatment failure will be a clear indicator of safety in this pilot study, whereas an observed proportion of 50% failure will be a clear indicator of failure. Using these guardrails, with at least 20 patients going to transplant, we will have 80.6% power to demonstrate a failure proportion of 20% (4 patients experiencing failure) versus a null of 50% (10 patients experiencing failure), with a one-sided alpha of 0.05. With 25 patients going to transplant, the power will increase to 86% (other parameters being the same).

For the secondary endpoint of death-censored graft loss, within 30 days of transplant 2.5% of patients undergoing a liver transplant in these settings experience graft loss. If ≥7.5% of patients in this study experience graft loss within 30 days of transplant, it will be considered a serious safety signal.

For the efficacy endpoints, radiologic and pathologic response rates will be assessed as proportions, and overall and recurrence-free survival will be assessed using the Kaplan Meier method.

2. SCHEMA



3. STUDY CALENDAR

Milestone	**Screening**	**I/O**		**Post I/O Eval[l]**	**LR Therapy[m]**	**Transplant[n]**	**Post-op**	**Long Term Follow-up**
Timing		**D1**	**Q4W**	**28 days post I/O**	**28 days post I/O minimum**	**72 days post I/O minimum**	**Q7 days for 30 days**	**Q3 mo for 1st yr then q6 mo up to 5 yrs**
Window	**-28 days**		**+/- 3 days**	**+/- 3 days**			**+/- 1 day**	**+/- 4 weeks**
Durvalumab[a]		X	X					
Tremelimumab[b]		X						
LR Therapy[c]					X			
Transplant						X		
Consent[d]	X							
Demographics	X							
Medical Hx	X						X[t]	
Con Meds	X							
Physical Exam[e]	X	X	X	X			X[t]	
Vital Signs	X	X	X	X		X		
Height	X							
Weight	X	X	X	X		X		
Child-Pugh	X							
ECOG PS	X	X	X	X	X			
AE/SAEs		X	X	X	X			
CBC w/diff	X	X	X	X	X	X	X	X
CMP	X	X	X	X	X	X	X	X
TSH, amylase, lipase[f]	X		X	X				
INR	X		X	X	X	X	X	
AFP	X			X	X	X		X
βhCG[g]	X							
CT Chest[h]	X			X				
MRI Liver[i]	X			X				X[o]
Bone scan (if clinically indicated)	X							
Tumor Assessments[r]	X			X				
Survival Data[q]					X	X	X	X
Rejection Data							X	X[p]
Correlative Blood collection[j]	X[j]			X[j]		X[j]	X[j]	
Stool collection[k]	X							
Tissue collection[l]						X[l]		

I/O: Immunotherapy; LR: Locoregional; CBC: Complete blood count; CMP: Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, urea, creatinine, calcium, protein, albumin, AST, ALT, alkaline phosphatase, bilirubin)

a. Up to 5 treatments
b. Tremelimumab is only administered one time on Day 1 of the first cycle – only 1 dose for the entire study. It is not given on the first day of every subsequent cycle.

c. Per treating physician discretion – TACE, SIRT, etc.
d. Every effort should be made to minimize the time between consent and starting treatment
e. Physical exam will be directed toward key symptoms, signs, and safety evaluations, per treating physician's discretion
f. If TSH is abnormal, then free T3 and/or free T4 should be checked
g. For women of childbearing potential only. Serum pregnancy test performed within 7 days prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.
h. With or without contrast, per treating physician discretion
i. With contrast
j. Correlative blood samples may be collected with other SOC labs include the following. See Correlative section #9 for more information and the Laboratory Manual.
    - Two 10 mL EDTA tubes which must be collected after eligibility is confirmed but prior to I/O..
    - Two 10 mL EDTA tubes collected at the post I/O evaluation timepoint.
    - Two 10 mL EDTA tubes collected 4 weeks post-transplant +/- 3 days.
k. Per correlative section #9. Stool sample must be collected after eligibility is confirmed but prior to I/O.
l. tissue will be sequenced by CARIS as a SOC process.
m. The post-I/O safety eval must occur 28 days following the final dose of durvalumab.
n. A minimum 28-day gap after I/O before beginning L/R is required. L/R therapy can continue/repeat per treating physician discretion.
o. At least after 72 days following final dose of durvalumab.
p. Every 6 months +/- 1 month for standard of care, survival and disease progression data may be abstracted from this imaging.
q. Transplant graft rejection data will be collected at 30 days after transplant and at 3 months and 6 months during long term follow-up.
r. Subjects should be contacted by telephone or seen in clinic every 3 months from the end of I/O for the first year then every 6 months for up to 5 years to assess for survival status. Time-points noted under L/R Therapy, Transplant, and Post-op are intended to indicate that depending on the timing of each these may contain q3month time-points from I/O at which this data collection should occur.
s. Tumor assessments must include measures for either RECIST 1.1 or mRECIST or both if institutionally allowed.
t. 30-day post-transplant SOC visit in oncology with a +/- 7 day window to include medical history and physical.

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4. ABBREVIATIONS AND DEFINITION OF TERMS

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

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

Abbreviation or special term	Explanation
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular

Abbreviation or special term	Explanation
IMT	Immunomodulatory therapy
IP	Investigational product
imAE	Immune-mediated adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression

Abbreviation or special term	Explanation
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
sPD-L1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

5. OBJECTIVES

5.1. Primary Objectives

1. To assess the safety of immunotherapy for treatment of HCC in patients listed for a liver transplant, with respect to cellular rejection rates.

5.2. Secondary Objectives

1. To assess the safety of immunotherapy for treatment of HCC in patients listed for a liver transplant, with respect to adverse events during treatment, and graft loss and mortality rates.
2. To assess the efficacy of immunotherapy for treatment of HCC in patients listed for a liver transplant, with respect to radiologic and pathologic responses, and survival outcomes.

5.3. Exploratory Objectives

1. To assess the correlation between peripheral blood immune cell profiles and clinical outcomes.
2. To assess the correlation between baseline stool sample microbiome profiles and clinical outcomes.
3. To assess the correlation between tumor genomic profiles and clinical outcomes.

6. BACKGROUND

6.1. Immunotherapy Background

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn 2004). PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The PD-1 receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). The PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T cell response. When PD-L1 binds to PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumor cells exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PDL1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PDL1 is commonly overexpressed on tumor cells or on nontransformed cells in the tumor microenvironment (Pardoll 2012). PDL1 expressed on the tumor cells binds to PD1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD1/PDL1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous antitumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**). In addition, high mutational burden e.g., in bladder carcinoma (**Error! Reference source not found.**) may contribute to the responses seen with immune therapy.

In contrast, CTLA-4 is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. (Fife and Bluestone, 2008) Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies 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. Therefore, it is expected that treatment with an anti-CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, data from agents in the anti-PD-1/PD-L1class shows clinical activity in a wide range of tumor types.

6.2. Durvalumab (MEDI4736) Background

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2)

with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.
To date durvalumab has been given to more than 12000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 15 Adverse Events. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

6.3. Tremelimumab Background

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (**Error! Reference source not found.**). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer. Details on the safety profile of tremelimumab monotherapy are summarized in Section 15 Adverse Events. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

6.4. Durvalumab in combination with tremelimumab

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (**Error! Reference source not found.**); therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue. In addition, other clinical studies have

since started looking at the combination in both NSCLC and other oncology indications. To date more than 3000 patients have received the combination using a number of doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Section 15 Adverse Events. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

6.5. Durvalumab + tremelimumab combination therapy dose rationale

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

6.5.1. Pharmacokinetics/Pharmacodynamics data

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

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. (For further information on PK observations in Study 006, please see the current IB). The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen. The durvalumab + tremelimumab combination regimen will be administered for 4 doses Q4W followed by durvalumab monotherapy Q4W until disease progression for up to a maximum further 8 doses or unless other specific discontinuation criteria are met.

6.5.2. Rationale for Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W or 20 mg/kg Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposures (AUC_{ss},0-28, $Cmax_{,ss}$, and $Cmin_{,ss}$) using the population PK model. A fixed dose of 750 mg Q2Wwas selected to approximate 10 mg/kg Q2W and a fixed dose of 1500 mg Q4W was selected to approximate 20 mg/kg Q4W (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) regimens yield similar median steady state Q2W and a fixed dose of
1500 mg Q4W was selected to approximate 20 mg/kg Q4W.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses=0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (**Error! Reference source not found.**). Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 kg to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (**Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**; **Error! Reference source not found.**). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (**Error! Reference source not found.**). In addition, the investigation of 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (**Error! Reference source not found.**).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. A pilot study in hepatocellular carcinoma (Kelley et al ASCO Annual Meeting 2020; Abstract 4508) tested various fixed dose combinations of durvalumab and tremelimumab in HCC and demonstrated the best efficacy and safety balance at the dose of 300 mg tremelimumab (1 dose) combined with 1500 mg durvalumab (every 4 weeks, starting with the first dose given together with tremelimumab (see more below).

