NCT 04989218

An open-label window of opportunity trial to evaluate the activity of durvalumab (MEDI4736) and tremelimumab with platinum-based chemotherapy (Gemcitabine and Cisplatin) in intrahepatic cholangiocarcinoma (ICC)

Document date: July 19, 2022

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Sponsor Investigator
Mehmet Akce, MD

Co-Investigators
Olumide Gbolahan, MD (Emory University Winship Cancer Institute)
Richard Kim, MD (Moffit Cancer Center)
Jason Denbo, MD (Moffit Cancer Center)
Bassel El-Rayes, MD (University of Alabama, Birmingham)
Sameer Al Diffhala (University of Alabama, Birmingham)
John Bart Rose, MD (University of Alabama, Birmingham)
Sushanth Reddy, MD (University of Alabama, Birmingham)
Grant William, MD (University of Alabama, Birmingham)
Darryl Outlaw, MD (University of Alabama, Birmingham)
Ursa Brown-Glaberman, MD (University of New Mexico)
Itzhak Nir, MD (University of New Mexico)
Ben Ferguson, MD (University of New Mexico)

Statistician
Kim Young-il, PhD (University of Alabama, Birmingham)

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PROTOCOL SIGNATURE PAGE

An open-label, window of opportunity trial to evaluate the activity of durvalumab/MEDI4736 (Durva) and tremelimumab (Trem) with platinum-based chemotherapy (Gemcitabine and Cisplatin/GemCis) in intrahepatic cholangiocarcinoma (ICC)

VERSION DATE: July 19, 2022

I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable institutional review board(s).

_____ _____

Signature of Site Investigator Date

_____

Site Investigator Name (printed)

_____

Site Investigator Title

_____

Name of Facility

_____

Location of Facility (City and State)

SYNOPSIS

TITLE	An open-label, window of opportunity trial to evaluate the activity of durvalumab/MEDI4736 (Durva) and tremelimumab (Trem) with platinum-based chemotherapy (Gemcitabine and Cisplatin/GemCis) in intrahepatic cholangiocarcinoma (ICC)
SHORT TITLE	Durvalumab and tremelimumab with platinum-based chemotherapy in intrahepatic cholangiocarcinoma
PHASE	Window of opportunity trial
OBJECTIVES	**Primary Objective** determine the activity of the combination of platinum-based chemotherapy (GemCis) combined with doublet immunotherapy (Durva/Trem) in 'borderline resectable' intrahepatic cholangiocarcinoma **Secondary Objectives** • Assess the feasibility of neoadjuvant platinum-based chemotherapy (GemCis) and doublet immunotherapy for high-risk but technically resectable (borderline resectable) intrahepatic cholangiocarcinoma. • Determine the safety of the combination of platinum-based chemotherapy (GemCis) and doublet immunotherapy (Durva/Trem) in borderline resectable intrahepatic cholangiocarcinoma • Determine feasibility of enrolling patients into a large Phase II/III trial of ICC. **Exploratory Objectives** Evaluate blood and tumor-based biomarkers that may be associated with improved ORR to combination of platinum-based chemotherapy (GemCis) and doublet immunotherapy (Durva/Trem)

KEY ELIGIBILITY CRITERIA (See Section 3 for full eligibility criteria)	Inclusion Criteria: • Histologically/cytologically confirmed diagnosed intrahepatic cholangiocarcinoma • Male or female, from age 18 years of age • Body weight >30 kg • Measurable disease based on RECIST 1.1 and have 1 or more radiologic features compatible with high risk (for resection and recurrence) but still considered technically surgically resectable by a multidisciplinary tumor board • Performance status of 0 or 1 on the ECOG performance scale within 3 days prior to 1st dose of study intervention • Adequate organ and marrow function Exclusion Criteria: • Previous systemic therapy for intrahepatic cholangiocarcinoma • Ampullary cancer, extrahepatic cholangiocarcinoma and gall bladder cancer • Any other histologic subtype except adenocarcinoma or mixed histology with adenocarcinoma/hepatocellular carcinoma. • Inflammatory bowel disease (ulcerative colitis or Chron's Disease), or primary sclerosing cholangitis
STATISTICAL CONSIDERATIONS	This is an open-label, window of opportunity, multicenter trial to determine the activity and safety of the combination of platinum-based chemotherapy (gemcitabine and cisplatin) with doublet immunotherapy (Durva/Trem) as preoperative therapy in patients with histologically and radiologically documented borderline resectable intrahepatic cholangiocarcinoma. The study will plan to enroll 20 patients across 4 centers over a 2-year period. It is estimated that each center will enroll 2 patients per year. This would potentially be the first part of a larger Phase II trial. Borderline resectable ICC makes up only about 20% of ICC which on its own is a rare entity. Accruing patients to a relatively large trial will be challenging. Limiting the sample size to 20 across 4 centers allows us to determine the feasibility of recruiting for a larger (Phase II or III) study and provides insights for designing larger studies. In addition, a key objective of this trial is to obtain correlative biomarkers to assess the effect of chemoimmunotherapy on the immune milieu of ICC. The above trial design allows us to explore clinical (radiologic), molecular response (RNA expression patterns) and immunologic response to 2 or more cycles of chemo-immunotherapy.

	Patients will receive durvalumab 1500mg by intravenous (IV) infusion on Day 1 every 3 weeks for up to a maximum of 4 cycles. Patients will also receive tremelimumab 300mg on Day 1 on the first cycle of treatment only. Additionally, patients will receive standard of care chemotherapy with gemcitabine 1000mg/m^2 and cisplatin 25mg/m^2 by IV infusion on Day 1 and Day 8 every 3 weeks for up to a maximum of 4 cycles. The combination of Durvalumab/MEDI4736 and Tremelimumab (doublet immunotherapy) with platinum-based chemotherapy will yield an objective of 52% and improve complete resection rates in intrahepatic cholangiocarcinoma. This will facilitate margin negative resection and ultimately reduce recurrence rates and improve survival. Carrying out this trial in the neoadjuvant setting provides an opportunity for discovery of biomarkers that may predict response to therapy.
TOTAL NUMBER OF SUBJECTS	N = 20
ESTIMATED ENROLLMENT PERIOD	Estimated ___18____ months after lead institution opens to accrual
ESTIMATED STUDY DURATION	Estimated 24 months

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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
BoR	Best objective response
BP	Blood pressure
C	Cycle
Cis	Cisplatin
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CCA	Cholangiocarcinoma
CR	Complete response
CRF	Case Report Form
CSA	Clinical study agreement
CSR	Clinical study report

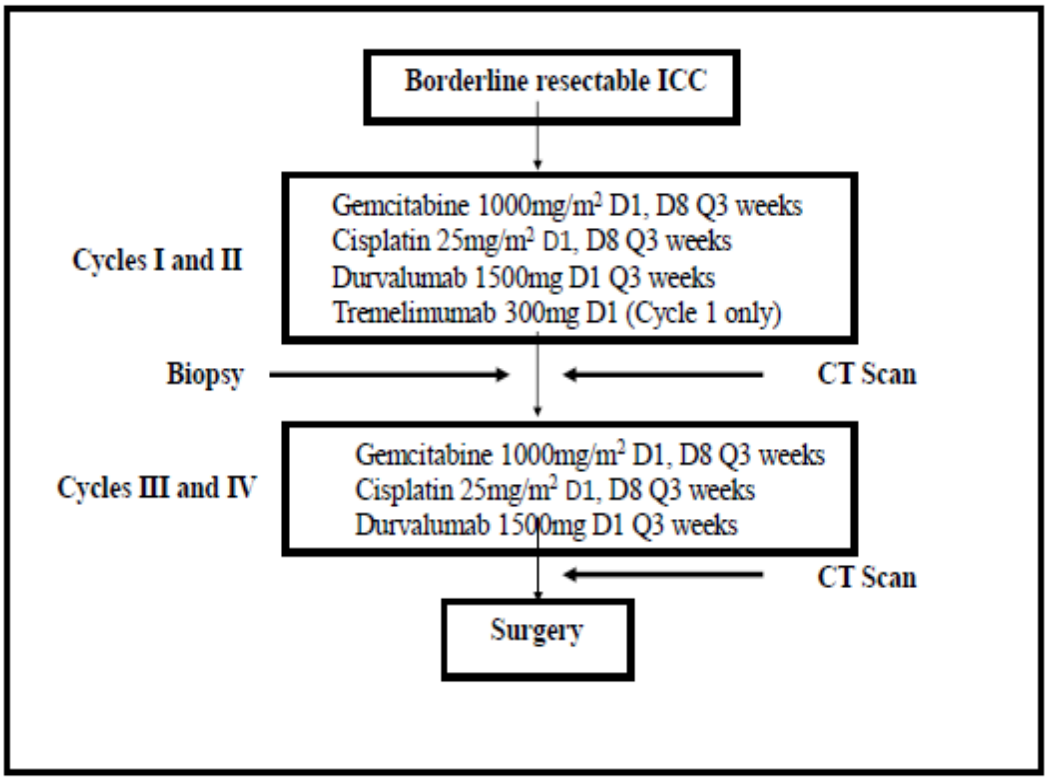
Abbreviation or special term	Explanation
CT	Computed tomography
CTNMO	Clinical Trials Network and Monitoring Office
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
Durva	Durvalumab
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
Gem	Gemcitabine
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
ICC	Intrahepatic Cholangiocarcinoma
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

Abbreviation or special term	Explanation
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
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

Abbreviation or special term	Explanation
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
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

Abbreviation or special term	Explanation
TSH	Thyroid-stimulating hormone
Trem	Tremelimumab
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

SCHEMA


Borderline resectable ICC
Cycles I and II
Gemcitabine 1000mg/m2 D1, D8 Q3 weeks
Cisplatin 25mg/m2 D1, D8 Q3 weeks
Durvalumab 1500mg D1 Q3 weeks
Tremelimumab 300mg D1 (Cycle 1 only)
Biopsy
CT Scan
Cycles III and IV
Gemcitabine 1000mg/m2 D1, D8 Q3 weeks
Cisplatin 25mg/m2 D1, D8 Q3 weeks
Durvalumab 1500mg D1 Q3 weeks
CT Scan
Surgery

