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A Multi-Center Randomized Phase II Study of Nivolumab in Combination with Gemcitabine/Cisplatin or Ipilimumab as First Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer [CA209-9FC]

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Study Drug: Nivolumab (Opdivo®)
Ipilimumab (Yervoy®)

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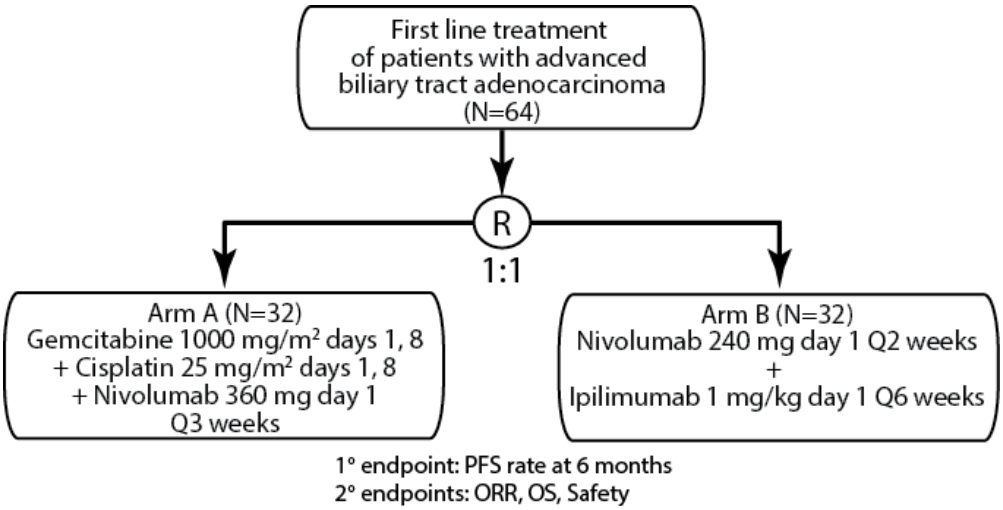
ABBREVIATIONS:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
BTC	Biliary Tract Cancer
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSU	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IND	Investigational New Drug
IRB	Institutional Review Board
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
p.o.	per os/by mouth/orally
PR	Partial Response
PRC	Protocol Review Committee
SAE	Serious Adverse Event
SD	Stable Disease
UaP	Unanticipated Problem
UMCCC	University of Michigan Comprehensive Cancer Center
WBC	White Blood Cells

STUDY SCHEMA



STUDY SYNOPSIS

Title	A Multi-Center Randomized Phase II Study of Nivolumab in Combination with Gemcitabine/Cisplatin or Ipilimumab as First Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer
Phase	Phase II
Methodology	Randomized, open-label
Study Duration	3 years
Study Center(s)	Multi-Center: up to 7 sites total including lead site: University of Michigan
Objectives	Primary objective: 1. Determine the PFS rate at 6 months in patients with advanced BTC treated with nivolumab, gemcitabine and cisplatin, or nivolumab and ipilimumab. Secondary objectives: 1. Evaluate the ORR, median PFS and OS of patients with advanced BTC. 2. Evaluate the safety of nivolumab in combination with gemcitabine and cisplatin, or ipilimumab in this patient population. Exploratory objectives: 1. To explore predictors of biomarker response and mechanisms of resistance based on the exploratory analysis of tumor tissue obtained through serial biopsies and blood. a) Levels of PD-L1 (B7-H1), PD-L2, CTLA-4, T cell subset, myeloid-derived cell subset infiltration by immunohistochemistry (IHC) at baseline, at 2 months and progression (for patients enrolled at University of Michigan). b) Whole exome genomic and transcriptomic (RNAseq) analysis for tumor biology and immune signature profiling at baseline and progression. c) PBMC collection for immune cell subset analysis including serum for future biomarker analysis.
Number of Subjects	64
Eligibility Criteria	1. Patients must have a pathologically confirmed adenocarcinoma of the biliary tract (intra-hepatic, extra-hepatic (hilar, distal) or gallbladder) that is not

	eligible for curative resection, transplantation, or ablative therapies. Tumors of mixed histology are excluded. 2. Patients may not have received prior systemic treatment (chemotherapy or targeted therapy) for advanced BTC. Prior adjuvant chemotherapy is permitted provided it was completed > 6 months from registration. 3. Prior radiation, chemoembolization, radioembolization or other local ablative therapies or hepatic resection is permitted if completed ≥ 4 weeks prior to registration AND if patient has recovered to ≤ grade 1 toxicity. Extrahepatic palliative radiation is permitted if completed ≥ 2 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity. 4. Patients must have radiographically measurable disease (as per RECISTv1.1) in at least one site not previously treated with radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation) either within the liver or in a metastatic site. 5. Must be ≥ 18 years of age 6. Must have a Child-Pugh score of A 7. Must have an ECOG performance status of 0-1 8. Ability to understand and willingness to sign IRB-approved informed consent 9. Willing to provide archived tissue, if available, from a previous diagnostic biopsy 10. Must be able to tolerate CT and/or MRI with contrast 11. Must have adequate organ function obtained ≤2 weeks prior to registration (absolute neutrophil count $\geq$1500/mm^3, hemoglobin $\geq$9 g/dL, platelets $\geq$100,000/mm^3, serum creatinine $\leq$ 1.5 x upper limit normal (ULN), creatinine clearance ≥ 50 mL/min, albumin $\geq$3.0 g/dL, AST/ALT $\leq$3.0 x ULN ($\leq$5 x ULN if liver metastasis), total bilirubin < 1.5 x upper limit normal, INR $\leq$ 1.5 upper limit normal) 12. Must not have a diagnosis of immunodeficiency, or have received systemic steroid therapy, or any other form of immunosuppressive therapy within 7 days prior to trial treatment. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed. 13. Must not have known Hepatitis B, Hepatitis C, or HIV seropositivity. Testing is not required in absence of clinical suspicion. 14. Must not have prior history of organ transplantation or brain metastasis. 15. Must not have undergone a major surgical procedure < 4 weeks prior to registration. 16. Must not have an active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ. Patients with history of malignancy are eligible provided primary treatment of that cancer was completed > 1 year prior to registration and the patient is free of clinical or radiologic evidence of recurrent or progressive malignancy. 17. Must have no ongoing active, uncontrolled infections (afebrile for > 48 hours off antibiotics). 18. Must not have received a live vaccine within 30 days of planned start of the study therapy. 19. Must not have a psychiatric illness, other significant medical illness, or social situation which, in the investigator's opinion, would limit compliance or ability to comply with study requirements. 20. Women must not be pregnant or breastfeeding since study drugs may harm the fetus or child. All females of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a negative screening pregnancy test. 21. Women of child-bearing potential and men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation, and for 5 months (for women) and 7 months (for men) following completion of study

	therapy. 22. Participants with an active, known or suspected autoimmune disease which may affect vital organ function, or has/may require systemic immunosuppressive therapy for management are excluded. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll. 23. Participants must not have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 7 days of start of treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
Study Product(s), Dose, Route, Regimen	Arm A: Gemcitabine 1000 mg/m2 IV Cisplatin 25 mg/m2 IV Nivolumab 360 mg IV Arm B: Nivolumab 240 mg IV Ipilimumab 1 mg/kg
Duration of Administration	Patients may be treated on study for no longer than 2 years. Arm A: If patient has stable disease after 8 cycles, then gemcitabine/cisplatin will be discontinued and patient will continue single agent nivolumab at 240 mg IV every 2 weeks, in absence of disease progression or unacceptable toxicity. Arm B: The patient can continue nivolumab and ipilimumab every 2 weeks in absence of disease progression or unacceptable toxicity.
Statistical Methodology	The trial is sized to compare each randomized treatment arm to a historical value for PFS in this patient population receiving standard treatment. The PFS proportion in this patient population at 6 months is 59%. Using this value as the null hypothesis, we hope to see an increase in the proportion of alive, progression-free patients to 80% or above in each of the combination arms. Thirty-two patients evaluable for the 6-month PFS endpoint are required to test this hypothesis with >80% power and at most 5% type I error (1-sided). A maximum of 64 evaluable patients will be enrolled.