6.6. Hepatocellular Carcinoma Background

Hepatocellular carcinoma (HCC) is an aggressive malignancy, developing most often in the setting of cirrhosis of the liver (Sohal et al Current Oncol Rep 2011; Gordan et al JCO 2020). For advanced disease, immunotherapy has now become standard of care – a combination of atezolizumab and bevacizumab has shown the best overall survival outcome so far (Finn et al NEJM 2020).

For earlier stage disease, however, there is no systemic therapy standard. The best treatment for HCC in the setting of cirrhosis is a liver transplant allowing potential cure for both the cancer and cirrhosis. Patients with HCC must meet institutional liver transplant criteria. Nonetheless, 25-35% of patients fail to reach liver transplant because of disease progression while waiting for a transplant (Sinha et al, Hepatology 2019) and approximately 15% experience HCC recurrence after transplant (Mehta et al, Transplantation 2020). Taken together, this constitutes a large subset of this patient population who cannot achieve a cure.

Given the success of immunotherapy in the advanced setting, it is imperative to study this in the pre-transplant setting, to improve the outcomes cited above. The major risk, of course, is graft

rejection by the primed immune system. Therefore, before a larger study may be conducted to assess efficacy of this approach, we will undertake this pilot trial to ensure safety – with the primary outcome focusing on acute cellular rejection of the transplanted liver.

6.7. Correlative Studies Background

In HCC, expression of PD-1 is increased on CD8+ T cells and interaction with its ligand PD-L1 on tumor cells blocks T cell signaling, proliferation, and cytokine secretion (Kim et al Gastroenterology 2018). PD-1 inhibitors block this interaction between PD-1 on activated CD4+ and CD8+ T effector cells and its ligands on tumor cells and have shown promise in HCC clinical trials. In CheckMate 040, an open-label phase1/2 dose escalation and expansion trial, patients with advanced HCC receiving the PD-1 inhibitor nivolumab, saw considerable reductions in tumor size and up to 20% objective response (El Khoueiry Lancet 2017). KEYNOTE-224 with the PD-1 inhibitor pembrolizumab confirmed clinical efficacy in patients who had progressed after treatment with sorafenib or were intolerant to the drug (Zhu et al Lancet Oncology 2018). However, in both studies, PD-L1 expression on tumor tissue was unexpectedly low and did not correlate with response rates, thus suggesting other mechanisms of checkpoint inhibitions may be at play. It has been proposed immune check point inhibition through PD-L1 signaling may be attributed to other immune cells in the HCC microenvironment, regulatory T cells (Tregs) as one candidate (Kalathil et al Cancer Research 2013; Iwata et al. Sci Rep 2016). In fact, in recent work Langerhans et al. investigated the ability of Tregs to trigger checkpoint inhibition in HCC. Following isolation of Tregs and CD8+ T cells from peripheral blood mononuclear cells (PBMCs) of HCC patients, Tregs inhibited IFN-gamma secretion and cytotoxicity of CD8+ T cells when functionally challenged against checkpoint inhibitor-negative tumor cell line. However, with the addition of PD-1/PD-L1 antibodies, IFN-gamma secretion was partially rescued indicating improved anti-tumoral activity.

It is well reported that T cell function is dysregulated in HCC. Not only do CD4+ and CD8+ T cells decrease in number, T cell functionality is dramatically affected which is often accompanied by an increased expression of inhibitory receptors (Sachdeva et al. World J. Hepatol 2015). Regulatory T cells (Tregs) exert negative effects on both helper and cytotoxic T cell subsets and have been shown to have increased numbers in the peripheral blood of HCC patients and correlate with disease progression (Ormandy et al. 2005, Fu et al. Gastroenterology 2007). Work by Fu et al. has focused on elucidating the inhibitory mechanisms of Tregs on effector T cells in HCC. Compared to normal controls, CD8+ T cells from HCC patients show a significantly decreased expression in CD107a, indicating decreased cytolytic activity. Interestingly, when activated PBMCs from HCC patients were depleted of Tregs, expression of CD107a is significantly higher than HCC PBMCs that are not depleted of Tregs. Furthermore, when functionally challenged to degranulate, levels of granzyme A, granzyme B, and perforin were significantly increased in HCC PBMCs depleted of Tregs compared to the un-depleted population (Fu et al Gastroenterology 2007).

T cell populations are frequently used as potential surrogates of immune responses in patients treated with immune checkpoint inhibitors. In the tremelimumab and durvalumab trial in advanced

HCC, circulating CD8+ T cells were noted to increase remarkably after treatment. Furthermore, an increase was associated with a better therapeutic response (Kelley R et al; ASCO 2020). Therefore, we intend to phenotypically profile the peripheral blood using flow cytometry with a focus on Ki67+ cells and CD3+ T cell populations, inclusive but not limited to CD8+, CD4+, and regulatory T cells. The absolute numbers and the proportional prevalence of T cells will be evaluated at three time points: baseline; post-immunotherapy; post-transplant. Results will be correlated with clinical outcomes to help us understand if safety and/or efficacy are correlated with the various T cell populations, which may serve as a direct pharmacodynamic surrogate of immunotherapy.

Non-invasive monitoring of circulating tumor cells and molecular alterations has been an established method of detecting minimal residual disease in hematologic malignancies. However, monitoring based on circulating-tumor DNA (ctDNA) for solid tumors has been limited by extremely low concentrations of ctDNA molecules, heterogeneity of tumor mutations among patients, and errors from high biological background noise or background noise from the assay itself. We propose to collect correlative blood for use with the Signatera™ assay with Natera Inc. A sample of tissue will be collected at surgery to help validate the assay. It is the first patient-specific, custom built ctDNA assay for detecting molecular residual disease, and monitoring treatment response or recurrence. Signatera is unique in its ability to detect ctDNA at a variant allele frequency (VAF) of <0.1% of cell free DNA (cfDNA) from plasma. We propose that this assay will allow us to more fully assess the correlation between tumor genomic profiles and clinical outcomes.

7. PATIENT SELECTION: ELIGIBILITY

7.1. Inclusion Criteria

1. Hepatocellular carcinoma, diagnosed either by biopsy or by combination of cirrhosis and imaging criteria (contrast-enhanced CT or MRI).

2. Tumor confined to liver with no vascular invasion and no evidence of extrahepatic disease.

3. Patient evaluated by institutional Liver Transplant team and deemed eligible for transplant.

4. At least 1 lesion, not previously irradiated, that qualifies as a RECIST 1.1 target lesion (TL) at baseline. Tumor assessment by computed tomography (CT) scan or magnetic resonance imaging (MRI) must be performed within 28 days prior to randomization.

5. No prior therapy for HCC at any time.

6. Age ≥18 years at the time of study entry.

7. ECOG score of 0 or 1

8. Child-Pugh Score of 5, 6, or 7

9. Body weight >30 kg

10. Patients must have adequate organ and marrow function as defined below:

Hemoglobin	≥9.0 g/dL
Absolute neutrophil count	≥1.0 × 109 /L
Platelet count	≥50 × 109/L
Serum bilirubin*	≤3 mg/dL
AST(SGOT)/ALT(SGPT)	≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN
Creatinine	< 1.5 ULN
Measured creatinine clearance	>40 mL/min
OR	
Calculated creatinine clearance (CL)	CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance: Males: Creatinine CL = (mL/min) $\frac{\text{Weight (kg) x (140 – Age)}}{\text{72 x serum creatinine (mg/dL)}}$ Females: Creatinine CL = (mL/min) $\frac{\text{Weight (kg) x (140 – Age)}}{\text{72 x serum creatinine (mg/dL)}}$ x 0.85

11. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

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

7.2. Exclusion Criteria

1. Extrahepatic disease.

2. Variceal bleeding during 3 months prior to registration.

3. Any autoimmune disease deemed a risk in the setting of immunotherapy per treating physician's judgment, such as PSC, PBC, autoimmune hepatitis, etc.

4. Any other illness or patient condition deemed a medical or logistical barrier for protocol therapy per treating physician's judgment.

5. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

6. Participation in another clinical study with an investigational product during the last 12 months Patients who have received other investigational agents previously who are no longer receiving these investigational agents may be eligible at the discretion of the PI.

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

8. History of allogenic organ transplantation.

9. History of another primary malignancy except for:
    a. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence
    b. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    c. Adequately treated carcinoma in situ without evidence of disease

10. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia
    b. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    c. Any chronic skin condition that does not require systemic therapy
    d. Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    e. Patients with celiac disease controlled by diet alone

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

12. History of leptomeningeal carcinomatosis

13. History of active primary immunodeficiency

14. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, Patients with a past or resolved HBV infection (defined as the presence of hepatitis B

core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

15. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
    c. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

16. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine while receiving IP and up to 30 days after the last dose of IP.

17. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 180 days after the last dose of durvalumab + tremelimumab combination therapy.

18. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.

19. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment.

20. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

7.3. Inclusion of Women and Minorities

Women and minorities will be included.

8. REGISTRATION PROCEDURES

8.1. Assignment of Screening and Subject Numbers

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to eligibility being confirmed. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. The screening number will become the subject's study number once they are confirmed to be eligible (registered).

Patients who are a screen-failures may not typically be re-screened at a later time to determine if they could meet eligibility criteria unless the UC PI determines that re-screening may be appropriate; such as, when the screen-failure was due to a procedure being out of window rather than an indication that a patient's health may preclude meeting eligibility.

Any patient for whom the UC PI does give express permission for re-screening will be provided with a new screening number for each instance for which they are being re-screened. Results from assessments performed during the prior screening period are acceptable in lieu of a repeat screening test if performed within the protocol specified time frames.

8.2. Patient Screening

All subjects must provide informed consent prior to the initiation of study procedures, including screening. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 7 days prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria as long as they have not yet started treatment; however, the cost of re-screening tests will not be covered by the study. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

8.3. Patient Registration

To determine if a patient meets eligibility criteria, the following documents should be compiled by research team and provided to the University of Cincinnati PI and UC Project Manager/Monitor as soon after the subject has consented as possible:

- Study informed consent form signed and dated by the patient.
- Source documents verifying every inclusion and exclusion criteria for the patient.

Upon receipt, the UC PI or qualified designee will confirm subject eligibility and the UC Project Manager/Monitor will perform a double check. Eligibility must be confirmed prior to the initiation of any study procedures. Once eligibility is confirmed, a research team member may then proceed to register the subject to enrolled status within the study EDC.

8.4. General Guidelines

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause significant treatment delays should be discussed with the Principal Investigator.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1. Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Lab
1	Peripheral blood immune phenotypes	Flow cytometry	*Exploratory* To determine changes in peripheral blood immune cell populations over the course of treatment, with a focus on CD3+ T cell populations	O	Baseline, post-immunotherapy, and post-transplant	Peripheral blood mononuclear cells isolated from whole blood	20mLs collected in EDTA tubes at each time-point	UCCC CTO Lab
2	Gut microbial composition	Metagenomic sequencing	*Exploratory* To evaluate differences in the gastrointestinal microbiome in patients that may act as biomarkers for response	O	Baseline	Stool sample collected via Omnigene stool collection kits	A small, dime sized amount of fecal matter as indicated by instructions in the Omnigene collection kit	Dr. Jordan Kharofa, UC Biorepository, and Cincinnati Children's Hospital Medical Precision Metagenomics Laboratory

Specimen Collection Schedule

Specimen Type	Baseline (Pre-treatment but after Eligibility Confirmed)	Post- immunotherapy	Post- transplant
Peripheral blood, 20mLs in two 10mL EDTA tubes	X	X	X (4 weeks post-transplant +/- 3 days)
Stool sample	X		

9.2. Exploratory/Ancillary Correlative Studies

9.2.1. Peripheral blood immune phenotypes

Collection of Specimen(s): Two 10mL EDTA blood collection tubes (purple top) for a total of 20mLs of whole blood will be collected at:

- Baseline (after eligibility confirmation but prior to I/O)
- Post-Immunotherapy
- Post-transplant

Handling of Specimens(s): Standard operating procedures; Do not shake of freeze tube; label each blood collection tube with the following information:

- Clinical trial study number: UCCC-GI-21-01
- Subject's ID: GI-21-01-01
- Date and time of collection: (example 3/18/2021, 15:00)
- Study time-point (Baseline)

Shipping of Specimen(s): Samples from subsites will be shipped ambient day of collection according to standard operating procedures outlined in the laboratory manual. Specimens are to be shipped to the UCCC CTO Translational Laboratory at:

- 3125 Eden Avenue, Vontz Room 1444, Cincinnati, OH 45267
- Sites must email study monitor and ctolabuccc@ucmail.uc.edu to provide notice of shipping and avoid shipping for arrival on Fridays and holidays as specified in lab manual.

Site(s) Performing Correlative Study:

- University of Cincinnati, UCCC CTO Laboratory (ctolabuccc@ucmail.uc.edu).

9.2.2. Gut microbial composition

Collection of Specimen(s): Patients will be provided with an Omnigene Stool Collection kit to take home for stool collection at the Baseline timepoint (after eligibility is confirmed, prior to I/O). Kit includes the following:

- Pre-paid return box
- Printed sample collection instructions
- Packaged sample collection kit
- Pre-printed sample label
- Biohazard bag
- 1 pair of latex-free exam gloves

Handling of Specimens(s): Specimens will be collected by the patient at home and handled according to SOPs provided with the collection kit.

Shipping of Specimen(s): Kits will be returned to the office of Dr. Jordan Kharofa and department study coordinator will coordinate delivery of kits to the UC Biorepository for sample processing.

Site(s) Performing Correlative Study: Dr. Jordan Kharofa, University of Cincinnati, UC Biorepository, Cincinnati Children's Hospital Medical Precision Metagenomics Laboratory Please consult the study laboratory manual for more details.

10. TREATMENT PLAN

The Study Calendar - Section 3 summarizes the trial procedures to be performed at each visit.

10.1. Agent Administration

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Regimen Description					
Agent	**Premedications ; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Durvalumab	None	1500 mg	IV	Q4W	4 weeks
Tremelimumab	None	300 mg	IV	1 dose on day 1 of only the first cycle	
The above for up to 4 months (5 doses durvalumab)					

10.2. Durvalumab + tremelimumab combination therapy

Tremelimumab 300 mg via IV infusion x 1 dose on day 1 of the first cycle, plus durvalumab 1500 mg via IV infusion Q4W starting on day 1, for up to a maximum of 4 months (5 doses of durvalumab). N.B If a patient's weight falls to 30kg or below (≤30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W after consultation between the investigator and study physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg Q4W).

Patients will be treated with the immunotherapy combination for up to 4 months. After a minimum 28 day gap following the final durvalamab dose, they will undergo locoregional therapy per institutional standards. Eventually, after a minimum 72-day gap from the end of immunotherapy, they will undergo liver transplant.

Tremelimumab will be administered first over 1 hour; the durvalumab infusion will then be started approximately 1 hour after the end of the tremelimumab infusion to allow for a 1 hour observation

period. Standard infusion time for each is 1 hour, however if there are interruptions, the total allowed time must not exceed 4 hours from the start of infusion at room temperature per infusion.

10.3. General Concomitant Medication and Supportive Care Guidelines

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 EDC REDCap and on concomitant medication logs. Restricted, prohibited, and permitted concomitant medications are described in the following tables. There are no prohibited therapies during the Post-Treatment Follow-up Phase.

10.3.1. Permitted concomitant medications

Table 1. 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 in the table below.	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
Inactivated viruses, such as those in the influenza vaccine	Permitted

10.3.2. Excluded concomitant medications

Table 2 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	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is

Prohibited medication/class of drug:	Usage:
study	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 or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs, • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
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.
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the UC PI.

10.4. Interim Safety Analysis

During immunotherapy, grade 3-5 AEs will be monitored and at 10 patients enrolled an interim safety analysis will be performed. We will halt enrollment and assess safety in detail to determine if the study should continue, in discussion with AstraZeneca if:

- Of the first 10 patients, if ≥3 patients have to discontinue immunotherapy due to treatment related AEs and/or
- Of the first 10, if ≥3 patients experience SAEs related to locoregional therapy after immunotherapy and/or
- Of the first 10, if ≥3 patients fail to reach liver transplant due to immunotherapy toxicity and/or
- Of the first 10 patients, if ≥3 deaths are encountered, from enrollment to up to 30 days after transplant

10.5. Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for up to 4 months or until one of the following criteria applies:

- Clinical disease progression
- RECIST 1.1 and/or mRECIST defined radiological progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw consent for the study treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
- Termination of the study by University of Cincinnati PI
- The drug manufacturer can no longer provide the study agents

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the study EDC (REDCAP) and within study source documentation.

10.6. Duration of Follow-Up

Patients will be followed for up to five years after completion of I/O (whether transplantation occurs or not), or until the subject withdraws consent to all follow-up procedures, is lost to follow-up, or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. See AE Section 15 for timing of collection and follow-up of AEs and SAEs.

10.6.1. Post-Treatment Safety Visit

The mandatory Post-Treatment Safety Follow-Up Visit should be conducted approximately 28 days (+/- 3 days) after the last dose of durvalumab or before the initiation of a new anti-cancer treatment, whichever comes first. The 30-day post-transplant visit is considered to be a standard of care time-point and is not the point at which the subject enters follow-up status for research purposes, see Survival Follow-up section 10.6.2 below.