1. BACKGROUND AND RATIONALE

1.1 Disease Background

A neoadjuvant therapeutic approach is accepted for malignancies with a high rate of recurrence and poor overall survival. This is established practice in resectable, and borderline resectable pancreatic cancer. It is increasingly embraced for resectable hilar cholangiocarcinoma (CCA) prior to liver transplant. Given the aggressive nature of intrahepatic cholangiocarcinoma (ICC) - a high rate of recurrence/metastases accompanied by poor overall survival- neoadjuvant therapy is justified. As such, many experts recommend perioperative therapy for 'borderline resectable' intrahepatic cholangiocarcinoma (ICC). Borderline ICC is characterized by features that may hamper complete resection with negative margins (R0 resection). Some of these features also portend a significantly increased risk of local and distant recurrence. Based on data from the ABC02 trial for locally advanced and metastatic CCA, the combination of gemcitabine and cisplatin (GemCis) is the most widely used perioperative regimen for borderline resectable ICC. The objective response rate of 20% with this regimen in ICC argues for the development of more potent systemic therapy combinations, including chemotherapy and immunotherapy. Patients with borderline resectable ICC represent a population that would benefit from these more potent combination regimens. At the same time, drug development in this setting provides the opportunity to explore biomarkers that may predict response to therapy.

1.1.1 Neoadjuvant therapy in intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) carries a grim prognosis. Most patients (50-60%) present with locally advanced, metastatic, and therefore incurable disease. About 20-30% of patients have resectable disease, and a further 20% present with tumors that are '**borderline resectable'. Tumors in the latter category are accompanied by high-risk features; large tumor size, multifocality, vascular invasion and regional lymph node involvement that suggest aggressive tumor biology. These features may render complete R0 challenging. This is important as achieving R0 resection provides the best opportunity for long term survival [1-5].** Following curative intent surgical resection, up to 60% of patients will recur with local and distant disease. Five-year overall survival therefore remains low at about 30%, and long-term cure rate is estimated to be only 10%.[6]

This state of affairs is similar to what obtains in pancreatic ductal adenocarcinoma (PDAC). Here, the therapeutic strategy has been based on development of more potent combination chemotherapy regimens in the metastatic setting (eg FOLFIRINOX) which have then been moved to the adjuvant and neoadjuvant settings [7-9]. Given the clinical similarities between the two entities, a similar approach may be required in ICC. However, drug development is hampered by the rarity of the disease. The role of neoadjuvant therapy in 'borderline resectable' ICC is thus still evolving. Many experts (within a multi-disciplinary tumor board setting) recommend systemic chemotherapy, usually gemcitabine and cisplatin to 'test the biology' of the disease and shrink the tumor, *a la* PDAC to increase the chances of R0 resection [10]. Neoadjuvant therapy is also employed in the relatively more common resectable and locally advanced perihilar and hilar cholangiocarcinoma. For example, in a retrospective study of 57 patients with perihilar CCA, neoadjuvant chemoradiotherapy (N=12) was associated with a median disease-free survival (DFS) of 26 months compared 15.1 months in patients who did not receive neoadjuvant therapy (N=45)[11]. Neoadjuvant therapy is also employed prior to transplant in patients with resectable hilar

cholangiocarcinoma [12]. Importantly, patients with locally advanced ICC who receive neoadjuvant chemotherapy with regimens that are potentially inferior to GemCis (including gemcitabine and oxaliplatin)[13] achieve similar survival outcomes as those who have resectable disease[14].

The potency of the systemic treatment regimen is critical to the success of neoadjuvant therapy. The combination of gemcitabine and cisplatin (GemCis) is the only licensed regimen for metastatic cholangiocarcinoma, and capecitabine is recommended in the adjuvant setting [15, 16]. Based on this, GemCis is usually deployed in the neoadjuvant setting for 'borderline resectable' ICC. **A single arm Phase II study is addressing the role of GemCis combined with nab-paclitaxel in high risk or borderline resectable ICC (NCT03579771)**. In addition, based on recent promising Phase II data in the locally advanced and metastatic settings[17], this regimen is being tested in a large randomized phase III trial (NCT03768414). However, in keeping with recent trends in oncology drug development, several trials are exploring the role of immunotherapy in combination with GemCis in metastatic ICC. This approach is justified given the recognized role of the immune system and tumor immune evasion mechanisms in determining outcomes in ICC [18].

1.1.2 The immune system in Intrahepatic Cholangiocarcinoma

Biliary tree cancers (BTC) are associated with chronic inflammation. The predominant inflammatory cells in BTC are T lymphocytes, and multiple studies have shown a prognostic role for tumor infiltrating cytotoxic lymphocytes (TIL) in cholangiocarcinoma [18]. One study reported CD8+ immunostaining in about 40% of CCA samples (N=16). The presence of CD8+ memory T cell infiltrates (12%) was associated with improved overall survival (HR 0.27, 95% CI 0.09-0.83, P=0.023)[19]. In addition, a systematic review and meta-analysis of 12 studies also suggested an association between improved clinical outcomes and higher expression of TILs. Despite this, in most patients with ICC, the tumor microenvironment is more immunosuppressive than pro-inflammatory [20]. Nearly 50% of patient samples express PDL1 (=/> 1%), although the numbers vary depending on the cut off employed, and whether tumor cells, inflammatory cells or both are assessed [21, 22]. PDL1 expression is induced in tumors (and some immune cells) as a negative regulator of cytotoxic effector T cells[23]. Accordingly, in an investigation of the 'genomic spectra' of cholangiocarcinoma, up to 40% of samples were grouped into a cluster characterized by increased expression of immune related genes, cytokines and immune checkpoints including PDL1 [24]. This cohort (Cluster 4 of 4) was associated with the poorest prognosis, suggesting the success of tumor immune suppressive and evasive maneuvers.

1.2 Immunotherapies

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[25]

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 [26]. It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273)[27]. 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.

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages [28]. Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment [29]. PD-L1 expressed on the tumor cells binds to PD-1 receptor on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor 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 [30-35] with responses that tend to be more pronounced in patients with tumors that express PD-L1. In addition, high mutational burden e.g., in bladder carcinoma [36] may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (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[37]. (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.

1.2.1 Durvalumab

Durvalumab 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 for use in the treatment of cancer. 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 [38]. *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism [38]. 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 8000 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 1.4.1.2**. Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.2.2 Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation (CD152), 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[39]. Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

To date tremelimumab has been given to more than 1500 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of tremelimumab monotherapy are summarized in Section 1.4.1.3. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.2.3 Durvalumab with tremelimumab and platinum-based chemotherapy

Because inhibition of CTLA4 and PD1/PDL1 activates the cytotoxic T-cells in a non-redundant fashion, the combination of antibodies against these 2 pathways provide at least an additive effect [40]. In melanoma, and RCC, the combination of an anti-PD1 agent (nivolumab) and ipilimumab (anti-CTLA4) is associated with significant survival benefit compared to either agent alone or with the standard of care treatment [41, 42]. This combination is being assessed in multiple Phase III studies for malignancies including NSCLC and hepatocellular cancer. In cancers, like NSCLC and small cell lung cancer (SCLC) ongoing studies are defining the role of combination immunotherapy with chemotherapy.

In addition to cytotoxicity that may potentially lead to an increase in the neoantigen load (albeit weakly), other mechanisms have been proposed to support an immunomodulatory role for traditional chemotherapy agents, including cisplatin [43, 44]. Based on preclinical models, cisplatin has been demonstrated to upregulate MHC class I antigen expression, fostering antigen presentation [45, 46]. In addition, cisplatin may down regulate an immunosuppressive microenvironment by reducing tumor myeloid suppressor cell and T reg infiltration and augment effector T cell recruitment and activity [47-49]. In the clinical setting, the combination of pembrolizumab with platinum-based chemotherapy is associated with a superior overall survival compared to chemotherapy alone in NSCLC [50] . Based on these, several trials are ongoing to evaluate the activity and efficacy of the combination of single or doublet immunotherapy with platinum-based therapy. The NILE trial is an ongoing randomized Phase III trial of durvalumab +/- tremelimumab with platinum-based chemotherapy in locally advanced/metastatic bladder cancer (NCT03682068). A similar trial (CASPIAN) is active in extensive stage small cell lung cancer (NCT03043872)

In cholangiocarcinoma, a phase III trial (Keynote 966) of GemCis and Pembrolizumab compared to GemCis alone is currently enrolling patients with locally advanced and metastatic cholangiocarcinoma (NCT04003636). A combination therapy of doublet immunotherapy (for instance, durvalumab and tremelimumab) with GemCis will be a natural progression of that study.

1.3 Research hypothesis

This is a window of opportunity pilot trial to assess the activity, safety and feasibility of doublet immunotherapy and platinum-based chemotherapy in resectable intrahepatic cholangiocarcinoma with high risk features. The hypothesis is that the combination of durvalumab/MEDI4736 and tremelimumab (doublet immunotherapy) with platinum-based chemotherapy (gemcitabine and cisplatin) will yield an objective of 52% and improve complete resection rates in intrahepatic cholangiocarcinoma. This will facilitate margin negative resection and ultimately reduce recurrence rates and improve survival. Carrying out this trial in the neoadjuvant setting potentially allows improved overall survival and also provides an opportunity for discovery of biomarkers that may predict response to therapy.