1.0 BACKGROUND AND RATIONALE

1.1 Biliary Tract Cancer - Disease Overview

Biliary tract cancer (BTC) develops as a result of malignant transformation of the biliary tract mucosa and is anatomically classified as intra-hepatic, extra-hepatic (hilar and distal) and gall bladder adenocarcinoma. BTC accounts for 10-15% of all primary liver cancer cases worldwide, and its incidence is rising (Shaib, Davila et al. 2004). Advanced BTCs are aggressive tumors with median survival time from diagnosis of less than 12 months (Valle, Wasan et al. 2010), and five-year overall survival (OS) of ~5% despite therapy (Nathan, Pawlik et al. 2007). The options for systemic chemotherapy for patients with advanced BTC remains limited with only a few meaningful improvements made over the past few decades. Valle et al randomly assigned 410 patients with locally advanced or metastatic BTC to receive gemcitabine with or without cisplatin in the phase III ABC-02 trial (Valle, Wasan et al. 2010). Patients on the gemcitabine cisplatin arm demonstrated an improvement in OS (11.7 versus 8.1 months; hazard ratio (HR), 0.64; 95% CI, 0.52 to 0.80; p>0.001) as compared to the gemcitabine alone arm. The following clinically relevant grade 3 and 4 adverse events were noted in the gemcitabine/cisplatin arm: neutropenia (25.3%), anemia (7.6%), thrombocytopenia (15.7%), abnormal liver function (16.7%), fatigue (18.7%), nausea (4%), vomiting (5.1%), impaired renal function (1.5%), infection (18.2%), deep vein thrombosis (2%), and thromboembolic event (3.5%). This result established the gemcitabine and cisplatin combination as a standard first line regimen for patients with advanced BTC.

1.2 Role of Checkpoint Inhibitors in BTC

T-cell activation requires dual signaling from the T-cell receptor and an additional co-stimulatory molecule (Peggs, Quezada et al. 2006, Robert and Ghiringhelli 2009). The first signal includes binding of the T-cell receptor to antigens presented by antigen presenting cells (APCs). Subsequently, the B7 (CD80, CD86) ligand binds to CD28 which is a co-stimulatory receptor. This signaling leads to T-cell proliferation, cytokine release and upregulation of the immune response. As a result, cytotoxic T lymphocyte antigen 4 (CTLA-4) is upregulated and competes with the CD28 receptor for B7 binding. CTLA-4 has higher affinity than the CD28 receptor and therefore T-cell response is ultimately down-regulated. PD-1 is a member of the CD28/CTLA-4 family of T-cell costimulatory receptors that includes CD28, CTLA-4, ICOS and BTLA (Freeman, Long et al. 2000). PD-1 is expressed on activated T cells, B cells and myeloid cells (Nishimura and Honjo 2001). There are 2 ligands, PD-L1 and PD-L2 that are specific for PD-1. Once they bind to PD-1, down-regulation of T-cell activation occurs (Latchman, Wood et al. 2001, Carter, Fouser et al. 2002). When the PD-1 ligand binds to the PD-1 receptor, T-cell activation is blocked. CTLA-4 and PD-1 are negative regulators of T-cell response that prevent autoimmunity and allows tolerance to self-antigens (Peggs, Quezada et al. 2006). If these interactions are interrupted, the checkpoint is turned off which can lead to enhanced antitumor T-cell activation.

Nivolumab (Opdivo™), a fully human immunoglobulin G4 programmed death-1 (PD-1) immune checkpoint inhibitor antibody, binds with high affinity to PD-1 receptors on T cells, blocking their interaction with PD ligands 1 and 2 (PD-L1/PD-L2) and restoring T-cell antitumor function (Rizvi, Hellmann et al. 2016). Twenty-three PD-L1 positive patients with advanced BTC were enrolled in the KEYNOTE-028 phase 1b trial of pembrolizumab (another anti-PD-1 antibody) monotherapy. Within this cohort of heavily pretreated patients, an ORR of 17.4% (N=4; 95% CI, 5.0-38.8) was demonstrated and an additional 4 patients had stable disease for a disease control rate of 35% (Bang, Doi et al. 2015). At the time of this report, the median response duration had not yet been reached (range, 5.4+ to 9.3+ weeks). Adverse events were generally consistent with previously reported safety data for pembrolizumab. There were no treatment-related deaths. Five patients,

including all responders, remain on treatment more than 40 weeks (Bang, Doi et al. 2015).

Ipilimumab (Yervoy™) is a fully human monoclonal immunoglobulin (Ig) G1κ specific for human CTLA-4. Ipilimumab binds to CTLA-4 and inhibits its interaction with B7 ligands (CD80, CD86) on APCs which can augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response (Ipilimumab Investigator Brochure, 2015). While the toxicity and clinical responses overlap, mechanisms of immune activation and range of responses appear to be different for ipilimumab and nivolumab. Preclinical data suggests the combination of nivolumab and ipilimumab enhances T-cell antitumor activity. This combination is FDA approved in patients with melanoma, and is being currently investigated in patients with non-small cell lung cancer (NCT02477826), bladder cancer (NCT02553642), advanced solid tumors (NCT01928394), pancreatic cancer (NCT01928394) and hepatocellular carcinoma (NCT01658878).

Melanoma. The combination of nivolumab plus ipilimumab was investigated in a phase III clinical trial in untreated melanoma and showed improved median progression-free survival (11.5 months; 95% CI, 8.9 to 16.7 months) compared to nivolumab or ipilimumab alone (P<.001) [12]. The most frequent treatment-related select adverse events of grade 3 or 4 were diarrhea (in 2.2% of patients in the nivolumab group, 9.3% of those in the nivolumab-plus-ipilimumab group, and 6.1% of those in the ipilimumab group), colitis (in 0.6%, 7.7%, and 8.7%, respectively), and increased alanine aminotransferase level (in 1.3%, 8.3%, and 1.6%, respectively) (Larkin, Chiarion-Sileni et al. 2015).

Small cell lung cancer (SCLC). CheckMate-032 is a phase 1/2 open-label trial, evaluating the safety and efficacy of *nivolumab* monotherapy, or *nivolumab* combined with *ipilimumab*, in advanced or metastatic solid tumors at different doses and schedules. The CheckMate-032 SCLC cohort included 180 patients with progressive disease after one or more prior lines of therapy, including a first-line platinum-based chemotherapy regimen. In this analysis, patients received *nivolumab* monotherapy 3 mg/kg administered intravenously every two weeks, or *nivolumab* 1 mg/kg plus *ipilimumab* 3 mg/kg, every three weeks for four cycles followed by *nivolumab* 3 mg/kg every two weeks. All patients were treated until disease progression or unacceptable toxicity. The confirmed objective response rate (primary objective) was 31% (n=14/45) in patients who received *nivolumab* plus *ipilimumab* and was 13% (n=7/55) with *nivolumab* alone. *Grade 3–4 treatment-related adverse events (TRAEs) occurred in 11% of pts in nivolumab alone arm, and 32% of patients in the nivolumab 1mg/kg + ipilimumab 3mg/kg arm; 5% and 13% discontinued due to TRAEs, respectively. One TR death due to myasthenia gravis occurred in the combination arm (Antonia, Lopez-Martin et al. 2016).*

Renal cell cancer (RCC). In the CheckMate-016 study, patients with metastatic RCC were randomized to either nivolumab 3 mg/kg + ipilimumab 1mg/kg (n=47) or nivolumab 1 mg/kg + ipilimumab 3 mg/kg (n=47). After a median follow-up of 22 months, the overall response rate was 40% in each arm, with median PFS of 6.6 months with nivolumab 3 + ipilimumab 1 and 9.1 months with nivolumab 1 + ipilimumab 3. Less frequent grade 3/4 treatment-related adverse effects were reported with nivolumab 3 + ipilimumab 1 compared with nivolumab 1 + ipilimumab 3 (38% vs 62%). The most common were ↑ lipase (15% vs 28%), ↑ ALT (4% vs 21%), diarrhea (4% vs 15%), ↑ AST (4% vs 13%), and colitis (0% vs 15%) respectively. The most common grade 3–4 select treatment-related AEs were gastrointestinal (4% vs 23%) and hepatic (6% vs 21%) respectively. High dose ipilimumab showed dose-related toxicity, which further supports development of nivolumab 3 mg/kg + ipilimumab 1mg/kg in the first-line setting (Hammers, Plimack et al. 2016).