10.6.2. Survival Follow-up

Once subjects experience confirmed progression, start a new anti-cancer therapy, or complete the I/O drug treatment regimen then subjects will move into the survival follow-up phase.

Subjects should be contacted by telephone or seen in clinic every 3 months for the first year then every 6 months for 5 years to assess for survival status until death, withdrawal of consent, the subject becomes lost to follow-up or at the end of the study, whichever occurs first. Subjects will be followed up to 5 years.

10.7. Discontinuation from Active Treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AEs and responses documented in REDCap and within source documentation. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see the study calendar). Patients who permanently discontinue drug for reasons other than objective RECIST and/or mRECIST disease progression should continue to have RECIST scans performed q12 weeks ±1 week for the first 48 weeks, and then q12-24 weeks ±1 week thereafter until RECIST 1.1 or mRECIST defined radiological PD plus an additional follow-up scan or death (whichever comes first) as defined by the study calendar.

If a patient is discontinued for RECIST 1.1 and/or mRECIST defined progression, then the patient should have 1 additional follow-up scan performed preferably at the next (and no later than the next) scheduled imaging visit, and no less than 4 weeks after the prior assessment of PD.

If a patient is discontinued because they are unable to receive a liver transplant once they have been enrolled onto this study, they will be considered to be "withdrawn" and not a screen-failure. As noted above, discontinuation from study treatment for any reason, including the inability to receive a liver transplant, will not impact a patient's continued participation in this study. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol as described above within this section.

All patients will be followed for survival until the end of the study. Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the study calendar as an alternative.

10.8. Lost to Follow-up

Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up."

In the absence of a clear withdrawal of consent, study teams should make every attempt to contact subjects during the follow-up phase to determine the patient's status.

Patients will be considered lost to follow-up only if:

1. 3 phone call attempts on separate days with varying times without establishing contact.
2. If unable to make contact with phone call attempts, a certified letter should be sent to the subject's last known address.
3. If the certified letter comes back (unable to be delivered), then patient may be considered lost to follow up.
4. If the initial certified letter is not returned as undeliverable in 4 weeks from the date of mailing and patient does not make contact, then a second certified letter should be sent and 4 weeks allowed for any response from the date of mailing.
5. If there is no response to 3 phone attempts or 2 delivered certified mail letters, then the subject may be considered to be lost to follow up.

Investigators should document all attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol. In order to support key end points of PFS and OS analyses, the survival status of all patients in the full analysis and the safety analysis sets should be re-checked, this includes those patients who withdrew consent or are classified as "lost to follow up."

- Lost to Follow up – site personnel should check hospital records, the patients' current physician, and a publicly available death registry (if available) to obtain a current survival status.

In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under applicable local laws to obtain a current survival status.

10.9. Withdrawal of Consent

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AEs. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow up (e.g., survival contact telephone calls)
- Withdrawal to the use of any samples

The withdrawal of consent must be documented in REDCap and in source documentation.

10.10. Restrictions During Study Participation

Restrictions during the study are different from exclusion criteria and apply once the patient has been randomized or started on investigational product.

10.10.1. Blood donation

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

10.11. Pregnancy

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

Female patient of child-bearing potential:

- Female patients of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study interventions) and intend to be sexually active with a non--sterilized male partner must use at least 1 **highly** effective method of contraception (Table 3) They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the total duration of the drug treatment and the drug washout period (180 days after the last dose of durvalumab + tremelimumab combination therapy). Non-sterilized male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential:

- Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide from the time of screening throughout the total duration of the drug treatment and the drug gap period (180 days after the last dose of durvalumab + tremelimumab combination therapy). However, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm

donation throughout this period. Vasectomised males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical study.

- Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing foetus from drug in ejaculate.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 3).

Females of childbearing potential definition:

Are defined as those who are not surgically sterile (ie, bilateral salpingectomy, 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.

- 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.

Highly effective methods of contraception definitions:

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

Barrier/Intrauterine methods	Hormonal Methods	Additional Allowed Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol -releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill	• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Tubal occlusion • Intrauterine device (provided coils are copperbanded)

[a] This is also considered a hormonal method

11. OTHER RESEARCH ACTIVITY SPECIFICATIONS

The Study Calendar - Section 3 summarizes the trial procedures to be performed at each visit.

11.1. Medical History

A medical history for each subject will be obtained by the Investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

Medical history must be graded per CTCAE v.5 to facilitate the identification of grade changes from baseline. Subjects will be asked about their medical conditions at each study visit (e.g., any new admissions or changes in existing conditions) and new medical history, if any, will be recorded throughout the study.

11.2. Prior and Concomitant Medications

Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirements, and record prior medication taken by the subject within 28 days before starting the trial (time of consent). Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

Concomitant Medications
The Investigator or qualified designee will record medication, if any, taken by the subject during the trial.

11.3. Adverse Events

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Calendar in Section 3 or more frequently if clinically indicated. Please refer to Section 15 for detailed information regarding the assessment and recording and reporting of AEs.

11.4. Full Physical Exam

The Investigator or qualified designee will perform a full physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Full physical exam requires assessment of major organ sites (Constitutional, Head and Neck, Cardiovascular, Pulmonary, Abdominal, Musculoskeletal, Lymph, Neurological, and Skin).

11.5. Directed Physical Exam

Except for at screening, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

11.6. Vital Signs

The Investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in the Study Calendar. Vital signs should include: temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

11.7. Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status (see Appendix 2) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Study Calendar.

11.8. Tumor Imaging and Assessment of Disease

Only the Investigator or qualified designee (MD only) may determine the assessment of disease recurrence.

Patients will undergo imaging (MRI of the liver, with contrast) at baseline and then at their 28 day post I/O safety evaluation after completion of durvalumab. If a patient has a PR or CR, confirmation scans are required no more than 4 weeks after the scan in which response was first observed.

Subjects will continue to have MRIs for standard of care every 6 months post-transplant from which their survival and disease status may be abstracted. In the event a subject does not receive a transplant they will still receive a standard of care MRI every 6 months from which survival and disease status may be abstracted.

11.9. Laboratory Safety Evaluations (Hematology, Chemistry and Other)

Laboratory tests for hematology, chemistry, and others are specified in Table 5

Table 5. Laboratory Tests

Hematology	Chemistry	Other
Hemoglobin	Albumin	Serum β-human chorionic gonadotropin†
Platelet count	Alkaline phosphatase	(β-hCG) †
WBC (total and differential)	Alanine aminotransferase (ALT)	Total triiodothyronine (T3)[a]
Red Blood Cell Count	Aspartate aminotransferase (AST)	Free thyroxine (T4)[a]
Absolute Neutrophil Count	CO_2 or bicarbonate	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Calcium	Prothrombin time PT/INR
	Chloride	Partial Thromboplastin Time (PTT)
	Glucose	Amylase
	Phosphorus	Lipase
	Potassium	Alpha Fetoprotein (AFP)
	Sodium	
	Creatinine	
	Magnesium	
	Total Bilirubin[b]	
	Direct Bilirubin	
	Total protein	

	Blood Urea Nitrogen	

† Done on all women of child-bearing potential

a. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
b. If total bilirubin is ≥2 x ULN (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.

12. DOSING DELAYS/MODIFICATIONS & TOXICITY MANAGEMENT

12.1. Durvalumab and tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in the durvalumab/tremelimumab Toxicity Management Guidelines (TMGs) in Appendix 1.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 10.7 Discontinuation of Active Treatment of this protocol and the Dosing Modification and Toxicity Management Guidelines in Appendix 1).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Appendix 1. These guidelines have been prepared to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting investigator.

Dose reductions are not permitted. In case of doubt, the treating physician should consult with the UC PI.

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the study calendar.

1. 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.

2. 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.

3. If the infusion related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. Standard infusion time is one hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature (otherwise requires new infusion preparation). For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in **Error! Reference source not found.**.

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

12.2. Dose Limiting Toxicities

The DLT assessment period is from the time of first dose of IP and ends upon administration of the first dose of IP on Cycle 2, Day 1 (28-day cycle).

Any treatment-related toxicities that first occurred during the DLT period must be followed for resolution to determine if the event qualifies as a DLT.

A DLT is defined as the occurrence of an adverse event (AE) that is **at least possibly related to the investigational product (IP) or investigational regimen (IR)**, with two exceptions: any grade of vitiligo or alopecia will not qualify as a DLT. AEs that are **at least possibly related to durvalumab- and/or tremelimumab-containing regimens** shall be assessed as DLTs if they meet known toxicity criteria.