1.4 Rationale for conducting this study

The purpose of the study is to assess the activity of doublet immunotherapy and platinum-based chemotherapy in resectable intrahepatic cholangiocarcinoma with high features. As noted in the background (**Section 1.1**), long term survival remains poor even in resectable intrahepatic cholangiocarcinoma as majority of patients recur. Patients with high risk features are more likely to have disease recurrence following curative intent resection. A neoadjuvant approach with systemic therapy improves margin negative resection (R0 resection with margins negative for microscopic tumor involvement) and this is an important prognostic determinant in ICC. A neoadjuvant approach may also treat micro-metastatic disease although this has not been proven in intrahepatic cholangiocarcinoma. Achieving significant shrinkage is therefore vital. The current standard therapy regimen used in this setting is the combination of gemcitabine and cisplatin which is associated with an ORR of 20-25%[15]. This study proposes to improve ORR from 25% to 52%. If the objectives are achieved, this will serve as justification to expand the use of this combination to a larger cohort of patients with locally advanced and metastatic biliary tree cancer.

Because this is a pilot study, and given the rarity of the disease entity, there will be no control group. All patients enrolled will receive the study intervention. There will be no blinding of investigators or patients. Patients will receive up to 4 cycles of interventional agents prior to surgical resection. Patients will receive imaging scans after the 2nd and 4th cycle (before surgery) of intervention agents. The primary endpoint of the study is objective response rate (ORR). The objective response rate is an easy to measure, early indicator of activity of intervention agents. Although it is clear that ORR is not a reliable predictor of overall survival, in the neoadjuvant setting, where the goal is to 'shrink' the tumor, an improvement in response rate is a useful surrogate for clinical benefit[51]. The short interval of scans (6 weeks) allows investigators to identify non responders. These patients may be encouraged to come off study and be treated based on the treating oncologist's choice. Since the investigational agents include 'standard of care' agents, a good argument can be made that these patients would not have benefitted from standard therapy only. Patients with at least stable disease after the 2nd treatment cycle will proceed with study interventions. However, patients with radiologic progression but who remain clinically stable may be allowed to continue treatment if the patient elects to, pending confirmation of progression and after a discussion between the investigator and sponsor-investigator.

An important secondary endpoint is safety of the study interventions. We have defined a dose limiting toxicity probability level of 20% with early stopping rules based on this. The time to accrual of patients will also provide insight into the feasibility and design of larger trials that may focus on resectable ICC with high risk features. Justifications for the different dosing and schedule of treatment are noted in the protocol below.

1.4.1 Gemcitabine + cisplatin combination therapy dose rationale

The dose of chemotherapy (gemcitabine and cisplatin) chosen for this trial is the standard approved dose and schedule based on the ABC02 trial. Medical oncologists use this regimen in patients with resectable ICC and high-risk features setting as described in this protocol (Inclusion criteria, **Section 4.1**). Multiple clinical trials aimed at improving the combination have added newer therapies to this backbone regimen.

1.4.2 Durvalumab + tremelimumab combination therapy dose rationale

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

1.4.2.1 Pharmacokinetics/Pharmacodynamics data

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3

mg/kg) are dosed together. While the median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data.

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

1.4.2.2 Clinical data

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the benefit-risk profile in an acceptable range of PK and pharmacodynamic values.

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. As a result, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection.

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

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts

demonstrated objective responses at all doses of tremelimumab and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response.

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development. 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 Sections 1.4.2. 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.

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

1.4.3 Rationale for 4 cycles of combination therapy before surgical resection

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[52].

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).

Registered clinical trials of neoadjuvant therapy for cholangiocarcinoma have administered 3-6 cycles of systemic therapy over 9 to 12 weeks (NCT02256982, NCT03603834, NCT03579771). With this approach patients receive optimal systemic therapy to facilitate tumor shrinkage without unduly delaying surgery. In addition, this time period is sufficient to test the biology of the disease, as patients whose tumors progress in this time period on systemic therapy have aggressive disease, and surgical extirpation would not have improved their overall outcome.

The combination regimen will be administered for 4 doses Q3W unless other specific discontinuation criteria are met.

1.4.4 Rationale for fixed dosing of durvalumab and tremelimumab

A population PK model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W or 20 mg/kg

Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposures (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)[53]. 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 [54-57]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters.

These fixed dose regimens are being investigated in early and late phase trials (NCT02527434, NCT03084471) and are already in use in the community. 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

The feasibility and safety of a 3-week dosing regimen of platinum chemotherapy and durvalumab + tremelimumab was explored in a phase 1b study carried out in South Korea and Japan (NCT02658214). Here, 32 patients with advanced solid tumors received 1120mg (equivalent to the 1500mg q4week dose) of durvalumab and 75mg (minimum available biologic effective dose) of tremelimumab in addition to 1st line chemotherapy. Also, data from the Canadian Clinical Trials Group provide early safety data for the combination of platinum doublet chemotherapy with doublet immunotherapy (NCT02537418). In addition, PK modelling suggests that 3-weekly dosing would result in slightly higher C_{max} and C_{min} but a lower Area under the Curve (AUC) compared to a 4-weekly regimen (AstraZeneca data). This suggests that a 3 weekly schedule would preserve activity without significantly impacting safety risks Based on this, the NILE study is an ongoing Phase III trial assessing the efficacy of 3- weekly cisplatin/carboplatin + gemcitabine in combination with durvalumab (1120mg) +/-tremelimumab (75mg) in locally advanced and metastatic bladder cancer. In our study, patients will receive 4 cycles of gemcitabine and cisplatin per standard of care on day 1 and day 8 in addition to a fixed dose of durvalumab 1500mg (supported by PK modeling data) on day 1 every 3 weeks for 4 cycles.

However, in the present study, 300mg of tremelimumab will be administered only once on Cycle 1 day 1. This is equivalent to 75mg of tremelimumab delivered every cycle for 4 cycles.

This is based on simulation data which suggests that the C_{max} obtained after a single dose administration of tremelimumab at 4mg/kg is 4 times higher than the predicted C_{max} after the 4^{th} cumulative dose of tremelimumab administered at 1mg/kg every 4 weeks regimen (78ug/ml vs 19ug/ml). This single administration of higher dose of tremelimumab may deliver better antitumor activity and reduce cumulative toxicity associated with repeated dosing. The safety of this immunotherapy dosing combination is currently being assessed in the ongoing Phase I/II HIMALAYA study in patients with hepatocellular cancer (NCT03298451). No new safety signals have been reported so far. Our study will add on to this by assessing the safety of the combination with platinum-based therapy.

1.5 Benefit-risk and ethical assessment

1.5.1 Potential benefits

The combination of chemotherapy with single agent immune checkpoint inhibitor therapy (anti PD1/PDL1) has consistently been associated with an improvement in ORR in the first line treatment of metastatic disease across multiple tumors. In NSCLC, this combination is associated with an ORR of about 50% compared to 20% with chemotherapy only[50, 58]. In addition, in the Phase III KEYNOTE-062 trial, involving patients with HER2-ve metastatic gastric cancer, the combination of chemotherapy and pembrolizumab (anti-PD1) was also associated with superior ORR compared to SoC chemotherapy only [59].

Similar results have been established in cholangiocarcinoma. Ueno and colleagues reported an ORR of 36.7% among 30 patients with locally advanced/ metastatic cholangiocarcinoma who received treatment in the first line setting with GemCis and nivolumab [60]. This was a single arm study. It is noteworthy, however, that historically, an ORR of about 20% is expected with SoC chemotherapy in cholangiocarcinoma. The median OS in this cohort was 15.4 months (90% CI 11.8 to not estimable) at the time of reporting. Interestingly, the combination of ipilimumab and nivolumab offered in the 3^{rd} line setting and beyond in another phase I study yielded a median OS of 10 months[61]. This is similar to the OS reported in the ABC02 trial with SoC chemotherapy administered in the first line. It is expected that the combination of doublet immunotherapy with GemCis will achieve a higher ORR than GemCis combined with an anti-PD1 agent alone.

While an ORR may not be an optimal surrogate for overall survival in the advanced and metastatic cancer setting [62], it may provide the opportunity to improve margin negative resection in the neoadjuvant setting. An ORR is therefore a useful metric in the neoadjuvant setting, and the combination of doublet immunotherapy with chemotherapy may potentially double the number of patients who become eligible for margin negative resection. Furthermore, a pathologic complete response, which is more likely with more potent systemic therapy may also be a marker for prolonged survival or cure.

There are risks inherent to neoadjuvant therapy trials. Tumors may progress in the time before surgical intervention. Given our current understanding of the biology of cancer, tumor progression while on standard therapy suggests aggressive disease. In a way, patients who fall into this category may have been spared surgical resection with the potential complications that may accompany it.

Surgery in this case may not have been helpful to the patient. Secondly, the use of systemic chemotherapy, and particularly in combination with immunotherapy may lead to adverse effects that may preclude eventual surgical resection. Safety guidelines are in place in this protocol to reduce the number of patients who may be impacted by this. In addition, exclusion criteria for this protocol have been designed to exclude patients who may be affected by this. We recognize that this is a risk that cannot be completely eliminated.

In summary, this study offers patients the opportunity of an increased likelihood of a margin negative resection which overall, increases the chance of long-term survival and potential for cure in this setting of high-risk disease.

1.5.1.1 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 immunosuppressant 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.

1.5.1.2 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicity, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

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 6.5% of patients experienced an SAE that was considered to be related to durvalumab 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.

1.5.1.3 Tremelimumab

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhea, 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; cytopenia 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, dyspnea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.
A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the tremelimumab IB.
IB.

1.5.2 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 (≥ 10% of patients) are fatigue, diarrhea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anemia, constipation, cough, abdominal pain, pyrexia, back pain, arthralgia, hypothyroidism, asthenia, edema peripheral, decreased weight, decreased hyponatremia and rash.

Approximately 15% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 16% 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.

1.5.3 Durvalumab + tremelimumab + gemcitabine + cisplatin

Preliminary data from the Canadian Clinical Trial Group (CCTG) Phase I study (NCT02537418), of single (durvalumab) or doublet immunotherapy (durvalumab and tremelimumab) in combination with platinum-based chemotherapy (including GemCis) in advanced and metastatic solid tumors suggests that the combination is tolerable with manageable side effects. Of the 118 patients who have received up 723 cycles of therapy, immune related adverse events (irAEs) were reported in 50% of patients. Grade 3 or higher irAE was documented in in 10%, mainly involving the skin and the gastrointestinal tract. Although biochemical abnormalities occurred in 74% of patients on chemotherapy and doublet immunotherapy, these were generally manageable. Importantly, only 15 patients (12%) discontinued therapy due to Grade 2 or higher irAEs. There were no grade 5 events reported [63].