1.3 Role of Chemotherapy in Conjunction with Checkpoint Inhibitors

Chemotherapy has been shown to lead to the upregulation of PD-L1 expression (Peng, Hamanishi et al. 2015). In addition, chemotherapy can enhance tumor antigen presentation by upregulating the production of tumor neoantigens, or expression of the MHC class I molecules to which these antigens bind. Alternatively, chemotherapy may upregulate co-stimulatory molecules (e.g. B7-1) or downregulate co-inhibitory molecules (e.g. PD-L1/B7-H1 or B7-H4) expressed on the tumor cell surface, enhancing the strength of effector T-cell activity. Chemotherapy may also render tumor cells more sensitive to T cell–mediated lysis through fas-, perforin-, and Granzyme B–dependent mechanisms (Emens and Middleton 2015). Gemcitabine is an example of an immunomodulatory chemotherapeutic agent with pleiotropic immune effects. Gemcitabine induces tumor cell apoptosis and enhances cross-priming of CD8+ T cells in animal models (Nowak, Lake et al. 2003). It also reverses defective cross-presentation of tumor antigens by tumor-infiltrating dendritic cells (McDonnell, Lesterhuis et al. 2015). Cisplatin is another immunomodulatory chemotherapeutic agent that has been showed to stimulate tumor infiltration of inflammatory APCs expressing relatively high levels of T-cell so-stimulatory ligands (e.g. B7).

The immunogenic properties of conventional chemotherapy and rapid emergence of chemotherapy resistance provide a good rationale for combining gemcitabine plus cisplatin with immunotherapy, particularly immune checkpoint inhibitors. CheckMate 012, a phase I, multicohort study, was conducted to explore the safety and efficacy of nivolumab as monotherapy or combined with current standard therapies in first-line advanced non-small cell lung cancer. Patients (n = 56) received nivolumab plus platinum-doublet concurrently every 3 weeks for four cycles followed by nivolumab alone until progression or unacceptable toxicity. Regimens were nivolumab 10 mg/kg plus gemcitabine-cisplatin (squamous) or pemetrexed-cisplatin (nonsquamous) or nivolumab 5 or 10 mg/kg plus paclitaxel-carboplatin (all histologies). The primary objective was to assess safety and tolerability. Secondary objectives included objective response rate and 24-week progression-free survival rate. The objective response rates for nivolumab 10 mg/kg plus gemcitabine-cisplatin was 33% along with progression-free and overall survival rates of 51% and 25% at 2 years, respectively (Rizvi, Hellmann et al. 2016).

1.4 Rationale

Patients with advanced, unresectable or metastatic BTC have a poor prognosis despite systemic chemotherapy. The median PFS with first-line gemcitabine and cisplatin is expected to be 8 months. The immunogenic properties of conventional chemotherapy and rapid emergence of chemotherapy resistance provide a good rationale for combining chemotherapy with immunotherapy, particularly immune checkpoint inhibitors (Rizvi, Hellmann et al. 2016). Monotherapy with pembrolizumab, another anti PD-1 antibody, has demonstrated activity in patients with heavily pre-treated, advanced BTC. Additionally, inhibition of CTLA-4 signaling via ipilimumab can also reduce T-regulatory cell function, and the combination of nivolumab and ipilimumab has been shown to improve clinical efficacy in several solid cancers in comparison with anti PD-1 alone.

Therefore, we hypothesize that PD-1 receptor inhibition in combination with systemic chemotherapy, or ipilimumab will improve the progression-free and overall survival in this population without increasing toxicity. These results are expected to have an important positive impact because they will provide a strong evidence-guided understanding of BTC microenvironment and identification of potential biomarkers of response (and resistance) to inform a phase III clinical trial of immunotherapy in BTC.

1.5 Correlative Studies

We will study the BTC tumor microenvironment through the use of pre-treatment tissue (all sites) as well as on-treatment (for patients at University of Michigan) and post-

treatment (optional for patients enrolled at all sites) tumor biopsies. In addition, blood will be collected as detailed in the schedule of events/study calendar. Identification of important biologic subsets of BTC patients that may have clinical efficacy from nivolumab and ipilimumab will be the overarching goal of these translational studies along with developing biologic insights for future therapeutic development. Biologic readouts for PD-1 and CTLA4 response biomarkers will be assessed along with specific markers of tumor infiltrating leukocytes (TILs). Biologic markers and RNA expression will be examined in the context of immunologic correlates, tumor biology, and therapeutic efficacy.

2.0 STUDY OBJECTIVES

2.1 Primary Objectives

2.1.1 Determine the PFS rate at 6 months in patients with advanced BTC treated with nivolumab, gemcitabine and cisplatin, or nivolumab and ipilimumab

2.2 Secondary Objectives

2.2.1 Evaluate the ORR, median PFS and OS of patients with advanced BTC.

2.2.2 Evaluate the safety of nivolumab in combination with gemcitabine and cisplatin, or ipilimumab in this patient population.

2.3 Exploratory Objectives

2.3.1 To explore predictors of biomarker response and mechanisms of resistance based on the exploratory analysis of tumor tissue obtained through serial biopsies and blood.

a) Levels of PD-L1 (B7-H1), PD-L2, CTLA-4, T cell subset, myeloid-derived cell subset infiltration by immunohistochemistry (IHC) at baseline (for all patients), at 2 months and progression (for patients enrolled at University of Michigan)
b) Whole exome genomic and transcriptomic (RNAseq) analysis for tumor biology and immune signature at baseline and progression
c) PBMC collection for immune cell subset analysis including serum for future biomarker analysis

2.4 Endpoints Assessment

2.4.1 Primary Endpoint Assessment: The progression-free survival (PFS) will be defined as time from date of treatment to date of radiological or clinical progression (leading to withdrawal from the study), or death from any cause, whichever comes first. Follow-up time will be censored at the date of last disease evaluation.

2.4.2 Secondary Endpoint Assessment: Overall response rate (ORR) will be determined as per the combined RECISTv1.1 and irRECIST criteria. Overall survival (OS) will be defined from the date of treatment to either date of death or censoring. Adverse events and reportable serious events are defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events (CTCAE) v4.03).

3.0 PATIENT ELIGIBILITY

Subjects must meet all of the eligibility criteria to be enrolled to the study. Study treatment may not begin until a subject is enrolled.

3.1 Eligibility Criteria

3.1.1 Patients must have a pathologically confirmed adenocarcinoma of the biliary tract (intra-hepatic, extra-hepatic (hilar, distal) or gallbladder) that is not eligible for curative resection, transplantation, or ablative therapies. Tumors of mixed histology are excluded.

3.1.2 Patients may not have received prior systemic treatment (chemotherapy or targeted therapy) for advanced BTC. Prior adjuvant chemotherapy is permitted provided it was completed > 6 months from registration.

3.1.3 Patients may have received prior radiation, chemoembolization, radioembolization or other local ablative therapies or hepatic resection if completed ≥ 4 weeks prior to registration AND if patient has recovered to ≤ grade 1 toxicity. Extrahepatic palliative radiation is permitted if completed ≥ 2 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity

3.1.4 Patients must have radiographically measurable disease (as per RECISTv1.1) in at least one site not previously treated with radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation) either within the liver or in a metastatic site.

3.1.5 Must be ≥ 18 years of age.

3.1.6 Must have a Child-Pugh score of A.

3.1.7 Must have an ECOG performance status of 0-1.

3.1.8 Ability to understand and willingness to sign IRB-approved informed consent.

3.1.9 Willing to provide archived tissue, if available, from a previous diagnostic biopsy.

3.1.10 Must be able to tolerate CT and/or MRI with contrast.

3.1.11 Must have adequate organ function obtained ≤ 2 weeks prior to registration:

absolute neutrophil count	≥ 1500/mm^3
hemoglobin	≥ 9 g/dL
platelets	≥ 100,000/mm^3
serum creatinine	≤ 1.5 x ULN
creatinine clearance	≥ 50 mL/min
albumin	≥ 3.0 g/dL
AST/ALT	≤ 3.0 x ULN (≤5 x ULN if liver metastasis)
total bilirubin	≤ 1.5 x ULN
INR	≤ 1.5 ULN

3.1.12 Must not have a diagnosis of immunodeficiency, or have received systemic steroid therapy, or any other form of immunosuppressive therapy within 7 days prior to trial treatment. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed.