13. PHARMACEUTICAL INFORMATION

13.1. Durvalumab and tremelimumab Pharmaceutical Information

13.1.1. Formulation/packaging/storage

Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Investigational product must be kept in original container until use to prevent prolonged light exposure.

Durvalumab
Durvalumab will be supplied by AstraZeneca as a 500 mg vial concentrate for solution for infusion. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume is 10 mL.
Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

Tremelimumab
Tremelimumab will be supplied by AstraZeneca as a 25 mg vial concentrate for solution for infusion. 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 label-claim fill volume is 1.25 mL. Tremelimumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from or practically free from visible particles.

13.1.2. Study drug preparation of durvalumab and tremelimumab

Based on average body WT of 75 kg, 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 300 mg Q4W tremelimumab (equivalent to 4 mg/kg Q4W) is included in the current study.

Preparation of durvalumab doses for administration with an IV bag
The dose of durvalumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Please refer to local prescribing information for in-use storage conditions and times.

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 30 mL (i.e. 1500 mg) of durvalumab to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL.

Durvalumab, whenever possible, should not be prepared at the same time as tremelimumab. This is because the tremelimumab needs to infuse over a 1-hour timeframe and then have a 1-hour observation time period prior to administration of durvalumab, and durvalumab has a 8-hour expiration from the time it is prepared. Therefore, whenever possible, durvalumab should be prepared closer to the end of the post-tremelimumab observation period. Standard infusion time for durvalumab is 1 hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line. The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include

the final flush time. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

Preparation of tremelimumab doses for administration with an IV bag

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

- A total of 24 hours at 2°C to 8°C (36°F to 46°F) of which 4 hours of those 24 can be at room temperature.

A dose of 300 mg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL and delivered through an IV administration set with a 0.2- or 0.22-µm filter. Add 15 mL (i.e. 300 mg) of tremelimumab to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time is 1 hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line. The IV line will be flushed according to local practices to ensure the full dose is administered. Infusion time does not include the final flush time. If either preparation time or infusion time exceeds the time limits a new dose must be prepared from new vials. Tremelimumab does not contain preservatives, and any unused portion must be discarded.

13.1.3. Agent Ordering Temperature Excursions and Agent Accountability

Agent Ordering

UC Health Investigational Drug Services licensure does not allow for the shipping of investigational IP across state lines. All agent shipping will be performed by AstraZeneca directly to each participating site.

When IP is received by the site if IP has not yet been prepared it may be transported to a satellite site following the normal SOPs and policies of the local institution. For example, transport of IP from UCMC to UC Health West Chester would be covered under these institutional policies.

Temperature Excursions

Temperature excursions that occur at site are the sponsors responsibility. The Sponsor is responsible for assessment and determination of suitability for use of any Study Drug where there is evidence of temperature deviations during storage or Study specific labelling.

Agent Accountability

Investigational Drug Services (IDS) Pharmacy at UC will maintain IP accountability which should consist of a record of the receipt, dispensing and final disposition of all agents received using institutional Drug Accountability Record (DARF) or other methods of recording, store

and maintain separate Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol, as well as temperature control records.

Each participating institution must designate an entity to perform the same inventory activities as above: IP receipt, dispensation, and destruction of all IP received as well as temperature control records

13.1.4. Investigator Brochure Availability

The current versions of the IBs will be accessible to site investigators and research staff.

14. STATISTICAL CONSIDERATIONS

14.1. Study Design/Endpoints

The primary endpoint of safety is a binary endpoint, and will be assessed in patients undergoing liver transplant. Safety will be assessed using "treatment failure", defined as rejection, graft loss, death, or loss to follow up within 30 days of transplant. Historically, 10-20% of patients are expected to experience acute cellular rejection within 30 days of transplant. We propose that an observed proportion of 20% failure will be a clear indicator of safety in this pilot study, whereas an observed proportion of 50% failure will be a clear indicator of failure. Using these guardrails, with at least 20 patients going to transplant, we will have 80.6% power to demonstrate a failure proportion of 20% (4 patients experiencing failure) versus a null of 50% (10 patients experiencing failure), with a one-sided alpha of 0.05. With 25 patients going to transplant, the power will increase to 86% (other parameters being the same).

14.2. Sample Size/Accrual Rate

A total of 30 patients are to be enrolled, to allow at least 20 transplants for adequate primary endpoint analysis.

During immunotherapy, grade 3-5 AEs will be monitored. In the pivotal study of durvalumab and tremelimumab (Kelley et al, Abstract 4508 at ASCO 2020), 16% had Tx related (TR) SAEs, and 11% had discontinuation of treatment due to TR AEs. We will use these guardrails for interim safety analyses at 10 patients. We will pause enrollment and assess safety in detail to determine if the study should continue, in discussion with AstraZeneca if:

- Of the first 10 patients, if ≥3 patients have to discontinue immunotherapy due to treatment related AEs and/or;
- Of the first 10, if ≥3 patients experience SAEs related to locoregional therapy after immunotherapy and/or;
- Of the first 10, if ≥3 patients fail to reach liver transplant due to immunotherapy toxicity and/or;
- Of the first 10 patients, if ≥3 deaths are encountered, from enrollment to up to 30 days after transplant.

14.3. Analysis of Secondary Endpoints

For the secondary endpoint of death-censored graft loss, 2.5% of patients undergoing a liver transplant in these settings experience graft loss. If ≥7.5% of patients in this study experience graft loss within 30 days of transplant, it will be considered a serious safety signal.
For the efficacy endpoints, radiologic and pathologic response rates will be assessed as proportions, and overall and recurrence-free survival will be assessed using the Kaplan Meier method.

14.3.1. Evaluation of Response

Radiologic response will be assessed after immunotherapy completion – prior to locoregional therapy initiation using RECIST 1.1 and/or mRECIST. Pathologic response will be assessed in the explanted liver. Recurrence-free survival and overall survival will be assessed for five years.

15. ADVERSE EVENTS: KNOWN RISKS AND REPORTING REQUIREMENTS

15.1. Overall Risks

Monoclonal antibodies directed against immune checkpoint proteins, such as programmed cell death ligand 1 (PD-L1) as well as those directed against programmed cell death-1 (PD-1) or cytotoxic T-lymphocyte antigen-4 (CTLA-4), aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects, can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

15.2. Known Risks of Durvalumab

Risks with durvalumab include, but are not limited to, cough/productive cough, diarrhea/colitis, pneumonitis, interstitial lung disease, dysphonia, alanine aminotransferase increased/aspartate aminotransferase increased, abdominal pain, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus (which may present as diabetic ketoacidosis), Diabetes Insipidus, hypophysitis/hypopituitarism and adrenal insufficiency), thyroiditis, hepatitis,/increases in transaminases, nephritis/increases in creatinine, ,night sweats, dysuria, pyrexia, oedema peripheral, upper respiratory tract infections, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, immune-mediated arthritis, myasthenia gravis, Guillain-Barré syndrome, infusion-related reaction, immune thrombocytopenia, noninfective encephalitis, and uveitis. Potential risk for durvalumab monotherapy includes subcutaneous injection site reaction, hypersensitivity reactions including

anaphylaxis and allergic reaction, cytokine release syndrome, and immunogenicity. Other rare or less frequent inflammatory events including neuropathy/neuromuscular toxicities vasculitis, non-infectious meningitis, psoriasis. For information on all identified and potential risks with durvalumab please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies AEs (all grades) reported very commonly (≥15% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.6 % of patients experienced an SAE that was considered treatment-related by the study investigator.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (please see Appendix 1) A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

15.3. Known Risks of Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase and clinical manifestations of pancreatitis, other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia. For information on all identified and potential risks with tremelimumab please always refer to the current version of the tremelimumab IB.

Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly (≥ 10% of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnoea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.
Further information on these risks can be found in the current version of the tremelimumab IB. A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.

15.4. Known Risks of Durvalumab + Tremelimumab

The safety of durvalumab + tremelimumab combination therapy was initially evaluated in the

ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and is being studied in a number of other ongoing clinical trials, in a number of different indications, and has to date shown a manageable safety and tolerability profile.

The types of risks with the combination of durvalumab + tremelimumab (based on an equivalent durvalumab dose of 20m/kg and a tremelimumab dose of 1mg/kg) are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006, other studies evaluating the combination, and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these immune-mediated toxicities. For information on all identified and potential risks with the durvalumab+tremelimumab combination please always refer to the current version of the durvalumab IB.

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20mg/kg and tremelimumab 1mg/kg AEs (all grades) reported very commonly (≥ 15% of patients) are diarrhoea, fatigue, decreased appetite, nausea, pruritus, constipation, and anaemia; AEs reported in ≥5% of patients that were considered by the investigator as treatment-related were diarrhoea, pruritus, fatigue, rash, hypothyroidism, decreased appetite, nausea, asthenia, and hyperthyroidism. Known risks of combination therapy includes amylase increased, lipase increased, pancreatitis and noninfective encephalitis. Potential risks of the combination treatment include pulmonary embolism and subcutaneous injection site reaction. Approximately 17% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 18% of patients experienced an SAE that was considered to be related to durvalumab and tremelimumab by the study investigator. A detailed summary of durvalumab + tremelimumab combination AE data can be found in the current version of the durvalumab IB.