1.5.4 Overall benefit-risk

Given the manageable toxicity profile of the platinum-based chemotherapy and doublet immunotherapy combinations, a phase III trial of GemCis and immunotherapy doublet (durvalumab and tremelimumab) is ongoing in the 1st line for locally advanced and metastatic bladder cancer (NCT03682068). **Interestingly, the dose of cisplatin administered per cycle is higher (70mg/m2 on day 1 every 3 weeks) in bladder cancer compared to CCA (25mg/m2 on days 1 and 8 every 3 weeks**). There have been no new safety signals reported with this combination *(*discussions with UAB principal investigator and AstraZeneca representatives) and adverse effects have been manageable. In addition, given the low ORR achieved with SOC treatment with gemcitabine and cisplatin, exploring a potentially more potent therapy combination is justified. This may improve surgical resection rates and provide improved long-term survival. Furthermore, because of the heterogenous nature of intrahepatic cholangiocarcinoma, administering systemic therapy in the neoadjuvant setting provides an opportunity to define patient **and tumor** specific characteristics that may determine response to therapy.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

Determine the objective response rate (ORR) of the combination of platinum-based chemotherapy (GemCis) combined with doublet immunotherapy (Durva/Trem) in borderline resectable intrahepatic cholangiocarcinoma

2.1.2 Secondary Objectives

- Assess the feasibility of neoadjuvant platinum-based chemotherapy (GemCis) and doublet immunotherapy for high-risk but technically resectable (borderline resectable) intrahepatic cholangiocarcinoma.
- Determine the safety of the combination of platinum-based chemotherapy (GemCis) and doublet immunotherapy (Durva/Trem) in borderline resectable intrahepatic cholangiocarcinoma
- Determine feasibility of enrolling patients into a large Phase II/III trial of ICC.

2.1.3 Correlative/Exploratory Objectives

Evaluate blood and tumor-based biomarkers that may be associated with improved ORR to combination of platinum-based chemotherapy (GemCis) and doublet immunotherapy (Durva/Trem)

2.2 Endpoints

2.2.1 Primary Endpoint

Evaluate the objective response rate (ORR) a composite of complete and partial responses, with the combination of platinum based (GemCis) and doublet immunotherapy (Durva/Trem) after 2 cycles of therapy and prior to surgical resection.

2.2.2 Secondary Endpoints

- Feasibility of administering this regimen will be assessed by 3 criteria
    - Determine the rate of completion of preoperative therapy (4 cycles).
    - Determine the rate of R0 resection with combination chemotherapy and doublet immunotherapy.
    - Determine pathologic complete response rate. (complete absence of foci invasive adenocarcinoma)
- Assess adverse events via NCI Common Toxicity Criteria for Adverse Events (CTCAE) v5 during therapy with stopping rules for dose limiting toxicity per Inova et al [64].
- Determine the time to complete enrollment of patients, and the number enrolled over a 24-month period.

3. ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

Subject must meet all of the following applicable inclusion criteria to participate in this study:

1. Histologically/cytologically confirmed diagnosed intrahepatic cholangiocarcinoma

2. Measurable disease based on RECIST 1.1 and have 1 or more radiologic features compatible with high risk (for resection and recurrence) but still considered technically resectable per multidisciplinary tumor board (Surgical oncologist, radiologist and medical oncologist minimum) meeting. High risk features would include at least 1 of the following criteria-
    - A large tumor (> 5cm) that would benefit from preoperative tumor shrinkage with systemic therapy
    - T1b-T4 tumor thought to be technically resectable
    - Multifocal tumors/ a tumor with satellite lesions confined to the same lobe, thought to be technically resectable
    - Suspicious or involved lymph nodes (N1) thought to be technically resectable
    - Tumor with any vascular involvement/invasion considered technically resectable
    - No extrahepatic metastases

3. 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. Written informed consent and any locally required authorization (e.g., Health Insurance Portability and Accountability Act in the US) obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.

4. Adult male or female age $\geq$18 years at time of study entry

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

6. Life expectancy of $\geq$ 6 months

7. Body weight >30 kg

8. Adequate normal organ and marrow function as defined below:
    - Hemoglobin $\geq$ 10.0 g/dL
    - Absolute neutrophil count (ANC $\geq$1.5 x 10^9/L ($\geq$ 1500 per mm^3)
    - Platelet count $\geq$100 x 10^9/L ($\geq$75,000 per mm^3)
    - Serum bilirubin $\leq$1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with the sponsor.
    - AST (SGOT)/ALT (SGPT) $\leq$2.5 x institutional upper limit of normal

- Measured creatinine clearance (CL) >60 mL/min or Calculated creatinine clearance CL>60 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

9. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrhoeic 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 amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

10. 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.

11. Provide archival tumour tissue sample or newly obtained core or excisional biopsy of a previously unirradiated tumour lesion. Tissue blocks are preferred but unstained cut slides acceptable. In addition, should be open to undergoing a biopsy after at least 2 cycles of therapy. Patients who do not undergo surgical resection after 4 cycles will be advised to undergo another biopsy.

3.2 Exclusion criteria

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

1. Has had previous local (surgery, radiation, embolizing procedure) or systemic therapy for borderline resectable intrahepatic cholangiocarcinoma.

2. Participation in another clinical study with an investigational product during the last 3 months.

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

4. Has ampullary cancer, extrahepatic cholangiocarcinoma or gall bladder cancer.

5. Patients with distant extrahepatic metastatic disease including distant (non-regional lymph nodes). **NOTE:** Regional lymph nodes depend on tumor site; for left sided lesions, regional

lymph nodes include inferior phrenic, hilar and gastrohepatic lymph nodes. For right sided lesions, regional lymph nodes include hilar periduodenal and peripancreatic lymph nodes.

6. Has any other histologic subtype except adenocarcinoma or mixed histology with adenocarcinoma/hepatocellular carcinoma.

7. Any unresolved toxicity NCI CTCAE Grade > 2 from previous anticancer therapy except for alopecia, vitiligo and the laboratory values defined in the inclusion criteria.

8. Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the sponsor-investigator.

9. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the sponsor-investigator. Any medical contraindication to the use of platinum-based doublet chemotherapy as judged by the treating physician.

10. . Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study drugs.

11. History of allogenic organ transplantation.

12. 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:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician
    - Patients with celiac disease controlled by diet alone

13. 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 diarrhoea, 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.

14. History of active primary immunodeficiency.

15. History of another primary malignancy except for
    - Malignancy treated with curative intent and with no known active disease ≥3 years before the first dose of IP and of low potential risk for recurrence
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
    - Adequately treated carcinoma in situ without evidence of disease

16. 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), 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. **hepatitis C**, Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Testing for HIV is not required at screening but patients with known HIV disease will be excluded from the study.

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

18. Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug. **NOTE:** Patients, if enrolled, should not receive live vaccine whilst receiving study drug and up to 30 days after the last dose of study drug.

19. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or180 days after the last dose of durvalumab + tremelimumab combination therapy.

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

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

22. Has had severe hypersensitivity (≥ Grade 3) to anti –PD1/PDL1 or anti-CTLA4 therapy and/or any of their excipients in the past.

23. Patients who have received prior anti–PD-1, anti–PD-L1 or anti–CTLA-4:
    - Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy. All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.
    - Must not have experienced a ≥Grade 3 immune related AE or an immune related neurologic or ocular AE of any grade while receiving prior immunotherapy. NOTE: Patients with endocrine AE of ≤Grade 2 are permitted to enrol if they are stably maintained on appropriate replacement therapy and are asymptomatic.
    - Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day.

24. 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.

4. SUBJECT REGISTRATION

All subjects must be registered through the UAB Clinical Trials Network and Monitoring Office's (CTNMO). Subjects must be registered prior to starting protocol therapy. Patients will be identified following discussions at multidisciplinary tumor board meetings or following discussions among at least a medical oncologist, radiologist and surgical oncologist that patients confirmed intrahepatic cholangiocarcinoma is resectable but has high risk features as defined in this protocol.

5. TREATMENT PLAN

This is an open-label, window of opportunity, multicenter trial to determine the activity and safety of the combination of platinum-based chemotherapy (gemcitabine and cisplatin) with doublet immunotherapy (durvalumab and tremelimumab) as preoperative therapy in patients with histologically and radiologically documented borderline resectable intrahepatic cholangiocarcinoma.

The study will plan to enroll 20 patients across 4 centers over a 2-year period. It is estimated that each center will enroll 2 patients per year.

5.1 Study Treatment Administration

All patients will receive the same treatment and each cycle equals 21 days. For cycle 1, enrolled patients will receive 1 dose of tremelimumab 300 mg via IV infusion over 60 minutes, which will be followed by durvalumab 1500 mg via IV infusion over 60 minutes. Cisplatin 25mg/m^2 and gemcitabine 1000mg/m^2 will be administered based on institutional guidelines and practice.

For cycles 2 to 4, tremelimumab will not be given. Patients will receive durvalumab 1500mg over 60 minutes followed by cisplatin 25mg/m^2 and gemcitabine 1000mg/m^2 administered as an IV infusion according to prescribing information or institutional standards.