3.1.13 Must not have known Hepatitis B, Hepatitis C, or HIV seropositivity. Testing is not required in absence of clinical suspicion.

3.1.14 Must not have prior history of organ transplantation or brain metastasis.

3.1.15 Must not have undergone a major surgical procedure < 4 weeks prior to registration.

3.1.16 Must not have an active second malignancy other than non-melanoma skin cancer or cervical carcinoma in situ. Patients with history of malignancy are eligible provided primary treatment of that cancer was completed > 1 year prior to registration and the patient is free of clinical or radiologic evidence of recurrent or progressive malignancy.

3.1.17 Must have no ongoing active, uncontrolled infections (afebrile for > 48 hours off antibiotics)

3.1.18 Must not have received a live vaccine within 30 days of planned start of the study therapy.

3.1.19 Must not have a psychiatric illness, other significant medical illness, or social situation which, in the investigator's opinion, would limit compliance or ability to comply with study requirements.

3.1.20 Women must not be pregnant or breastfeeding since study drugs may harm the fetus or child. All females of childbearing potential (not surgically sterilized and between menarche and 1 year post menopause) must have a negative screening pregnancy test.

3.1.21 Women of child-bearing potential and men must agree to use 2 methods of adequate contraception (hormonal plus barrier or 2 barrier forms) OR abstinence prior to study entry, for the duration of study participation and for 5 months (for women) and 7 months (for men) following completion of study therapy.

3.1.22 Participants with an active, known or suspected autoimmune disease which may affect vital organ function, or has/may require systemic immunosuppressive therapy for management are excluded. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.1.23 Participants must not have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 7 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Patient registration and randomization for this trial will be centrally managed by the Oncology Clinical Trials Support Unit (i.e. the Coordinating Center) of The University of Michigan Comprehensive Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the participating site on the Screening and Enrollment Log provided by the Coordinating Center.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been

determined, a copy of the completed Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to [redacted]

A Multi-Site Coordinator of the Coordinating Center, who acts as the registrar, will review the submitted documents and process the registration. Sites should inform the Multi-Site Coordinator of a potential registration by 5 p.m. on the day prior to registration. Same day registrations cannot be guaranteed.

The registrar will send an email to the requesting site registrar to confirm patient registration and randomization and to provide the study identification number and randomization number assigned to the patient. In addition, a copy of the completed Eligibility Worksheet signed and dated by the registrar will be sent back to the requesting site registrar.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment Dosage and Administration

Protocol treatment must start within 14 calendar days of randomization otherwise the patient will be taken off study. Re-screening is allowed.

5.1.1 Arm A: Nivolumab once every 3 weeks in combination with gemcitabine and cisplatin was evaluated in the CheckMate 012 trial in non-small cell lung cancer (Rizvi, Hellmann et al. 2016). The safety profile of nivolumab plus gemcitabine and cisplatin is consistent with that expected for individual agents. Nivolumab 360 mg every 3 week dose has/is being investigated in multiple clinical trials in combination with chemotherapy for ease of administration (NCT02967133, NCT02864251 and NCT02434081).

TABLE 1. Arm A – Regimen Description

Agent	Prophylaxis	Dose	Route[2]	Schedule[3]		Cycle Length
Gemcitabine	per institutional policy	1000 mg/m^2 per commercial package insert	IV over 25 – 35 minutes **before** cisplatin	Cycles 1 through 8	Days 1 and 8	3 weeks (21 days)
Cisplatin		25 mg/m^2 per commercial package insert	IV over 25 – 65 minutes **after** gemcitabine		Days 1 and 8	
Nivolumab[1]		360 mg per commercial package insert	IV over 25 – 65 minutes **after** cisplatin		Day 1	
		240 mg per commercial package insert	IV over 25 – 65 minutes		Day 1	
		240 mg per commercial package insert	IV over 25 – 65 minutes	Day 1 of Cycles 9+		2 weeks (14 days)

[1] If both gemcitabine and cisplatin are discontinued prior to 8 cycles of protocol treatment, then nivolumab may be continued alone at 240 mg IV every 2 weeks. If the patient has stable disease on imaging after 8 cycles, then they will discontinue gemcitabine and cisplatin, and continue single agent nivolumab at 240 mg IV every 2 weeks, in absence of disease progression or unacceptable toxicity.

[2] Infusion times may be extended as needed for safety (e.g. infusion reaction occurs). These instances should be documented in the patient medical records.

[3] As per section 5.6, patients may not be treated on study for longer than 2 years.

5.1.2 Arm B. Nivolumab and ipilimumab combination has been studied in multiple cancers and is FDA approved for melanoma. The safety profile of nivolumab plus ipilimumab is consistent with that expected for individual agents (Larkin, Chiarion-Sileni et al. 2015). Nivolumab 240 mg every 2 week dose is FDA approved for use in renal cell carcinoma, metastatic melanoma and non-small cell lung cancer.

TABLE 2. Arm B – Regimen Description[1]					
Agent	**Prophylaxis**	**Dose**	**Route[2]**	**Schedule[3]**	**Cycle Length**
Nivolumab	per institutional policy	240 mg per commercial package insert	IV over 25 – 65 minutes **before** ipilimumab	Day 1 of each Cycle	2 weeks (14 days)
Ipilimumab		1 mg/kg per commercial package insert	IV over 25 – 65 minutes **after** nivolumab	Day 1 of every 3rd Cycle	

[1] The patient can continue nivolumab every 2 weeks and ipilimumab every 6 weeks, in absence of disease progression or unacceptable toxicity.
[2] Infusion times may be extended as needed for safety (e.g. infusion reaction occurs). These instances should be documented in the patient medical records.
[3] As per section 5.6, patients may not be treated on study for longer than 2 years.

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.4). Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.3. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Table 3: Dose Modifications			
Arm A			
Gemcitabine	**Current Dose**	**Percentage Decrease**	**Modified Dose**
	1000 mg/m^2	20%	800 mg/m^2
	800 mg/m^2	20%	640 mg/m^2
	640 mg/m^2	100%	Discontinue
Cisplatin	25 mg/m^2	20%	20 mg/m^2
	20 mg/m^2	20%	16 mg/m^2
	16 mg/m^2	100%	Discontinue
Nivolumab	360 mg	100%	Discontinue
	240 mg	100%	Discontinue
Arm B			
Nivolumab	240 mg	100%	Discontinue
Ipilimumab	1 mg/kg	100%	Discontinue

5.2.1 All dose reductions will be permanent unless otherwise noted.

5.2.2 If more than one toxicity occurs requiring dose reduction, the dose administered should be based on the most severe toxicity.

5.2.3 Treatment delay of more than 28 days from last intended therapy will result in treatment discontinuation.

5.2.4 If one of the drugs is discontinued due to toxicity attributed to that agent, the patient will be allowed to continue a modified regimen with the remaining study arm agent/s. For Arm A however, monotherapy with cisplatin is not permitted, though monotherapy with gemcitabine is allowed. Additionally, if both gemcitabine and cisplatin are held, then also hold nivolumab. If both gemcitabine and cisplatin are discontinued, then nivolumab may be continued alone at 240 mg.

5.2.5 Nivolumab and/or ipilimumab cannot be dose reduced in response to toxicity, and can only be discontinued as per detailed algorithms for immune-therapy toxicity management in Appendix III.

5.2.6 Patients on Arm B may be allowed to continue nivolumab monotherapy if toxicity is deemed related to ipilimumab and deemed safe to continue as per the treating investigator.

5.2.7 Investigators should consider dose re-calculation of gemcitabine and/or cisplatin with change in BSA as per standard of care/institutional guidelines. However, a change in BSA by 10% or more should lead to a dose re-calculation.

5.2.8 Investigators should consider dose re-calculation of ipilimumab with change in weight as per standard of care/institutional guidelines. However, a change in weight by 10% or more should lead to a dose re-calculation.

5.2.9 Missed Dose: If the regimen held or missed was to be given on Day 1 then that next cycle will not be considered to start until the day the first dose is actually administered. Held doses of either or both gemcitabine and cisplatin on Day 8 will be considered omitted.