15.5. Adverse Events Definition

An adverse event is defined as the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered

The severity (grade) of an adverse event may be determined by a study coordinator using the CTCAE version 5.

The causal relationship (attribution) to study drug/device/intervention is determined by a study physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

1. Unrelated – The AE is clearly NOT related to the study intervention
2. Unlikely – The AE is doubtfully related to the study intervention
3. Possible – The AE may be related to the study intervention

4. Probable – The AE is likely related to the study intervention
5. Definite – The AE is clearly related to the study intervention

The expectedness of the occurrence of an adverse event is determined by a study physician and should be used to help determine whether prompt reporting requirements to regulatory authorities (IRB, FDA etc…) are required are required (such as when the AE is an SAE).

1. Expected – An adverse event is expected if it is described as an anticipated risk in the Investigator Brochure (IB) and described within this protocol as a known adverse event.
2. Unexpected – If an adverse event is not described within the IB, or within this protocol or consent form as an expected risk to subjects then the AE will be considered to be unexpected.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

15.6. Serious Adverse Events Definition

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, time period following the final durvalamab dose , follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

1. Results in death
2. Is immediately life-threatening
3. Requires in-patient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability or incapacity
5. Is a congenital abnormality or birth defect in offspring of the patient
6. Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above:
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

Adverse Events (AEs) for **malignant tumors** reported during a study should generally be assessed as **Serious** AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a **Non-Serious** AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of

malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is *not* the tumor for which entry into the study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

The following are NOT considered to be SAEs for the purposes of this protocol:

1. Elective surgery, planned prior to signing consent.
2. Admissions per protocol for planned medical/surgical procedures
3. Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)

15.7. Durvalumab + tremelimumab adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring An AESI may be serious or non-serious. AESI's that are serious should be reported per SAE criteria but otherwise do not require specific reporting to AstraZeneca as they occur.

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

If the Investigator has any questions in regards to an event being an imAE, the Investigator should promptly contact the UC PI.

AESIs observed with durvalumab ± tremelimumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases

- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, thyroiditis, 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
- Intestinal Perforation

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Neuromuscular toxicities (such as Guillain-Barre syndrome and myasthenia gravis)
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.
- Psoriasis

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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

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

15.8. Recording & Collection of Adverse Events & Serious Adverse Events

All Serious Adverse Events (SAEs) and Adverse Events will be collected from the initiation of study drug and for 90 days after the last dose of durvalumab+tremelimumab or before initiation of a new anti-cancer therapy (whichever occurs first) must be collected. If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable. During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events

continue after the patient has discontinued study drug or the study has completed. Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the study EDC REDCap.

Concomitant illnesses/conditions that existed before entry into the study are to be documented as medical history and graded at baseline, but will not be considered AEs unless the illness or condition worsens in severity per CTCAE or becomes more frequent in occurrence after initiating protocol therapy.

AEs, including laboratory abnormalities that are assessed as clinically significant or require intervention, should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be recorded as a separate AE.

All AEs must be collected and recorded following current UCCC CTO workflows or institution specific requirements.

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

The following variables will be collected for each AE (and for SAEs as applicable):

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of the SAE

The grading scales found in the NCI CTCAE, version 5 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation

in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE, version 5 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

15.9. Study Recording Period and Follow-up for AEs & SAES

If a patient 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 patient 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.

15.10. Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 1, the Toxicity Management Guidelines, for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

15.11. Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine AE reporting mechanisms outlined within this protocol.

15.12. Second Malignancy - New Cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study; these are unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

15.13. Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/PI at the next monitoring visit and should be documented in REDCap. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/PI as an SAE within 24

hours. It should also be documented in REDCap.

- The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in REDCap.
- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual timeframes.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in REDCap as part of survival data. If the death occurred as a result of an event that started after the defined safety follow up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

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

15.14. Reporting of SAEs & AEs to regulatory authorities

All SAEs have to be reported, whether or not considered causally related to the investigational product.

SAEs should be reported using a MedWatch form within 24 hours of becoming aware of the initial SAE or any follow-up information regarding the SAE. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting

The study team will report SAEs to the UCCC DSMB, IRB of record and FDA according to their respective prompt reporting timeframes. Sub-sites must report SAEs determined to be attributable to the study interventions within 24 hours to the University of Cincinnati PI and study monitor.

15.15. Reporting of SAEs to AstraZeneca

Investigators or other site personnel at participating sub-sites must inform the University of Cincinnati PI & study monitor of each SAE regardless of attribution. The University of Cincinnati and each respective sub-site are responsible for directly informing AstraZeneca of SAEs occurring at all sites. All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product.

- SAEs related to the Investigational Product (IP) must be provided to AstraZeneca in an ongoing basis as individual case reports.

- SAEs unrelated to the IP must be provided to the Company as individual case reports as a quarterly line listing.

At the end of the study a final unblinded summary line listing of all SAEs provided to the IRB of record, FDA and/or AstraZeneca during the study, must be provided to AstraZeneca to enable reconciliation of safety information held by AstraZeneca for its product(s).

Send SAE reports (individual case reports and line listings) and accompanying cover page to Company (TCS) via Email: AEmailboxclinicaltrialTCS@astrazeneca.com

SAEs that do not require expedited reporting to the FDA or IRB of record still need to be reported to AstraZeneca provided as a quarterly listing.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to AstraZeneca at the same time the FDA and IRB of record are notified of these events.

15.16. Reporting of Deaths to AstraZeneca

All deaths must be recorded and reported as outlined in Section 15.13 In addition, all SAEs resulting in death or death of unknown cause must be reported to AstraZeneca via AEMailboxClinicalTrialTCS@astrazeneca.com within 7 calendar days of awareness or sooner when required.

15.17. Other Events Requiring Reporting

15.17.1. Overdose

Use of durvalumab or tremelimumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab or tremelimumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE forms in REDCap.
- An overdose without associated symptoms will only be reported in REDCap as an AE "other" unanticipated problem.

Any overdose of a study patient with durvalumab or tremelimumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the University of Cincinnati PI and Monitor.

The UC PI and monitor must report these to AstraZeneca Patient Safety or designee using the designated Safety e-mailbox AEmailboxclinicaltrialTCS@astrazeneca.com within 7 calendar days or sooner when required.

If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to AstraZeneca Patient Safety using the designated Safety e-

mailbox AEmailboxclinicaltrialTCS@astrazeneca.com

15.17.2. Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, 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 University of Cincinnati PI and Monitor. The University of Cincinnati must report these events to AstraZeneca Patient Safety using the designated Safety e-mailbox AEmailboxclinicaltrialTCS@astrazeneca.com within 7 calendar days or sooner when required, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

- 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 patient will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study patient 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 University of Cincinnati and AstraZeneca.

15.17.3. Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- Pregnancy discovered before the study patient has received any study drugs.
- Pregnancy of a female partner of male patient, providing there is no restriction of male patient fathering a child.

15.17.4. Maternal Exposure

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

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

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

The University of Cincinnati will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days. The University of Cincinnati must report to AstraZeneca Patient Safety using the designated Safety e-mailbox AEmailboxclinicaltrialTCS@astrazeneca.com within 7 calendar days or sooner when required, for pregnancies with SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

15.17.5. Paternal Exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy..

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 combination therapy should, if possible, be followed up and documented.

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

15.17.6. Medication Errors

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error. If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the University of Cincinnati PI and study Monitor within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The University of Cincinnati will work with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days. The University of Cincinnati must report to AstraZeneca Patient Safety using the designated Safety e-mailbox within 7 calendar days or sooner when required if there is an SAE associated with the medication error and within 30 days for all other medication errors.

16. MEASUREMENT OF EFFECT

16.1. Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response 28 days after

completion of I/O +/-3 days. . In addition to a baseline scan, confirmatory scans should also be obtained (not less than 4) weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using RECIST version 1.1 and/or the mRECIST guidelines (both when institutionally allowed).

Definitions

Evaluable for Toxicity. All patients will be evaluable for toxicity from the time of their first treatment with *Durvalumab*

Evaluable for Response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

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.

16.1.1. Disease Parameters

Measurable Disease:

Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest X-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease.

Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

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.
When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be 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, and be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

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.

16.1.2. Methods for Evaluation of Measurable Disease

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

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

imaged but are assessable by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) 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 (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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 [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

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.

16.1.3. Response Criteria

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below.

16.1.3.1. 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 (<1 cm). Note: continue to record the measurement even if <10 mm and considered CR. Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [*Eur J Ca* 45:228-247, 2009]) before CR can be accepted.