Drug	Dose[1]	Route[2]	Schedule[3]	Cycle Length	Total # of Cycles
Tremelimumab	300 mg	Intravenously (IV) over 1 hour **before** durvalumab	Day 1	3 weeks (21 days)	1
Durvalumab	1500 mg	IV 1 hour **after** completion of tremelimumab	Day 1		4
Gemcitabine	1000 mg/m^2	IV per institutional standards	Day 1, 8		
Cisplatin	25 mg/m^2		Day 1, 8		

[1] Dosing calculations should be based on actual body weight where applicable. Institutional standards for recalculating the dose based on weight changes should be used. All doses should be rounded up or to the nearest milligram per institutional standard.
[2] Tremelimumab will be administered first followed by durvalumab. Cisplatin + gemcitabine will then be administered. Infusion administration times performed outside the above recommended windows will not be considered as protocol deviations.
[3] A window of ± 3 days may be applied to all study visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's chart and electronic case report forms (eCRFs).

5.2 Study Medications

On the first infusion day, patients will be monitored, and vital signs collected/recorded in eCRF prior to, during and after infusion of study medications. Prior to the beginning of the infusions (measured once from approximately 30 minutes before up to 0 minutes [i.e., the beginning of the infusion]), approximately 30 minutes during the infusion (halfway through infusion) and at the end of the infusion (approximately 60 minutes ±5 minutes). If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

For subsequent infusions BP, pulse and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Patients should be carefully monitored, and BP and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated.

A 60-minute observation period after each immunotherapy agent is administered is recommended at least for Cycle 1.

5.2.1 Tremelimumab

Tremelimumab will be administered over 1 hour (± 15 minutes). Tremelimumab will be administered first followed by durvalumab approximately 60 minutes (maximum 2 hours) after the end of the tremelimumab infusion. If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature per infusion. Institutional standards for patient monitoring during tremelimumab infusion should be utilized. Please refer to the current IB for more detailed information.

5.2.2 Durvalumab

Durvalumab will be administered over 1 hour (± 15 minutes). If there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature per infusion. If no issues are seen after durvalumab is given during the first cycle, the observation period after durvalumab administration may be reduced to 30 minutes. Institutional standards for patient monitoring during durvalumab infusion should be utilized. Please refer to the current IB for more detailed information.

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of durvalumab may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤ Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion related reaction is ≥ Grade 3 or higher in severity, study drug will be discontinued.

For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in the Appendix

NOTE: If a patient's weight falls to 30 kg or below (≤ 30 kg), then the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q3W after consultation between the sponsor-investigator and site investigator, 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.

5.3 Dose Limiting Toxicities

Dose-limiting toxicities (DLTs) will be evaluated during the first 2 cycles of study treatment (over a 6-week period). In other words, the period for evaluating DLTs will be from the time of first administration of tremelimumab Cycle 1 Day1 until Cycle 2 Day 21 (1 dose of tremelimumab and 2 doses of durvalumab). Patients who do not remain on the study up to this time for reasons other than DLT may be replaced following consultation among the site investigator and sponsor-investigator. Grading of DLTs will follow the guidelines provided in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Since safety is a key secondary objective of this study, stopping boundaries, based on a Pocock style continuous reassessment method will be employed (see Section 12.7). Patients will be assessed on an ongoing fashion and if the numbers of dose limiting toxicities (DLT) reach the threshold based on those rules, a decision will be made to stop the study.

A DLT is defined as the occurrence of an adverse event (AE) that is at least possibly related to the 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 any of the following criteria:

Hematologic toxicity:

- Grade ≥ 3 neutropenia complicated by fever >38.3°C
- Grade 4 neutropenia (lasting more than 7 days)

- Grade ≥ 3 thrombocytopenia with significant bleeding
- Grade 4 thrombocytopenia (regardless of duration)
- Grade 4 anemia (regardless of duration)

Non-hematologic toxicity:

- Any Grade 4 non-immune-mediated AE
- Any Grade 4 immune-mediated AE, excluding endocrinopathies
- Any Grade 3 non-immune mediated AE that does not resolve to Grade ≤ 1 or baseline within 28 days with optimal medical management
- Any Grade 3 immune-mediated AE – excluding diarrhea/colitis, pneumonitis, hepatitis, rash, neurotoxicity, myocarditis, myositis/polymyositis, endocrinopathies and nephritis – that does not resolve to Grade ≤ 1 or baseline within 28 days after onset of the event despite optimal medical management including systemic corticosteroids
- Grade 3 diarrhea or colitis that does not resolve to Grade ≤ 1 within 14 days [both immune- and non-immune-mediated indicated here; the same is the case if not specified in remaining bullet points below]
- Grade 3 noninfectious pneumonitis
- Grade 2 noninfectious pneumonitis that does not resolve to ≤Grade 1 within 3 days of the initiation of maximal supportive care
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3×ULN with concurrent increase in total bilirubin (TBL) ≥2×ULN without evidence of cholestasis or alternative explanations (e.g., viral hepatitis, disease progression in the liver; i.e., "Hy's Law")
- ALT or AST >8×ULN or TBL>5×ULN
- Grade 3 immune-mediated rash that does not resolve to ≤Grade 1 or baseline within 28 days
- Grade 2 rash covering > 30% BSA that does not resolve to ≤Grade 1 or baseline within 28 days
- Any grade of immune-mediated rash with bullous formation
- Grade 3 immune-mediated neurotoxicity (excluding Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 28 days
- Grade 2 or 3 immune-mediated peripheral neuromotor syndrome (such as Guillain-Barre and myasthenia gravis) that does not resolve to ≤Grade 1 within 28 days or that exhibits signs of respiratory insufficiency or autonomic instability
- Grade 3 immune-mediated myocarditis
- Any symptomatic immune-mediated myocarditis that does not become asymptomatic within 3 days of initiating optimal medical management including systemic corticosteroids
- Grade 2 or 3 immune-mediated myositis/polymyositis that does not resolve to Grade ≤1 within 28 days of initiating optimal medical management including systemic corticosteroids or that exhibits signs of respiratory insufficiency regardless of optimal medical management
- Immune-mediated increase in creatinine >3×ULN, or >3×baseline for patients with a baseline creatinine elevated above ULN

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 as specified in the DLT criteria above.

Immune-related AEs are defined as AEs of an immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

Safety assessments will be performed on an ongoing basis based on a continuous reassessment method. The rate of Grade 3 or higher adverse events that fail to return to Grade 2 or less within 1 week, and immune related adverse events that require high dose corticosteroids use will be factored into the decision about continued enrollment of patients in the trial.

5.4 Standard of Care Medications

Package inserts and institutional standards for all aspects of administration of gemcitabine and cisplatin. This includes pre-medications, hydration, infusion times (windows), patient monitoring and side effect management.

5.4 Concomitant Medications

5.4.1 Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. 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," are to be administered per site 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 are permitted.

5.4.2 Prohibited Concomitant Medications

Patients should not receive any other systemic therapy for cancer unless specified in the protocol. If a patient needs palliative radiation therapy or other such local therapy for the treatment of limited areas of symptomatic disease or limited areas of progression, such as painful bone lesions, study therapy will be interrupted while receiving such therapy. Study therapy may be re-initiated after completion of such palliative therapy after **discussion with the sponsor-investigator. Following are the prohibited medications.**

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than durvalumab and tremelimumab
- Radiation therapy
    - **NOTE:** Palliative radiation therapy to symptomatic lesions or to the brain or limited areas of progression may be allowed at the investigator's discretion. This must be

discussed with the sponsor investigator. It is important that at least one target lesion remains untreated with treatment other than study therapy.

- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an immune related adverse event or for use as a pre-medication before chemotherapy or to treat contrast related allergy or for treatment of COPD/asthma exacerbation. The use of replacement doses of corticosteroids while on study is allowed.
- Herbal and natural remedies which may have immune-modulating effects

Subjects may receive other medications that the investigator deems to be medically necessary to manage the patient's cancer such as bone modifying agents in patients with bone metastases and growth factors for management of neutropenia.

5.5 Contraception

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

5.5.1 Female patient of child-bearing potential

Females of childbearing potential must be willing to abstain from heterosexual activity or agree to use a highly effective method of contraception from the time of informed consent until 180 days (durvalumab/tremelimumab) or 90 days (durvalumab) after treatment discontinuation. Females of childbearing potential randomized to Arm B must be willing to abstain from heterosexual activity or agree to use a highly effective method of contraception until 180 days (tremelimumab/durvalumab) or 90 days (durvalumab) after treatment discontinuation. Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with the treating physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female subjects should also refrain from breastfeeding throughout this period.

Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

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

chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

5.5.2 Male subjects with a female partner of childbearing potential

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days (durvalumab/tremelimumab) or 90 days (durvalumab). Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period. Female partners (of childbearing potential) of male subjects must also use a highly effective method of contraception throughout this period.

5.5.3 Contraception Options

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in the table below. 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; and triphasic combined oral contraceptive pills).

Highly Effective Methods of Contraception (<1% Failure Rate)

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

[a] This is also considered a hormonal method

5.5 Blood donation

Subjects should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab or 180 days following last infusion of tremelimumab.

6. TOXICITIES AND DOSE DELAYS/DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events. Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations. Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations.

6.1 Dose Delays/Dose Modifications

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). Please see 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.

Following the first dose of study drug, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. 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 Investigator should consult with the sponsor-investigator. Broadly, if a patient develops an immune related adverse event that precludes further immunotherapy use but the patient remains fit to continue SoC and there is no evidence of clinical or radiologic progression, the patient may continue treatment in this protocol with SoC agents only based on SoA. All toxicities will be graded according to NCI CTCAE, Version 5.0.

6.2 Discontinuation from Protocol Therapy

In addition to discontinuation from therapy related to toxicities as outlined in the section above, a subject will also be discontinued from protocol therapy and followed per protocol under the following circumstances outlined below. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

- Documented disease progression per RECIST 1.1. Site investigator determines a change of therapy would be in the best interest of the subject
- Subject requests to discontinue protocol therapy for any reason
  - If a subject decides to prematurely discontinue protocol therapy ("refuses treatment"), the subject should be asked if he or she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.
- Female subject becomes pregnant
- Protocol therapy is interrupted for ≥ 28 days from the expected day of the next treatment.