TABLE 4. Day 1 Dose Modifications for Hematologic Toxicity for Gemcitabine and Cisplatin in Arm A	
Hematologic Toxicity	**Dose Adjustment for Gemcitabine and/or Cisplatin**
ANC[1] ≥ 1000/mm^3 AND Platelets ≥ 100,000/mm^3	Treat as scheduled
ANC[1] < 1000/mm^3 OR/AND Platelets < 100,000/mm^3	Hold both gemcitabine and cisplatin up to a maximum of 28 days until ANC ≥ 1000/mm^3 AND platelets ≥ 100,000/mm^3 then resume at next lower dose level for either or both gemcitabine and cisplatin as detailed in Table 3. If not resolved, then discontinue all treatment.
[1]Note: Growth factors may be added for low ANC BEFORE a dose reduction is instituted at the treating physician's discretion.	

Table 5: Day 8 Dose Modifications for Hematologic Toxicity for Gemcitabine and Cisplatin in Arm A		
Hematologic Toxicity	**Dose Adjustment for Gemcitabine**	**Dose Adjustment for Cisplatin**
ANC[1] ≥1000/mm^3 AND Platelets ≥ 75,000/mm^3	No change in dose	No change in dose
ANC[1] 500-999/mm^3 OR Platelets 50,000-74,999/mm^3	Decrease Day 8 dose by 1 dose level for this cycle Consider decrease Day 1 & 8 by 1 dose level for subsequent cycles	Decrease Day 8 dose by 1 dose level for this cycle Consider decrease in Day 1 & 8 dose by 1 dose level for subsequent cycles
ANC[1] <500/mm^3 OR Platelets <50,000/mm^3	Hold Day 8 treatment Decrease Day 1 & 8 by 1 dose level for subsequent cycles	Hold Day 8 treatment Decrease in Day 1 & 8 dose by 1 dose level for subsequent cycles

Table 6: Day 1 & 8 Dose Modifications for Non-Hematologic Toxicity for Gemcitabine and Cisplatin in Arm A		
Non-Hematologic Toxicity	**Dose Adjustment for Gemcitabine**	**Dose Adjustment for Cisplatin**
Alopecia, anemia, venous thromboembolism	No modification to doses	

Grade ≥3 Nausea and vomiting (ongoing after maximal anti-emetic therapy)	Consider decrease or discontinuation of cisplatin	No change in dose
Grade ≥2 Hyperbilirubinemia	Hold both gemcitabine and cisplatin up to a maximum of 28 days until toxicity resolves to Grade ≤ 1, then resume at same doses as before. If not resolved, then discontinue all treatment. Doses will not be modified for cholangitis attributable to biliary obstruction/stent occlusion unless this occurs in the setting of >grade 3 neutropenia	
Grade ≥3 possibly attributable to cytotoxic treatment	Hold all protocol treatment and monitor toxicity weekly. If toxicity resolves to ≤ Grade 1 within 4 weeks, treatment may be resumed with one dose level reduction gemcitabine and cisplatin.	
≥Grade 3 Peripheral neuropathy	No change in dose	Hold cisplatin up to a maximum of 28 days until toxicity resolves to Grade ≤ 2, then resume at same dose or next lower dose level.
≥Grade 2 Creatinine increase (>1.5 x ULN)	No change in dose	Hold cisplatin and assess hydration and general medical status of the patient. Cisplatin may be resumed if creatinine improves to <1.5 x ULN with 1 dose level reduction.

Note: Laboratory abnormalities that are not directly attributable to treatment (i.e., hyperglycemia) or not clinically relevant (i.e., lymphopenia) do not require modification of dosing. All dose adjustments for toxicity of gemcitabine and/or cisplatin will be described in the clinical record.

5.3 Management Algorithms for Immuno-Oncology Agents

Nivolumab and ipilimumab are associated with immune related adverse events secondary to the unrestrained T cell activation. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events:

Gastrointestinal
Renal
Pulmonary
Hepatic
Endocrinopathies
Skin
Neurological

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria in Appendix III must be reported as SAEs.

Please refer to Appendix III for algorithm details.

5.4 Concomitant Medications/Treatments

The following concomitant medications or treatments are not permitted while the patient is currently receiving therapy on the protocol:

- Other investigational agents
- Immunosuppressive medications, including systemic corticosteroids, excluding prophylactic use of steroids per institutional protocol.
- Concurrent radiation

5.5 Other Modalities or Procedures

None

5.6 Duration of Therapy

Treatment may continue for a total of 2 years (discontinue gemcitabine/cisplatin in Arm A after 8 cycles) or until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.7 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.6 apply. Document in the source the reason for ending protocol therapy and the date the patient was removed from treatment. All patients who discontinue treatment should comply with protocol specific follow-up procedures as outlined in Section 5.8. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.8 Duration of Follow-Up

After treatment discontinuation, follow-up for survival and initiation of any other anti-cancer therapies will be documented every 3 months via telephone or office visit documentation for up to 2 years from treatment discontinuation or until death, whichever comes first, or 3 years after first date of treatment initiation for those that remain on treatment. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5.9 Off Study Criteria

Patients can be taken off study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation from study will be documented and may include:

5.9.1 Patient withdraws consent (termination of treatment and follow-up);

5.9.2 Patient becomes pregnant;

5.9.3 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;

5.9.4 Termination of the study by the Sponsor-Investigator, or the FDA;

5.9.5 Patient completes protocol treatment and follow-up criteria;

5.10 Patient Replacement

All patients who receive at least one dose of study therapy will be considered evaluable.

Patients enrolled in the study will be considered non-evaluable under the following case scenarios and replaced by additional patients:

1. Patients who received no investigational therapy.
2. Patients who withdrew consent for study therapy prior to first response evaluation.
3. Patients meeting off study criteria 5.9.2 and 5.9.3.

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures

Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

6.2 Time and Events Table/Schedule of Events/Study Calendar

Table 7. Study Calendar								
Procedures	Screening[1]	Arm A			Arm B		EOT Visit[8]	Follow-Up Q3 months +/- 1 week[9]
		Cycle 1		Cycle X	Cycle 1	Cycle X		
		Day 1	Day 8	Day 1	Day 1	Day 1		
Informed Consent	X							
History, Physical Examination	X	X		X[12]	X	X[13]	X	
Weight, BSA	X	X		X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	
Performance Status	X	X		X[12]	X	X[13]	X	
Toxicity Evaluations		X	X	X[12]	X	X[13]		
Scans with Tumor Measurements	X			X[5]		X[5]		
CBC with differential	X	X	X	X[12]	X	X[13]		
CMP[2]	X		X	X[12]	X	X[13]		
TSH, free T4, free T3, random cortisol, lipase	X			X[11]		X[11]		
CA 19-9, CEA	X	X		X[10]	X	X[10]	X	
PT, PTT	X							
Pregnancy Test[3]	X	X						
Concomitant Medication Review	X	X		X[12]	X	X[13]		
ECG	X							
Research Blood[4]		X		X	X	X	X	
Tissue[6]	X			X		X	X	
Study Drug Administration[7]		X	X	X	X	X		
Survival Follow-up								X

1. All screening procedures to be completed within 2 weeks of registration, except imaging which should be ≤ 4 weeks.
2. Comprehensive metabolic panel includes BUN/creatinine, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin and total protein.
3. Required for females of childbearing potential. Serum or urine pregnancy test per site investigator discretion.

4. Specimens will be collected prior to administration of initial dose, prior to Cycle 4 Day 1 drug administration, and at time of EOT (drawn only once per time point). Refer to the lab manual for sample collection and processing details.
5. MRI or CT (abdomen/pelvis) with contrast along with CT chest with/without contrast will be assessed every 8 ± 1 weeks. Imaging assessment of scans at the site should be completed by either a radiologist or an imaging core, and not by the oncologist nor via abstraction of data from the subjective/clinical radiology report.
6. Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery. Procurement of tissue is mandatory for enrollment however, all biopsies are optional. If tissue from initial biopsy is not available, a repeat biopsy is NOT required and patient will be eligible for enrollment. Cycle X Day 1 biopsies will only be collected for patients enrolled at the University of Michigan, and should be completed after at least 4 cycles of treatment and prior to the 9th cycle of treatment. Refer to the lab manual for sample collection and processing details.
7. See Section 5.1 for details. Study drug administration with associated labs will have a window of ± 3 days.
8. End of treatment (EOT) visit should be completed within 30 days of last treatment. And if possible, biopsy should be collected prior to start of subsequent therapy.
9. Patients will be followed every 3 months via telephone or office visit documentation for up to 2 years from treatment discontinuation or until death, whichever comes first, or 3 years after first date of treatment initiation for those that remain on treatment.
10. Check CA 19-9 and CEA every 6 +/- 1 weeks prior to infusion. May be delayed if infusion is not scheduled within the window.
11. Check TSH, free T3, free T4, and lipase every 6 +/ - 1 weeks prior to infusion. May be delayed if infusion is not scheduled within the window. Random cortisol is required only at baseline.
12. Required every CXD1 for cycles 1 through 8, and every even cycle thereafter (e.g. cycles 10, 12, 14, etc.).
13. Required every odd cycle (e.g. cycles 3, 5, 7, etc.).