Partial Response (PR): At least a 30% decrease in the sum of the measures (longest diameter for tumor lesions and short axis measure for nodes) 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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

16.1.3.2. 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 [<1 cm] 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 UC Principal Investigator.

16.1.3.3. 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.

Integration of target, non-target, and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for This Category Also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm & confirmation ≥ 4 wks.
CR	Non-CR/non-PD	No	PR	Normalization of tumor markers, tumor nodes <10 mm & confirmation ≥ 4 wks.
CR	Not all evaluated	No	PR	confirmation ≥ 4 wks
PR	Non-PD/not all evaluated	No	PR	confirmation ≥ 4 wks
SD	Non-PD/not all evaluated	No	SD	Documented at least once ≥4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	no prior SD, PR or CR
Any	PD	Any	PD	no prior SD, PR or CR
Any	Any	Yes	PD	no prior SD, PR or CR
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

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." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions. If the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

16.1.4. Duration of Response

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

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

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

16.1.5. Progression-Free Survival

Measured from the time of treatment allocation to the time of discovery of the first evidence after treatment of any tumor (local, regional, metastatic, or second primary) or death from any cause, whichever occurs first.

16.2. Other Response Parameters: mRECIST

The modified Response Evaluation Criteria in Solid Tumors (mRECIST) was developed in 2008 by the American Association for the Study of Liver Disease (AASLD) as an amended version of the RECIST, a method of measuring tumor response to treatment. mRECIST was developed specifically for HCC.

Contrast-enhanced CT or MRI is the imaging modality of choice for evaluating lesions.
European Association for the Study of the Liver (EASL) guidelines recommend evaluating for mRECIST criteria 1 month after undergoing treatment (surgery, locoregional therapy or initiation of systemic chemotherapy). mRECIST) This may be used in liver lesions meeting the following criteria:

- Can be accurately measured in at least one dimension as 10 mm or more (measure longest diameter).
- Suitable for repeat measurement.
- Intratumoral arterial enhancement on contrast-enhanced CT or MRI.

Target Lesion Responses are defined as the following (RECIST 1.1 is listed for comparison):

	RECIST 1.1	**mRECIST**
Complete response	Disappearance of all target lesions	Disappearance of any intratumoral arterial enhancement in all target lesions
Partial response	At least a 30% decrease in the sum of diameters of target	At least a 30% decrease in the sum of diameters of

	lesions, taking as reference the baseline sum of the diameters of target lesions	viable (enhancement in the arterial phase) target lesions, taking as reference the baseline sum of the diameters of target lesions
Stable disease	Any cases that do not qualify for either partial response or progressive disease	Any cases that do not qualify for either partial response or progressive disease
Progressive disease	An increase of at least 20% in the sum of the diameters of target lesions, taking as reference the smallest sum of the diameters of target lesions recorded since treatment started	An increase of at least 20% in the sum of the diameters of viable (enhancing) target lesions, taking as reference the smallest sum of the diameters of viable (enhancing) target lesions recorded since treatment started

Non-Target Lesion Responses are defined as the following (RECIST 1.1 is listed for comparison)

	RECIST 1.1	**mRECIST**
Complete response	Disappearance of all non-target lesions	Disappearance of any intra-tumoral arterial enhancement in all non-target lesions
Incomplete response or Stable Disease	Persistence of one or more non-target lesions.	Persistence of any intra-tumoral arterial enhancement in one or more non-target lesions.
Progressive disease	Appearance of one or more new lesions and/or unequivocable progression of an existing non-target lesion.	Appearance of one or more new lesions and/or unequivocable progression of an existing non-target lesion.

17. STUDY OVERSIGHT, DATA REPORTING & REGULATORY

17.1. Study Oversight and Ethical Conduct

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 and patient data protections.

This protocol is monitored at several levels, as described in this section. The UC Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events. The UC Principal Investigator has access to the data at all times through the study EDC, REDCap.

This study will also be reviewed in accordance with the UCCC CTO's SOPs, policies and guidance which may include periodic routine or for cause internal auditing. The study team must adhere to the current policies, SOPs, guidance and workflows of the UCCC CTO, or respective institutional practices in the conduct of this protocol.

All study investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via REDCap and timely reporting of adverse events. This includes timely review of data collected on electronic CRFs submitted via REDCap as well as review of any source documentation collected locally.

This study will also be reviewed in accordance with the enrolling institution's data safety monitoring plan.

17.2. Data Reporting

Data collection and storage at the University of Cincinnati will be managed by the University of Cincinnati Cancer Center, Clinical Trials Office (UCCC CTO). The UCCC CTO will maintain storage of all clinical data in accordance with federal guidelines and GCP. Data will be entered into the secure study EDC, REDCap and into the CTO CTMS. All hardcopies of data will be securely maintained (in a locked room or cabinet) and will only be accessible to members of the study team or UCCC CTO personnel.

Study data collected at sub-sites should be stored securely per local policies and be made accessible to UC as required.

17.3. Data Safety Monitoring Board

Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. Immediately after the study is approved and before the first patient is enrolled, investigators will meet, develop and finalize all measurements/variables for the study. Each patient, once enrolled, will be provided a unique ID for the study. Personal information, such as name, SSN, address, phone number and DOB, will be de-identified whenever possible from study records. Confidentiality will be maintained during the phases of the trial including preparation of interim results, review, and response to internal auditing or DSMB or IRB recommendations.

Exceptions may be made under circumstances where there are serious adverse events or when it is deemed appropriate for patient safety.

Study progress will be monitored regularly by the UCCC Data Safety Monitoring Board (DSMB). Membership consists of persons independent of, and without any conflicts of interest with, this trial. The DSMB includes experts in the fields of relevant clinical expertise (oncology) and biostatistics.

It is the responsibility of the UC Investigator to ensure that the DSMB is apprised of all new safety information relevant to the study. Study progress & safety information will be prepared by the DSMB Coordinator with input from the UC PI as to the current status of the trial. This compiled information presented to the DSMB will include: a narrative summary from the UC PI as to trial progress and identification of any trends of significance or explanation of any SAEs or other safety related events; the accrual rate with projected completion date for the accrual phase; exclusion rates and reasons when relevant; pretreatment characteristics of patients accrued when relevant; and, the frequency and severity of adverse events.

The DSMB will function in an advisory capacity and recommendations/requests from the DSMB will be reviewed by the UC investigator and promptly addressed.

The study data from participating sub-sites will be reviewed remotely via the study EDC REDCap and in person by the Study Monitor as per the study Monitoring Plan (Plan kept on file with UCCC CTO office).

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19. APPENDIX 1 TOXICITY MANAGEMENT

	Toxicity Management Guidelines (TMGs)	
	Drug Substance	Durvalumab and Tremelimumab
	TMG Version	September 2023

ANNEX TO PROTOCOL

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

Note: Annex is to be used in any clinical trial protocol within which patients are treated with Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy

VERSION HISTORY

September 2023

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either durvalumab or tremelimumab or a combination of these two immune checkpoint inhibitors (ICI) is used in combination with other anti-cancer drugs (e.g., antineoplastic chemotherapy, targeted agents). These other anticancer drugs can be administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination ICI regimens, with specific instructions for ICI dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and nonimmune–mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in clinical study protocol (CSP) – whether that is durvalumab alone, tremelimumab alone, or durvalumab + tremelimumab in combination, or durvalumab +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to CSP, which for the purposes of submission and approval of substantial updates is maintained as a standalone document. TMG updates are iterated by date, and should be used in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version specified in the CSP.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy –September 2023

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.

Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider the need for glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- **Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation**
- **Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy**
- **Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .**

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

- Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435
- Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology (ASCO) Guideline Update. J Clin Oncol 2022;39(36):4073-4126.
- Haanen J, et al. Management of toxicities from immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guideline for diagnosis, treatment, and follow-up. Annals Oncol 2022;33(12):1217-1238.
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PEDIATRIC CONSIDERATIONS REGARDING IMMUNE-MEDIATED REACTIONS

Dose Modifications

The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.

Toxicity Management

- All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended.
- The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients.
- The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients.
- The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist.
- For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist.
- With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

SPECIFIC IMMUNE-MEDIATED REACTIONS

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease). − Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients 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 etiologies 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 (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (CT) scan. − Consider Pulmonary and Infectious Diseases consults.
	Grade 1	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** − 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.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1.	**For Grade 2** − Monitor symptoms daily and

		If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper (≤10 mg prednisone or equivalent).	consider hospitalization, as clinically indicated. – Consider Pulmonary and Infectious Diseases Consults; – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). Consider HRCT or chest CT with contrast, Repeat imaging study as clinically indicated − 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 no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (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 or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Consider discussing with Clinical Study Lead.