6.3 Discontinuation from Protocol Activities

If a subject decides to discontinue from all protocol activities and not just from protocol therapy, a final evaluation should be completed at the time of the subject's protocol withdrawal. An

explanation of why the subject is withdrawing from the protocol will be recorded on the eCRF. A final assessment of adverse events will be recorded on the eCRF.

7. STUDY CALENDAR & EVALUATIONS

Study Evaluation Cycle = 21 days	Screening	On Treatment				Off Treatment		Safety follow up visit[10]
		Cycle 1		Cycle 2 -4		Pre-Surgery	Surgery	
	-28 days	Day 1 ± 3 days	Day 8 ± 3 days	Day 1 ± 3 days	Day 8 ± 3 days	Within 4-6 weeks		30/90 days post last dose + 7 days
REQUIRED ASSESSMENTS								
Informed Consent	X							
Medical History[1]	X							
Physical Exam	X	X	X	X	X	X		D30
Vital signs and ECOG Performance Status[2]	X	X	X	X	X	X		D30
ECG[3]	X	As clinically indicated						
AEs & concomitant medications[11]	X	X	X	X	X	X		X
LABORATORY ASSESSMENTS								
Complete Blood Cell Count with diff (CBC)[4]	X	X	X	X	X	X		D30
Comprehensive Metabolic Profile (CMP)[4]	X	X	X	X	X	X		D30
CA19-9	X			C3D1		X		
Amylase and Lipase[5]	X	X		X		X		
Thyroid Function Testing[5]	X	X		X		X		
PT/PTT/INR	X							
Hepatitis and HIV Testing[5]	X							
Pregnancy test (serum or urine) (WOCBP)[5]	X	X		X		X		
Urinalysis[5]	X	X		X		X		
DISEASE ASSESSMENT								
CT of chest[6]	X			C3D1		X		
CT or MRI of abdomen and pelvis[6]	X			C3D1		X		
TREATMENT EXPOSURE[7]								
Tremelimumab 300 mg		X						
Durvalumab 1500 mg		X		X				
Cisplatin 25 mg/m^2		X	X	X	X			
Gemcitabine 1000 mg/m^2		X	X	X	X			
SPECIMEN COLLECTION								
Archival Tumor Tissue[8]	X							

Study Evaluation Cycle = 21 days	Screening	On Treatment				Off Treatment		Safety follow up visit[10]
		Cycle 1		Cycle 2 -4		Pre-Surgery	Surgery	
	-28 days	Day 1 ± 3 days	Day 8 ± 3 days	Day 1 ± 3 days	Day 8 ± 3 days	Within 4-6 weeks		30/90 days post last dose + 7 days
Fresh Tumor Tissue[8]		X[8]		C3D1		@ surgery or per fresh biopsy		X[8]
Peripheral Blood Samples[8]		X		C3D1		X[8]		D30[8]
FOLLOW-UP								
Survival Status, Subsequent Therapy								X

Key to Footnotes

1: Medical History; other data to be obtained during this assessment includes a smoking history questionnaire and trial awareness question. In addition, prior anti-cancer treatment should be documented including medications (chemotherapy, checkpoint inhibitors, etc) radiation or surgery. Medical history will include diagnosis and staging such as pathology report and TNM staging documentation. AJCC staging manual v8 will be utilized.

2: Vital signs to include temperature, pulse, respirations, blood pressure weight, and height (screening only) and ECOG performance status.

3: Any clinically significant abnormalities detected require triplicate ECG results. During treatment, ECG should be performed as clinically indicated per site investigator discretion.

4: CBC with differential and platelet to include: WBC, ANC, Hgb, Hct, PLT. CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen, LDH and albumin; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase. CBC and CMP may be performed more frequently if clinically indicated per site investigator discretion. Results for LFTs, electrolytes, full blood count and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or designee prior to dosing.

5: Thyroid Function testing should be performed at screening, then every cycle. TSH will be obtained. T4 and T3 including free versus total testing is at the discretion of the site investigator. If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1. Hepatitis B surface antigen, hepatitis C antibodies, and HIV testing should be performed at screening. For women of childbearing potential (WOCBP): urine or serum βhCG if clinically appropriate. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Testing is required 7 days prior to initiation of study treatment but may be done on Day 1 if results are available

and reviewed by the treating physician or designee. During treatment, testing should be performed prior to each cycle. A urinalysis will be performed at screening then prior to each cycle. Results to include: bilirubin, blood, glucose, ketones, pH, protein, specific gravity and white blood cells.

6: RECIST assessments will be performed on images from CT (preferred) or MRI, each preferably with IV contrast of the chest, abdomen (including liver and adrenal glands) and pelvis. Pelvic imaging is recommended only when primary or metastatic disease in the pelvic region is likely. Additional anatomy should be imaged based on signs and symptoms of individual patients at baseline and follow-up. Baseline assessments should be performed no more than 28 days before Cycle 1 Day 1 and ideally, should be performed as close as possible to and prior to the start of the study regimen. The confirmatory scans should be performed preferably at the next scheduled imaging visit and no less than 4 weeks after the prior assessment of PD (in the absence of clinically significant deterioration). If an unscheduled assessment was performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their next scheduled visit. The type of tumor imaging should remain consistent. Tumor imaging to be done after treatment discontinuation is at discretion of site investigator based on standard of care practice. If tumor assessments are available for subjects who have not yet experienced progressive disease (PD) at the time treatment is discontinued, the follow-up tumor evaluations will be documented in the eCRF until PD or death is confirmed, or until another treatment is initiated. A window of ± 7 days is allowed.

7: See Section 5 for specifics regarding study treatment administration.

8: Archival tissue is required if available. Tissue blocks are preferred but unstained cut slides acceptable. If archival tissue is not available, a newly obtained core or excisional biopsy of a previously unirradiated tumor lesion is required. A biopsy prior to Cycle 3 Day 1 is optional but strongly encouraged. For subjects undergoing surgery, sample of tissue is required. For subjects not undergoing surgery, a biopsy is optional and strongly encouraged. If a biopsy is performed at progression per standard of care, a sample of tissue is required for correlative analysis. See Correlative Laboratory Manual (CLM) for details regarding these samples.

9: Blood samples will be collected for correlative analysis prior to treatment on (1) Cycle 1 Day 1, (2) Cycle 3 Day 1 and (3) after completion of 4 cycles of treatment. The last sample may be obtained at the pre-surgical visit or the Day 30 safety visit. See Correlative Laboratory Manual (CLM) for details regarding these samples.

10: Safety Follow Up: The safety follow-up visit should only occur when subjects permanently stop study treatment for whatever reasons (toxicity, progression, or other reason) and should be performed 30 days (+ 7 days) after the last dose of study treatment. All AE (SAE) considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first. For those subjects undergoing surgery, the pre-surgery visit may include the Day 30 safety visit testing. The D90 assessment of adverse events may be done via email, phone call or other avenues as appropriate. If either of these visits coincide with the pre-surgical or surgical visit, safety follow up may be done at that time.

11: It is recommended that patients are contacted 2 weeks after receiving the first 3 cycles of durvalumab (Cycle 1 Day 15 Cycle 2 Day 15, and Cycle 3 Day 15) to ensure early identification and management of toxicities. This may be performed by study staff via email, phone call or other avenues as appropriate.

8. BIOSPECIMEN STUDIES AND PROCEDURES

All samples described below should be collected Monday through Thursday. Additional details for all correlatives described below can be found in the Correlative Laboratory Manual (CLM).

8.1 Proposed Correlative Analyses

- Determine changes in tumor mRNA gene expression pattern following treatment with combination platinum-based chemotherapy and doublet immunotherapy compared to pretreatment samples. (Correlatives priority # 1)
- Assess changes in the phenotype of peripheral circulating CD4 Helper, CD4/FOxP3+ regulatory T cells and CD8 + T cells (Correlatives priority # 2) with a focus on activation vs exhaustion
- Assess the change in the level of circulating soluble PDL1, HMGB1 and ATP secretion with therapy (Correlatives priority # 3)
- The Ventana SP263 assay will be used for PDL1 testing. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT). **A positive PDL1 test is not required to screen and enroll patients to this study.**
- Blood for flow cytometry and ELISA, cfDNA and TCR analysis
- Whole Exome Sequencing

8.2 Tissue Samples

See the CLM for additional information regarding tissue for correlative analysis.

8.2.1 Archival Tissue

Formalin-fixed paraffin-embedded (FFPE) tumor tissue block ideally collected within 6 months prior to registration is required if available for the following analyses:

- Diagnosis confirmation
- Whole exome sequencing
- Immunohistochemistry
- PDL1 assessment if judged to be sufficient (in quality and quantity)
- Nucleic acid extraction

Tissue should ideally have been collected within 6 months prior to registration. A copy of the original pathology report must be provided, and the tissue collection date must be recorded so the sample age can be derived. Where archival tissue block is not available, 2 H& E stained slides and 20-30 unstained, uncharged, air dried slides would be required.

8.2.2 Fresh Tissue

If archival tissue is not available or insufficient to perform the above analyses, a biopsy is required prior to treatment initiation. A biopsy is optional but strongly encouraged if clinically feasible after 2 cycles of treatment/prior to Cycle 3 Day 1. After Cycle 4, tissue is required for correlative analysis from the surgical specimen. If the subject does not undergo surgery, a fresh biopsy is optional but strongly encouraged. If a biopsy is performed for standard of care purposes at progression, a sample is required for correlative analysis. A copy of the radiology and operative reports from the tissue removal procedure and the diagnostic anatomic pathology report is required to accompany all specimens. As much as possible, interventional radiology guided core- biopsies

are encouraged to enable collection of high-quality tissue with sufficient tumor content for the biomarker studies which are integral to this study.