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Immunotherapy drugs such as nivolumab and ipilimumab can initially cause inflammation in the early stages of treatment. Immune-related RECIST (irRECIST) utilizes RECISTv1.1 but considers an inflammatory response (or "pseudo-progression") as normal. The main difference between RECISTv1.1 and irRECIST is that patients can stay on trial after the first progressive disease (PD) assessment (as per RECISTv1.1) if using immune-related RECIST criteria. This PD per RECISTv1.1 is then re-labeled as immune related stable disease (irSD) per irRECIST and requires addition of unidimensional measurements of all new lesions (that meet the definition of target lesion) to be added to the sum of longest diameters (SLD) calculation for response assessment. Importantly, immune-related progression (irPD) must be confirmed by a follow-up scan at least 4 weeks (within 4-8 weeks) following the initial PD/irSD assessment in order to take the patient off the trial.

Subjects that are deemed to have clinical progression and unstable should not be continued on therapy after PD (per RECISTv1.1) and are therefore not required to have repeat tumor imaging for confirmation as per irPD definition. It is at the discretion of the site investigator whether to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision by the site investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for primary endpoint, PFS at 6 months. All patients that receive at least one dose of study therapy will be considered evaluable. Patients enrolled and/or randomized to therapy but that never receive study therapy will be replaced.

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

7.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung)

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

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

Note: Tumor lesions that are situated in a previously irradiated area will only be considered measurable, if they have had subsequent progression by at least 5 mm.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm using CT scan), are considered non-measurable disease. Bone lesions without measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (non-nodal lesions with the longest diameter), be representative of all involved organ(s), but in addition should be those that lend themselves to reproducible repeated measurements. If a non-nodal lesion is either not present or is initially measured with longest diameter <10mm as a non-target then grows to ≥10mm after baseline, this lesion then becomes a new target lesion as per irRECIST criteria. The non-nodal longest diameter is then added to the sum of diameters, and patient response is calculated with the new lesion.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. Pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the nodal measurement. All other pathological nodes (those with short axis ≥10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease. If a non-target lymph node grows to ≥15mm after baseline, this node then becomes a new target lesion as per irRECIST. The nodal short axis is then added to the sum of diameters, and patient response is calculated with the new lesion.

Non-target lesions. All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required, and these lesions should be followed as ‘present’, ‘absent’, or in rare cases ‘unequivocal progression’

(more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

7.1.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start date and never more than 4 weeks before the beginning of the treatment.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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

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

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

7.1.4 Response Criteria

7.1.4.1 Evaluation of Target Lesions

Prior to the first PD assessment, patients will be evaluated according the following RECISTv1.1 response:
Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR (taking as reference the baseline sum LD) nor sufficient increase to qualify for PD (taking as reference the smallest sum LD since the treatment started).

After the first PD assessment per RECISTv1.1 (=irSD per irRECIST), patients will be evaluated for irPD at least 4 weeks apart according to the following definition:

Immune-related Progressive Disease (irPD): At least a 20% increase in the sum of the LD of target lesions (with a minimum absolute increase of 5 mm), taking as reference the smallest sum LD recorded since the treatment started, or appearance of new lesions since the last evaluation.

7.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions. All lymph nodes should be non-pathological in size (<10 mm short axis)

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Although a clear progression on non-target lesions in absence of stable target lesions is exceptional, *the opinion of the treating physician should prevail in such circumstances*.

7.1.4.3 Evaluation of Best Overall Response

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

Evaluation as per combined RECISTv1.1/irRECIST

Target Lesions	Non-Target Lesions	New Lesions	Overall Response per RECISTv1.1	Overall Response per irRECIST	Confirmed Response for this Category Requires:
CR	CR	No	CR	NA	≥4 wks. confirmation
CR	CR Non-CR/PD	No	PR	NA	≥4 wks. confirmation
PR	CR Non-CR/PD	No			
SD	CR Non-CR/PD	No	SD	NA	Documented at least once ≥4 wks. from baseline
PD	Any	Any	PD	irSD	≥4 wks. confirmation
Any	PD*	Any			
Any	Any	Yes			
PD	Any	Any	NA	irPD	No further confirmation required
Any	PD*	Any			
Any	Any	Yes			

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

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

NA=not applicable

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

7.1.4.4 Treatment Beyond Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.

Subjects treated on either Arm A or B will be permitted to continue study treatment beyond initial RECISTv1.1 defined PD, assessed by the investigator, as long as they meet the following criteria:

- Investigator determined clinical benefit
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

A radiographic assessment/ scan should be performed within 4-8 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD (termed irPD). The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Study Calendar (see Table 7).

Immune-related Progressive Disease (irPD): For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD, unequivocal worsening of NT lesions, or appearance of new lesions since the last evaluation. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression (i.e. irPD).

7.1.5 Duration of Response

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

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

7.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

7.2 Safety/Tolerability

Analyses will be performed for all patients having received at least one dose of study drug. The study will use the CTCAE version 4.0.3 for reporting of non-hematologic adverse events (http://ctep.cancer.gov/reporting/ctc.html).

8.0 ADVERSE EVENTS

8.1 Adverse Event Reporting Requirements

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial and is done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Data on adverse events will be collected from the time of the initial study treatment administration through 100 days after the last dose of study treatment. Any serious adverse event that occurs more than 100 days after the last study treatment and is considered related to the study treatment or intervention must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study treatment for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study treatment administration is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial study treatment administration through 100 days following the last dose of the study treatment must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment or intervention. However, with regards to laboratory and vital sign abnormalities, only those which require protocol treatment to be modified or treatment to be rendered should be reported as AEs or SAEs.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study treatment is also considered an adverse event. However, anticipated fluctuations of pre-existing conditions, including the disease under study, that don't represent a clinically significant exacerbation or worsening, need not be reported as AEs.

8.2 Definitions

8.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

- Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

8.2.2 Serious Adverse Event

An adverse event is considered "serious" if, in the view of either the investigator or sponsor-investigator, it results in any of the following outcomes:

- Death. Note, if death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- A life-threatening adverse event. An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It

does not include an adverse event that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.
- An important medical event. Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

8.2.3 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
   AND
3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.2.4 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.

- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.2.5 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, or in the protocol.

8.3 Adverse Event Characteristics

8.3.1 CTCAE Term

(AE description) and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.3. A copy of the CTCAE version 4.0.3 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.3.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

RELATED

Definite – The AE *is clearly related* to the study treatment.
Probable – The AE *is likely related* to the study treatment.
Possible – The AE *may be related* to the study treatment.

UNRELATED

Unlikely – The AE *is doubtfully related* to the study treatment.
Unrelated – The AE *is clearly NOT related* to the study treatment/intervention.

8.4 Serious Adverse Event Reporting Guidelines

8.4.1 Reporting procedures for multi-site trials

All serious adverse events (SAEs) and unanticipated problems (UPs), regardless of causality to study drug, will be reported to the Principal Investigator and also to the Coordinating Center. All SAEs and UPs must be reported to the Coordinating Center within 24 hours of first awareness of the event. Events should be reported using the Coordinating Center's SAE form as available in the study database. A copy of the SAE form as available in the study database should be sent to the Coordinating Center via fax at [redacted] or via email to [redacted] within 24 hours of the site's knowledge of the event.

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

All SAEs and UPs will be reported to the IRB per current institutional standards.

The Coordinating Center will disseminate information regarding SAEs and UPs to the participating sites within 5 days of review of the information by the Coordinating Center's Principal Investigator (or designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study drug. The Coordinating Center will be responsible for reporting of events to the FDA and supporters, as appropriate (outlined below).