	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Hospitalize the patient – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results – Supportive care (e.g., oxygen). – If no improvement within 2 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 or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression,

	study protocol for defining the CTCAE grade/severity)		other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – 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). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – 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 events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	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 and/or calprotectin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity improves to Grade ≤1, then study drug/study regimen can be	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

		resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	(e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Consider further evaluation with imaging study with contrast. – Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent 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 or relevant practice guidelines. **Caution: it is important 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.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** – For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (≤10 mg prednisone per day, or equivalent). – For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study	**For Grade 3 or 4** – Urgent GI consult and imaging and/or colonoscopy as appropriate. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (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 or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		investigator, in discussion with AstraZeneca Clinical Study Lead. **For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy:** **A. Permanently discontinue tremelimumab for Grade 3 diarrhea/colitis. HOLD durvalumab until resolution to Grade ≤1; durvalumab alone can be resumed after completion of steroid taper (<10 mg prednisone per day or equivalent)** **B. Permanently discontinue both durvalumab and tremelimumab for 1) Grade 4 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/studyregimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis ***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 hepatocellular carcinoma**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin .
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	– No dose modifications. – If it worsens, then consider holding therapy.	– Continue transaminase and total bilirubin monitoring per protocol.

secondary tumour involvement of the liver with abnormal baseline values [BLV])	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	– Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). – Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3 × ULN AND	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.

		bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	− If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5- ≤ 10 x ULN	− Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). − **If in combination with tremelimumab, do not restart tremelimumab.**	− Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. - Check CPK and aldolase (to rule out myositis) − Perform Hepatology Consult, abdominal workup, and imaging as appropriate. − If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug/study regimen.	− 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 an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** − Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis **(elevated transaminases and total bilirubin)** ***Infliximab should not be used for management of immune-related hepatitis.***	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). − Monitor and evaluate AST, ALT, ALP, and T. Bili. − For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg).

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])			– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
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 >ULN and ≤2.5×BLV,	– 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**	
	ALT or AST > 2.5- ≤ 5X BLV and ≤ 20xULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5×BLV . – If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5×BLV , resume study drug/study regimen after completion	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. - Consider checking creatinine phosphokinase (CPK) and aldolase (to rule out myositis) – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead.

		of steroid taper (<10 mg prednisone, or equivalent).	– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, 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. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN	– Withhold durvalumab and permanently discontinue tremelimumab – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. - Check CPK and aldolase (to rule out myositis) – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune- mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue study drug/study regimen.	**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consider Consulting a nephrologist. – Consider imaging studies to rule out any alternative etiology – 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, decreased urine output, or proteinuria). Follow urine protein/creatinine ratio every 3-7 days
	Grade 1	No dose modifications.	**For Grade 1** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. – Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion	**For Grade 2** – Consider including hydration, electrolyte replacement, and diuretics as clinically indicated – Follow urine protein/creatinine ratio every 3-7 days – Carefully monitor serum creatinine as clinically warranted.

		of steroid taper (<10 mg prednisone, or equivalent).	– Consult nephrologist and consider renal biopsy if clinically indicated. – Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out – If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Follow urine protein/creatinine ratio every 3-7 days – 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 of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant
Dermatologic Adverse Events (Including Pemphigoid)	**Any Grade**	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.**

			– **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID 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 improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**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 (<10 mg prednisone, or equivalent).	**For Grade** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 4** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

			– Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). 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. – 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.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide

			assessment of early morning adrenocorticotropin hormone (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, 3, or 4	– For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve. – Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – 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 T1DM, 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. – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression,

	study protocol for defining theCTCAE grade/severity)		viral infection, concomitant medications, substance abuse). – 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. – 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) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** – Consider IV hydration – Consider Gastroenterology referral

	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) - Consider antibiotic for bacterial coverage until cultures/panel results are back – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study regimen	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization.

			– Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. –	**For Any Grade** – Consider neurology consult – Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. – Exclude bacterial and viral infections. (i.e. HSV)Consider IV acyclovir until polymerase chain reactions are available.
	Grade 2	**For Grade 2** Permanently discontinue study drug/study regimen.	**For Grade 2** – Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisolone 1–2 mg/kg/day – For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	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 Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis
Demyelinating Disease (optic neuritis, transverse myelitis, acute demyelinating encephalomyelitis (ADEM))	**Any Grade**	**General Guidance** – Permanently discontinue immunotherapy – Consider MRI of the spine and brain	**For Any Grade** – Consider neurology consult – Inpatient care – Consider prompt initiation of high methylprednisolone pulse dosing – Strongly consider IVIG or plasmapheresis

		– Once imaging is complete, consider lumbar puncture Consider testing to rule out additional aetiologies: B12, copper, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel	
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the Clinical Study Lead, as needed. – Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2** – Consult a neurologist. – Consider EMG/NCS

			– Consider discussing with the Clinical Study Lead, as needed. – Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally – If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. – **Treat per Guillain-Barré Syndrome recommendations**
Guillain-Barré Syndrome (GBS)		General Guidance	– Recommend hospitalization – Obtain neurology consult – Obtain MRI of spine to rule out compression lesion – Obtain lumbar puncture – Antibody tests for GBS variants – Pulmonary function tests – Obtain electromyography (EMG) and nerve conduction studies – Frequently monitor pulmonary function tests and neurologic evaluations – Monitor for concurrent autonomic dysfunction – Initiate medication as needed for neuropathic pain
	Grade 2-4	Grade 2-4 Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		General Guidance	– Obtain neurology consult – Recommend hospitalization – Obtain pulmonary function tests

			− Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies − Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis − Obtain electromyography (EMG) and nerve conduction studies − Consider MRI of brain/spine to rule out CNS involvement by disease − Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)
	Grade 2	Permanently discontinue	− Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) − Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	Permanently discontinue	− Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement − Start plasmapheresis or IVIG − Consider rituximab if refractory to plasmapheresis or IVIG − Frequent PFT assessments − Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** − Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (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) − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with

			baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – 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). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	– If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy – Supportive care (e.g., oxygen). – If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **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.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

	defining the CTCAE grade/severity)		– 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, and; 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 Clinical Study Lead. **- Consider that patients may present with or progress to rhabdomyolysis. Treat signs and symptoms as per institutional protocol or local clinical practice.** – Initial work-up should include clinical evaluation, **creatine kinase, aldolase**, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) 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.

Grade 1	– 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 Clinical Study Lead.
Grade 2	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – 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 3 days, consider additional – immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3	**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	**For Grade 3** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.

		days or if there are signs of respiratory insufficiency.	– If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (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 or relevant practice guidelines). **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.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**Grade 4** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – 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 starting another immunosuppressive therapy such as a TNF inhibitor (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 or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

[1] SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
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 (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
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 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	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline	
Grade 4	Permanently discontinue study drug/study regimen	

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 Clinical Study Lead."

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	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 or study protocol prior to subsequent doses. – Consider steroids for patients who have previously experienced infusion reaction; use of steroid premedication may be permitted in these situations
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 standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	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 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	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 Clinical Study Lead."

List of Abbreviations

AChE	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotropic hormone	imAE(s)	Immune-mediated adverse event(s)
ALT	Alanine aminotransferase	INR	International normalized ratio
ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CSP	Clinical Study Protocol	MRCP	Magnetic resonance cholangiopancreatography
CT	Computed tomography	MRI	Magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events	NCCN	National Comprehensive Cancer Network
CTLA-4	Cytotoxic T-lymphocyte antigen-4	NCI	National Cancer Institute
DILI	Drug-induced liver injury	PD-L1	Programmed cell death ligand-1
ECG	Electrocardiogram	PJP	Pneumocystis jirovecii pneumonia
ECHO	Echocardiogram	PO	By mouth
ESMO	European Society of Medical Oncology	SCAR	Severe cutaneous adverse reaction
GI	Gastrointestinal	SITC	Society for Immunotherapy of Cancer
HBcAb	Hepatitis B core antibody	SJS	Stephen Johnson Syndrome
HBeAg	Hepatitis B envelope antigen	T1DM	Type 1 diabetes mellitus
HBsAg	Hepatitis B surface antigen	T3	Triiodothyronine
HBV	Hepatitis B virus	T4	Thyroxine
HCC	Hepatocellular cancer	TEN	Toxic Epidermal Necrolysis
HCV	Hepatitis C virus	TMG(s)	Toxicity management guideline(s)
HgA1c	Hemoglobin A1C	TSH	Thyroid stimulating hormone
ICI(s)	Immune checkpoint inhibitor(s)	ULN	Upper limit of normal

20. APPENDIX 2 PERFORMANCE STATUS CRITERIA

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

21. APPENDIX 3 FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al*., 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

References

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al*. (2009). A new equation to estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
2. Levey, A.S., J. Coresh, T. Greene, *et al*. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 145:247-254.
3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.