8.3 Peripheral Blood

Blood collection for correlative analysis is required and will occur prior to Cycle 1 Day 1 of treatment, after 2 cycles of treatment/prior to Cycle 3 Day 1 and after completion of Cycle 4. The following analyses are proposed:

- Whole exome sequencing
- phenotype of peripheral circulating CD4 Helper, CD4/FOxP3+ regulatory T cells and CD8 + T cells with a focus on activation vs exhaustion
- level of circulating soluble PDL1, HMGB1 and ATP secretion with therapy
- Blood for flow cytometry and ELISA, cfDNA and TCR analysis

Please see the CLM for more information about blood biospecimen collection and banking

8.4 Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples collected for study-specific correlative research. The UAB tissue biorepository and the CCTS specimen processing and biorepository unit will manage the banked samples. Samples will be coded and banked indefinitely in and may be used for future unspecified cancer-related research.

8.5 Confidentiality of Biospecimens

Samples will be identified by the subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number.

9. CRITERIA FOR DISEASE EVALUATION

9.1 Measurable Disease

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

9.1.1 Malignant Lymph Nodes

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

9.2 Non-measurable Lesions

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

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

9.3 Target Lesions

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

9.4 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.

9.5 Evaluation of Target Lesions

NOTE: In addition to the information below, also see the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters
Progressive Disease (PD)	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

9.6 Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject 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 site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

9.7 Evaluation of Best Overall Response

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

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

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the

residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

10. DRUG INFORMATION

10.1 Tremelimumab

Tremelimumab is an anti-CTLA-4 antibody being explored as a single-agent, and in combination with durvalumab, for the treatment of several malignancies.

10.1.1 Supplier/How Supplied

Tremelimumab will be supplied by AstraZeneca either as a 300-mg or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal label-claim fill volume is 20.0 mL for the 300-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original container until use to prevent prolonged light exposure.

Tremelimumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from or practically free from visible particles.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.1.2 Preparation

Total time from needle puncture of the tremelimumab vial to the start of administration should not exceed:

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

Tremelimumab 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 in-line filter. 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 during infusion, the total allowed time should not exceed 8 hours at room temperature. Do not co-administer other drugs through the same infusion line.

In the event that 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.

10.1.3 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to aseptic technique.

Tremelimumab vials should be disposed at the site following local procedures for the disposal of anticancer drugs.

10.1.4 Dispensing

Tremelimumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Tremelimumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.1.5 Adverse Events

Risks with tremelimumab monotherapy include, but are not limited to, GI effects (colitis, diarrhea, 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, dyspnea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

10.2 Durvalumab

Durvalumab 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). Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma IFNγ.

Refer to the Investigator’s Brochure for additional information regarding this drug.

10.2.1 Supplier/How Supplied

Durvalumab will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density

of 1.054 g/mL. The label-claim fill nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

Durvalumab is a sterile, clear to opalescent, colorless to slightly yellow solution, free from visible particles.

Drug product should be kept in original packaging until use to prevent prolonged light exposure. Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

10.2.2 Preparation

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

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

A dose of 1500 mg 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.

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

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

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.

10.2.3 Handling and Disposal

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to aseptic technique.

Durvalumab vials should be disposed at the site following local procedures for the disposal of anticancer drugs.

10.2.4 Dispensing

Durvalumab must be dispensed only from official study sites and to eligible subjects under the supervision of the site investigator. Durvalumab should be stored in a secure area according to local regulations. It is the responsibility of the site investigator to ensure that study drug is only dispensed to subjects.

10.2.5 Adverse Events

Adverse events for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These adverse events are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy.

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

10.3 Gemcitabine and Cisplatin

All aspects of chemotherapy preparation and administration will be based on local practices and guidelines at investigation sites. Package insert for both drugs should be utilized for details.

These drugs are commercially available.

11 ADVERSE EVENTS

CTCAE v5 will be utilized to grade all adverse events.

11.1 Definitions

11.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

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.

11.1.2 Serious Adverse Event (SAE)

A SAE is an adverse event that:

- Results in death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study drug(s)
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization for >24 hours or prolongation of existing hospitalization. **NOTE:** Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse.
- 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.

11.1.3 Adverse Events of Special Interest (AESIs)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the study drug(s) and may require close monitoring and rapid communication by the site investigator to the sponsor-investigator. An AESI may be serious or non-serious. The rapid

reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the study drug(s). If any AESI occurs in the course of the study, then the site investigators or other site personnel should report to the UAB CTNMO **within 1 business day** of becoming aware of the event. The CTNMO will report to AstraZeneca **within 1 business day** of becoming aware of the event.

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

11.1.4 Unexpected Adverse Event

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, prescribing information or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

11.1.5 Relatedness

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	Adverse Event is ***not related*** to the study drug(s)
Unlikely	Adverse Event is ***doubtfully related*** to the study drug(s)
Possible	Adverse Event ***may be related*** to the study drug(s)

Probable	Adverse Event is ***likely related*** to the study drug(s)
Definite	Adverse Event is ***clearly related*** to the study drug(s)

11.2 Reporting

11.2.1 Adverse Events

- AEs will be recorded from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- AEs will be recorded regardless of whether or not they are considered related to the study drug(s).
- All AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first.

11.2.2 Serious Adverse Events (SAEs)

11.2.2.1 Site Requirements for Reporting SAEs to UAB CTNMO

- SAEs will be reported from time of signed informed consent until 90 days after discontinuation of study drug(s) or until a new anti-cancer treatment starts, whichever occurs first.
- SAEs include events related and unrelated to the study drug(s).
- All SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within the EDC system.
- SAEs will be reported on the SAE Submission Form **within 1 business day** of discovery of the event.
- All SAEs related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.

The site will submit the completed SAE Submission Form to CTNMO **within 1 business day** of discovery of the event**.** The form will be submitted to the CTNMO electronically by email (pamdixon@uab.edu). The site investigator is responsible for informing the IRB and/or other local regulatory bodies as per local requirements.

The original copy of the SAE Submission Form and the email correspondence must be kept within the study file at the study site.

Once the SAE has resolved (see resolution guidelines listed above), sites must submit a follow-up SAE Submission Form within a reasonable timeframe to the CTNMO electronically to **pamdixon@uab.edu**

11.2.2.2 Requirements for Reporting SAEs to AstraZeneca

The CTNMO will report all SAEs to AstraZeneca **within 1 business day** of receipt of the SAE Submission Form from a site. Follow-up information will be provided to AstraZeneca as it is received from site. Send SAE report and accompanying cover page by way of email to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com.

11.6 Other events requiring reporting

11.6.1 Overdose

Use of tremelimumab or durvalumab 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 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 eCRF.

If an overdose of a study drug(s) occurs in the course of the study, then the site investigator or other site personnel will inform the CTNMO **within 1 business day** of becoming aware of the event. The UAB CTNMO will report the event to AstraZeneca **within 1 business day** of becoming aware of the event.

11.6.2 Pregnancy

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

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

11.6.3 Maternal exposure

If a patient becomes pregnant during the course of the study, the study drug(s) should be discontinued immediately. Pregnancy itself is not regarded as an AE unless there is a suspicion that the study drug(s) 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 site investigator or other site personnel will inform the CTNMO **within 1 business day** of becoming aware of the event. The UAB CTNMO will report the event to AstraZeneca **within 1 business day** of becoming aware of the event.

11.6.4 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of study drug. Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of study drug should, if possible, be followed up

and documented.

11.6.5 Reporting of deaths to AstraZeneca

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of study drug safety follow-up period must be reported to AstraZeneca as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the CTNMO **within 24 hours** and the CTNMO will report to AstraZeneca as a SAE **within 24 hours**. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

11.4 Sponsor-Investigator Responsibilities

The UAB CTNMO will send a SAE summary to the sponsor-investigator **within 1 business day** of receipt of SAE Submission Form from a site. The sponsor-investigator will promptly review the SAE summary and assess for expectedness and relatedness.

11.5 Responsibilities to FDA

If an IND is assigned, CTNMO will manage the Investigational New Drug Application (IND) associated with this protocol on behalf of the sponsor-investigator. The UAB CTNMO will cross-reference this submission to the AstraZeneca's parent IND at the time of submission. A copy of these documents will be available to AstraZeneca upon request.

For protocols conducted under an IND, CTNMO will be responsible for all communication with the FDA in accordance with 21CFR312 including but not limited to the 7- and 15-Day Reports, as well as an Annual Progress Report. A copy of these documents will be available to AstraZeneca upon request.

For protocols exempt from the requirements of an IND, the above stated requirements are not applicable. The CTNMO will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

11.6 IND Safety Reports Unrelated to this Trial

AstraZeneca will provide to the UAB CTNMO IND safety reports from external studies that involve the study drug(s) per their guidelines. CTNMO will forward safety reports to the sponsor-investigator who will review these reports and determine if revisions are needed to the protocol or consent. CTNMO will forward these reports to participating sites **within 1 business day** of receiving the sponsor-investigator's review. Based on the sponsor-investigator's review, applicable changes will be made to the protocol and informed consent document (if required). All IND safety reports will also be made available to sites via the EDC system.

Upon receipt from CTNMO, site investigators (or designees) are responsible for submitting these safety reports to their respective IRBs, as per their IRB policies.

12 STATISTICAL METHODS

12.1 Study Design

This is a multi-center open-label window of opportunity study. Objective response rate is the primary endpoint and safety assessment is a major secondary objective. The eligible population includes adults with resectable intrahepatic cholangiocarcinoma and high-risk features (borderline resectable).

12.2 Sample Size and Accrual

The primary endpoint of this pilot trial is objective response rate (ORR). Twenty patients (20) will be treated in this study and we expect to accrue this number over 24 months across 4 institutions. Given the historical objective response rate of 25% and using one-sided exact test for single proportion, we will have 80% power to reject 25% ORR at α=0.05 when we observe ORR of 52% (Ho: Po=0.25 vs. Ha: Pa=0.52) from the study sample. For further investigation of the treatment with larger study (N=100), the presented ORR, 52%, will be detectible with 99% power at α=0.05 and ORR, as less as 37%, will be detectible with 82% power at α=0.05.