8.4.2 Reporting procedures to BMS

All Serious Adverse Events (SAEs) occurring from the initial study treatment administration through 100 days following the last dose of the study treatment will be reported by the Coordinating Center to BMS Worldwide safety. Any SAEs occurring after 100 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to BMS Worldwide safety.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to BMS Worldwide Safety [redacted]).

If only limited information is initially available or an ongoing SAE changes in its intensity or relationship to the study drug, or if new information becomes available, a follow-up report will be generated and sent to BMS Worldwide Safety within 24 hours of receipt.

8.4.3 Reporting procedures to FDA

In this trial, serious, unexpected adverse events believed to be definitely, probably or possibly related to the study treatment will be reported to the Food and Drug Administration via the MedWatch 3500A Form. The Michigan IND/IDE Assistance Program (MIAP) (University of Michigan) will assist the IND Sponsor in reporting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32. This reporting could include the initial report and follow-up reports when appropriate for the event.

8.5 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.6 Reporting of Pregnancy

Pregnancies that occur during study participation or within 5 months of last study dose should be reported to the Coordinating Center via e-mail at CTSU-Oncology-Multisite@med.umich.edu immediately upon site's knowledge of the event.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research; and
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

8.8 Safety Report Reconciliation

The Sponsor will reconcile the clinical database SAE reports transmitted to BMS Global Pharmacovigilance [redacted]. Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to [redacted] The data elements listed on the GPV&E reconciliation report will be used for identification purposes. If the Investigator determines a report was not transmitted to BMS GPV&E, the report should be sent immediately to BMS.

8.9 Stopping Rules

The DSMC comprised of the principal investigator, co-investigators at University of Michigan, study statistician, and multi-site coordinator will be responsible for the continuous monitoring of the study for treatment tolerability and efficacy. During the monthly meetings current study data will be reviewed and the decision to continue, hold, or stop accrual to either treatment arm of this study will be formally considered. There are no formal stopping rules for this study.

9.0 DRUG INFORMATION

9.1 Gemcitabine

9.1.1 Other Names

Gemzar

9.1.2 Classification

Gemcitabine (difluorodeoxycytidine) is a pyrimidine antimetabolite, which is an analogue of deoxycytidine. It was initially synthesized as a potential antiviral drug but selected for anticancer development because of its activity in *in-vivo* and *in vitro* tumors. Gemcitabine is approved for the treatment of patients with BTC and will be obtained commercially.

9.1.3 Mechanism of Action

Gemcitabine kills cells undergoing DNA synthesis and blocks the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized by nucleoside kinases to diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing the reactions that generate deoxynucleoside triphosphates for DNA synthesis, resulting in reductions in deoxynucleotide concentrations, including dCTP. Gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP by the action of the diphosphate enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands, which eventually results in the initiation of apoptotic cell death.

9.1.4 Pharmacokinetics

1. Distribution: Gemcitabine plasma protein binding is negligible. The volume of distribution is increased with the infusion length. In a pharmacokinetics study of patients with various solid tumors, the volume of distribution of gemcitabine was 50 L/m2 following infusions lasting <70 minutes. For long infusions (70 to 285 minutes), the volume of distribution rose to 370 L/ m^2.

2. Metabolism: Gemcitabine is metabolized intracellularly to form active gemcitabine di- and tri-phosphates. The gemcitabine di- and triphosphates do not appear to circulate in plasma in measurable amounts. Gemcitabine is metabolized by the liver to form the inactive uracil derivative, 2'-deoxy-2',2'-difluorouridine (dFdU). The inactive metabolite does not appear to accumulate with weekly dosing; however, it is excreted by the kidneys and may accumulate in patients with decreased renal function.

3. Elimination: Following a single 1,000 mg/m2 /30 min [14C]-gemcitabine infusion, 92% to 98% of the dose was recovered within 1 week after gemcitabine administration. Urinary excretion of the parent drug and the dFdU metabolite accounted for 99% of the excreted dose, and less than 1% of the dose was excreted in feces. The renal clearance of gemcitabine is less than 10%; therefore, the parent drug appears to be almost completely metabolized to the inactive dFdU.

   Clearance of gemcitabine is affected by age and gender and is lower in women and the elderly. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Studies showed that gemcitabine half-life for short infusions ranged from 42 to 94 minutes, for long infusions it varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions. The terminal phase half-life for the active metabolite, gemcitabine triphosphate, in mononuclear cells ranges from 1.7-19.4 hours.

9.1.5 Storage, Preparation and Stability

Refer to the current FDA-approved package insert for storage, stability and special handling information.

9.1.6 Dosing and Administration

See Section 5.1

9.1.7 Availability

Gemcitabine is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

9.1.8 Handling and Disposal

Handling and disposal of gemcitabine should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Recommended safety measures for preparation and handling of gemcitabine include laboratory coats and gloves.

9.1.9 Adverse Effects

1. Side Effects: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Adverse

effects reported in >20% to 100% of subjects treated with gemcitabine include: flu-like symptoms, nausea, vomiting, rash, alopecia, infection, myelosuppression including anemia, leukopenia, neutropenia, and thrombocytopenia, muscle weakness, hematuria, paresthesia, sensory neuropathy, fatigue, somnolence, hearing loss, peripheral edema. Adverse effects reported in 4% to 20% of subjects include: diarrhea, constipation, stomatitis, dyspnea, capillary leak syndrome, posterior reversible encephalopathy syndrome (PRES). Adverse effects reported in 3% or less of subjects include: arrhythmias, supraventricular arrhythmias, congestive heart failure, myocardial infarction, desquamation and bullous skin eruptions, gangrene, cerebrovascular accident, hepatic failure, adult respiratory distress syndrome (ARDS), anaphylaxis, renal failure, pulmonary fibrosis, pulmonary edema, and, Interstitial, pneumonitis. Grade 3 and 4 adverse events in combination with cisplatin for BTC from the phase trial are as listed in Table 2 of the publication (Valle, Wasan et al. 2010).

2. Pregnancy and Lactation: Category D. Gemcitabine may cause fetal harm when administered to a pregnant woman. This agent has produced teratogenic effects in mice and rabbits when administered at a dose of < 2 mg/m2. Adverse effects included decreased fetal viability, weight and morphologic defects. There is no data on gemcitabine administration during human pregnancy, and it is not currently known if metabolites are excreted in human milk. However, many drugs are excreted in human milk, and there is a potential for adverse effects in nursing infants. Therefore, the use of gemcitabine should be avoided in pregnant or nursing women because of the potential hazard to the fetus or infant.
3. Drug Interactions: Per gemcitabine package insert, no formal drug interaction studies have been performed to date. When gemcitabine was administered with cisplatin there was minimal or no effect on the pharmacokinetics of the studied drugs.

9.2 Cisplatin

9.2.1 Other Names

CDDP, Platinol, NSC-119875

9.2.2 Classification

Cisplatin is an alkylating agent, which inhibits DNA synthesis by producing cross-linking of parent DNA strands (cell-cycle phase-nonspecific). Cisplatin is approved for the treatment of patients with BTC and will be obtained commercially.

9.2.3 Mechanism of Action

Cisplatin (cis-diamminedichloroplatinum) is a heavy metal complex containing a central platinum atom surrounded by two chloride atoms and two ammonia molecules in the cis position. It is water soluble and acts as a bifunctional alkylating agent with cell cycle nonspecific characteristics. The intra-strand cross-links, in particular with guanine and cytosine, change DNA conformation and inhibit DNA synthesis leading to the cytotoxic and anti-tumor effects of cisplatin. Although cisplatin seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents and that cisplatin does not exhibit cross-resistance with other alkylating agents or nitrosoureas.

9.2.4 Pharmacokinetics

1. Absorption: Following rapid IV injection of cisplatin over up to one hour, peak plasma drug and platinum concentrations occur immediately. When cisplatin is administered by IV infusion over 6 or 24 hours, plasma concentrations of total platinum increase gradually during the infusion and peak immediately following the end of the infusion.

2. Distribution: Following intravenous dosing, cisplatin distributes rapidly into tissues, with highest concentrations in the liver, prostate and kidney. Plasma levels of cisplatin decay in a biphasic mode with an initial half-life of 25 to 49 minutes, and a secondary phase ranging from 58 to 73 hours. This prolonged phase is due to protein binding, which exceeds 90%. Cisplatin penetrates poorly into the CNS.