Patients who are incorrectly enrolled because they do not fully meet eligibility or deteriorate between screening and first study treatment can be replaced following consultation with the sponsor, and as long as the goal sample size has not been met. Withdrawn patients will only be replaced following a discussion with the investigator and sponsor-investigator and if it is thought to be feasible and the sample size has not been reached. Patients who discontinue from the study (related to toxicity, patient's/physician's choice or disease progression) after receiving at least 2 cycles of study treatments will not be replaced. Patients who discontinue from the study before receiving at least 2 cycles of study treatment may be replaced. Such patients may be replaced following consultation between investigator and sponsor-investigator. The UAB CTNMO should be made aware of all communications regarding replacement of subjects.

12.3 Endpoints

12.3.1 Primary Endpoint

Evaluate the objective response rate (ORR) with the combination of platinum based (GemCis) and doublet immunotherapy (Durva/Trem) after 2 cycles of therapy and prior to surgical resection.

12.3.2 Secondary Endpoints

- Feasibility will be assessed by 3 criteria
    - Determine the rate of completion of preoperative therapy (4 cycles).
    - Determine the rate of R0 resection with combination chemotherapy and doublet immunotherapy.
    - Determine pathologic complete response rate (complete absence of foci of invasive adenocarcinoma).
- Assess adverse events via NCI Common Toxicity Criteria for Adverse Events (CTCAE) v5 during therapy with stopping rules for dose limiting toxicity per Inova et al [64].
- Determine the time to complete enrollment of patients, and the number enrolled over a 24-month period.

12.4 Assessment of Safety

Safety analysis will be performed on data from all patients who receive at least 1 dose of study drug (On cycle 1 Day 1). Safety assessments will be conducted in a continuous fashion based on a 6-week (2 cycles) DLT period and will impact the number of patients who are eventually enrolled in the study. At least 1 laboratory or vital sign measurement is required for inclusion in the analysis of each specific parameter. To assess a change from baseline, a baseline measurement is also required.

Adverse events per CTCAE v 5.0 will be monitored and collected. Adverse events for safety analysis will be collected over 2 full cycles for each enrolled patient. This study will be set up to ascertain that adverse events are rare, and to end the study (before enrollment of the full sample size) in the event of an increased rate of adverse events. Twenty patients (20) are planned to be enrolled in this pilot study.

12.5 Assessment of Efficacy

The analysis of the primary efficacy endpoint of ORR is based assessment of response after treatments. Based on this, only patients who receive at least 2 cycles of study treatment, and an on-treatment imaging scan will be included in the efficacy analysis set.

12.6 Data Analysis Plans

12.6.1 Analysis Plans for Primary Objective

See Section 12.2.

12.6.2 Analysis Plans for Secondary Objectives

The primary endpoint of the study is to evaluate the objective response rate (ORR) of the combination of doublet immunotherapy (durvalumab and tremelimumab) and platinum-based therapy (gemcitabine and cisplatin) in resectable intrahepatic cholangiocarcinoma with high risk features. Objective response rate (Complete Response + Partial Response) will be collected based on RECIST. The number of patients with an ORR will be reported as a percentage of the total number of patients analyzed for efficacy. Actual values and changes from baseline in tumor burden will be summarized by time-point.

Patient characteristics at baseline will be collected and summarized by presenting descriptive statistics for overall and per site. Differences of the characteristics between patients with an objective response and those without will be summarized. Tumor response will be summarized using descriptive statistics.

For continuous variables, means and standard deviations will be reported. Student t-tests will be used to compare means where necessary. Where appropriate, medians and interquartile ranges will be reported for presenting distribution of measures. Wilcoxon rank sum test will be considered as a nonparametric test of t-test. Categorical measures will be presented as counts and percentages and will be compared using the z-test of proportions and χ^2 test of association. For rare outcomes such that the χ^2 test of association is not appropriate, Fisher's exact test will be used. Results will be determined to be statistically significant when the accompanying statistical test yields a probability of 0.05 or less.

12.6.3 Analysis Plans for Exploratory Objectives

Whole exome sequencing of biopsy specimens will be performed in conjunction with the Human Tissue Resource Center Pathology Core Facility and the laboratories of Dr Karina Yoon to assess baseline, therapy-induced changes, and status upon progression (where applicable). Flow cytometry will be performed on blood samples to determine baseline, and treatment-induced changes in the circulating immune cells (particularly CD4+, Helper T cells, CD8+ cytotoxic T cells) in the peripheral blood. Additionally, ELISA will be performed on serum samples to determine baseline, and treatment-induced changes in markers of immunogenic cell death (HMGB1, ATP) and circulating soluble PDL1 levels. The incidence of biomarkers will be summarized using descriptive statistics. Comparisons of molecular changes in tumors, and cellular and humoral changes in the blood pre and post treatment will be performed according to documentation of the efficacy endpoints (i.e. responders with a CR or PR vs non-responders with SD and PD). Exploratory analysis with Logistic regression will be used to assess if there are any biomarkers associated with clinical response or disease progression. All analysis will be exploratory.

12.7 Interim Analysis/Criteria for Stopping Study

Sequential boundaries will be used to monitor dose-limiting toxicity rate. The accrual will be halted if excessive numbers of dose-limiting toxicities are seen relative to the number of patients treated on an ongoing basis (Table 1). Based on the calculations below, the probability of early stopping is based on the following assumptions; (α) = 0.05 and a dose-limiting toxicity rate (θ) = 0.2. To summarize this approach, suppose that Z_i (i=1,2) represents the standardized test statistic at the *i*th look (note that i=2 corresponds to the final look), then

$$|Z_i| \geq B_i,\ i=1,2$$

Where *B* denote the corresponding boundary points (critical values)

At first interim looks:

Reject H_0 if $|Z_i| \geq 2.178$ (*i.e.* $p < 0.0294$)

Otherwise, continue

At the final look:

Reject H_0 if $|Z_i| \geq 2.178$ (*i.e.* $p < 0.0294$)

We recommend the use of Pocock-type boundary for two reasons. First, it provides the best chance for early trial termination, because of its properties at the final stage of analysis if interim analysis were not planned. Second, the Pocock-type boundary allow for early stopping at each interim analysis only in the presence of a large difference. Since this study will simultaneously evaluate, a therapeutic model, the decision to stop the study early does little with regards to the logistics of the study, patients would still need to be followed in order to complete the study.

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	4	5	5	5	6	6	6	7	7	7	8	8	8	9	9

13 TRIAL MANAGEMENT

13.1 Data and Safety Monitoring Plan (DSMP)

The study will be conducted with guidance from the University of Alabama at Birmingham (UAB) Comprehensive Cancer Center's DSMP.

Oversight activities include:

- Review and process all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution Data Safety Monitoring Committee according to University of Alabama at Birmingham (UAB) Comprehensive Cancer Center's DSMP.

13.2 University of Alabama at Birmingham (UAB) Comprehensive Cancer Center's Data Safety Monitoring Committee

Sites will provide the following for the University of Alabama at Birmingham (UAB) Comprehensive Cancer Center's DSMC to review:

- Adverse event summary report
- Audit results if applicable
- Data related to stopping/decision rules described in study design
- Study accrual patterns
- Protocol deviations

The University of Alabama at Birmingham (UAB) Comprehensive Cancer Center's DSMC will review study data every quarter. Documentation of DSMC reviews will be provided to sponsor-investigator and AstraZeneca. Issues of immediate concern by the DSMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate.

13.3 Data Quality Oversight Activities

Remote validation of data will be completed on a continual basis throughout the life cycle of the study. The CTNMO will provide data handling and edit checking services and queries will be transmitted to the site to address in a timely fashion. Corrections will be made by the study site personnel.

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause audits may be performed as necessary. During onsite monitoring visits, source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by the UAB CTNMO or its designee.

The trial site may also be subject to quality assurance audit as well as inspection by appropriate regulatory agencies.

13.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to the CTNMO for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

14. DATA HANDLING AND RECORD KEEPING

14.1 Data Management

Data will be collected through a web based clinical research platform (EDC system), a system compliant with Good Clinical Practices and Federal Rules and Regulations. UAB Clinical Trial network and monitoring office (CTNMO) personnel will coordinate and manage data for quality control assurance and integrity. Select data will be collected and entered into the EDC system by study site personnel from participating institutions.

14.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in the EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and the UAB CTNMO.

14.3 Record Retention

To enable evaluations and/or audits from Health Authorities, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and retained by the site investigator in compliance with the site contract. No records will be destroyed until the UAB CTNMO confirms destruction is permitted.

14.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on

secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, AstraZeneca, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

15 ETHICS

15.1 Institutional Review Board (IRB) Approval

The final study protocol and the final version of the informed consent form must be approved in writing by an IRB. The site investigator must submit written approval by the IRB before he or she can enroll subjects into the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB, as local regulations require.

Progress reports and notifications of serious and unexpected adverse events will be provided to the IRB according to local regulations and guidelines.

15.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki. Conduct of the study will be in compliance with ICH Good Clinical Practice, and with all applicable federal (including 21 CFR parts 56 & 50), state, or local laws.

15.3 Informed Consent Process

The site investigator will ensure the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

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APPENDIX 1

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution toGrade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

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

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

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

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
			anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] − Consider Pulmonary and Infectious Disease consults. − Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. − Hospitalize the patient. − Supportive care (e.g., oxygen). − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** − Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). - When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
			– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
	(Perforation: invasive intervention not indicated)		perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, fever; ileus; peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay . – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
	indicated; Grade 4 Perforation: life-threatening consequences; urgent intervention indicated)		

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	• No dose modifications. • If it worsens, then treat as Grade 2.	– Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	• Hold study drug/study regimen dose until resolution to Grade≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

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

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

Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** - **For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Grade 1 (serum creatinine >ULN to 1.5×ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4 (Grade 3: serum creatinine	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated.

	>3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)		– Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4 (or life-threatening):** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (or life-threatening):** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis,

		or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.

	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate. –

	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict

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

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

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

Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) * Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** − Monitor symptoms daily, hospitalize. − Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. − Supportive care (e.g., oxygen). − If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.

Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1:** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

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

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.