3. Metabolism: Cisplatin is non-enzymatically transformed to one or more metabolites that are extensively protein bound and have minimal cytotoxic activity. The non-protein bound (unchanged) fraction is cytotoxic.

4. Elimination: Urinary excretion is incomplete. Following bolus injection or infusion over a dose range of 40-140 mg/m2 varying in length from 1-24 hours, from 10 to about 40% of the administered platinum is excreted in the urine in 24 hours. Renal clearance of free platinum exceeds the glomerular filtration rate, indicating that cisplatin or other platinum containing molecules are actively secreted by the kidneys. Renal clearance of free platinum is nonlinear and variable, and is dependent on dose, urine flow rate, and individual variability in the extent of active secretion and possible tubular reabsorption.

9.2.5 Storage, Preparation and Stability

Refer to the current FDA-approved package insert for storage, stability and special handling information.

9.2.6 Dose and Administration

See Section 5.1

9.2.7 Availability

Cisplatin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

9.2.8 Handling and Disposal

Handling and disposal of cisplatin should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Recommended safety measures for preparation and handling of gemcitabine include laboratory coats and gloves.

9.2.9 Adverse Effects

1. Side Effects: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Adverse effects reported in >20% to 100% of subjects treated with cisplatin include: nausea, vomiting, myelosuppression, anemia, leucopenia, thrombocytopenia, nephrotoxicity (acute renal failure and chronic renal insufficiency), and ototoxicity. Adverse effects reported in 4% to 20% of subjects include: alopecia, dysgeusia, diarrhea, hypersensitivity reaction, confusion, vestibular

dysfunction, peripheral neuropathy, blurred vision or altered color perception. Adverse effects reported in 3% or less of subjects include: secondary malignancy and seizure. Other published literature suggests risk of thromboembolic events.

2. Pregnancy and Lactation: Category D. Cisplatin can cause fetal harm when administered to a pregnant woman. In mice, cisplatin is teratogenic and embryotoxic. This drug has been found to be excreted in human milk and because of the potential for serious adverse reactions in nursing infants, patients receiving cisplatin should not breast feed.

3. Drug Interactions: During cisplatin therapy, plasma levels of anticonvulsant agents (valproic acid, phenytoin, and carbamazepine) may become sub-therapeutic and should be monitored. Concomitant use with aminoglycosides, tacrolimus, and amphotericin B increase risk of nephrotoxicity. Concomitant use with loop diuretics and aminoglycosides increase risk of ototoxicity. Concurrent use with lithium may result in reduced lithium plasma concentration. Concurrent use with warfarin may result in increased INR. Concurrent use with thioctic acid may result in decreased cisplatin effectiveness and should be avoided.

9.3 Nivolumab

9.3.1 Other Names

Opdivo, BMS-936558, MDX-1106, ONO-4538

9.3.2 Classification

Immunomodulatory; checkpoint inhibitor

9.3.3 Mechanism of Action

Nivolumab is a fully human IgG4 programmed death 1 (PD-1) immune checkpoint inhibitor antibody that selectively blocks the interaction between PD-1, which is expressed on activated T cells, and PD-1 ligand 1 (PD-L1) and 2 (PD-L2), which are expressed on immune cells and tumor cells.

9.3.4 Pharmacokinetics

1. Distribution: Nivolumab has linear pharmacokinetics after single and multiple dosing within the range 0.1 mg/kg to 10 mg/kg. The volume distribution (Vd) is 8L. 2.
2. Elimination: Clearance is independent of dose in the range 0.1 mg/kg to 10 mg/kg. The total body clearance is 9.5 mL/hr, and the elimination half-life of is approximately 26.7 days. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights.

9.3.5 Storage, Preparation and Stability

Nivolumab is supplied a sterile solution (Opdivo Intravenous) which comes in vials of 100 mg/10 mL (10 mL). Nivolumab vials must be stored at a temperature of 2*C to 8*C and should be protected from light. If stored in a glass front refrigerator, vials should be stored in the carton.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the Investigator Brochure section for “Recommended Storage and Use Conditions” and/or pharmacy

reference sheets. Briefly, withdraw the required volume and transfer into an IV container. Dilute with either NS or D5W to a final concentration of 1 to 10 mg/mL. Mix by gentle inversion; do not shake.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

The administration of undiluted and diluted solutions of nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°- 8°C (36°-46°F) and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

9.3.6 Dose and Administration

See Section 5.1
Nivolumab is to be administered as a 30 (± 5 minute) intravenous infusion, using a pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of 0.9% sodium chloride Injection or 5% Dextrose Injection.

9.3.7 Availability

Bristol Myers Squibb (BMS) will provide the study drug.

9.3.8 Handling and Disposal

Handling and disposal of nivolumab should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

9.3.9 Adverse Effects

1. Adverse Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2069 patients. Below is the CAEPR for BMS- 936558 (Nivolumab, MDX-1106).

   Please refer to the Investigator Brochure Addendum for the Comprehensive Adverse Events and Potential Risks (CAEPR) List.

   Adverse events reported on BMS-936558 (Nivolumab, MDX- 1106) trials, but for which there is insufficient evidence to suggest that there was a

reasonable possibility that BMS- 936558 (Nivolumab, MDX-1106) caused the adverse event:
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Pericarditis; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Vestibular disorder

ENDOCRINE DISORDERS - Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism)

EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Enterocolitis; Flatulence; Gastrointestinal disorders - Other (mouth sores); Mucositis oral; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain

HEPATOBILIARY DISORDERS - Bile duct stenosis; Hepatobiliary disorders - Other (autoimmune hepatitis) IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Encephalitis infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Alkaline phosphatase increased; CPK increased; GGT increased; Investigations - Other (blood LDH increased); Investigations - Other (CRP increased); Investigations - Other (eosinophil count increased); Investigations - Other (protein total decreased); Investigations - Other (thyroxine free increased); Investigations - Other (triiodothyronine free decreased); Investigations - Other (WBC count increased); Lymphocyte count increased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage; Nervous system disorders - Other (autoimmune neuropathy); Stroke

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (nephritis); Renal and urinary disorders - Other (tubulointerstitial nephritis)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease); Respiratory, thoracic and mediastinal disorders - Other (lung infiltration); Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Periorbital edema; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea); Toxic epidermal necrolysis

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis
Note: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent. Adverse events occurring in < 1%, post marketing, and/or case reports: Hemophagocyticlymphohistiocytosis, rhabdomyolysis and polymyositis have been reported in patients received more than one dose of combination therapy (nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks) for the treatment of metastatic gastric adenocarcinoma and advanced bladder cancer, respectively.

2. Pregnancy and Lactation: Pregnancy: Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of reproductive potential should use highly-effective contraception during therapy and for at least 5 months after treatment has been discontinued. Men receiving nivolumab and who are sexually active with women of child bearing potential should adhere to contraception for a period of 7 months after the last dose of nivolumab.

   Lactation: It is not known if nivolumab is excreted into breast milk. Due to the potential for serious adverse reactions in the nursing infant, the manufacturer recommends women to discontinue breastfeeding during treatment with nivolumab.

3. Drug Interactions: Nivolumab is not expected to have any effect on cytochrome P450 or other drug metabolizing enzymes in terms of inhibition or induction, and is, therefore, not expected to induce these types of PK-based drug interactions. No incompatibilities between nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

9.4 Ipilimumab

9.4.1 Other Names

(BMS-734016, MDX-010, YERVOY®) (NSC 732442) (IND-119672)

9.4.2 Classification

Immunomodulatory; checkpoint inhibitor

9.4.3 Mechanism of Action

Cytotoxic T-lymphocyte antigen-4 CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a full human monoclonal immunoglobin (Ig) antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands,

CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

9.4.4 Pharmacokinetics

1. Absorption: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes.
2. Distribution: Ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Based on population pharmacokinetic analysis, the mean volume of distribution (% coefficient of variation) at steady state was 7.47 liters (10%).
3. Metabolism: Not applicable. Monoclonal antibodies are usually degraded into amino acids and small peptides, independently from CYP450 or other drug-metabolizing enzymes.
4. Elimination: Clearance increased with body weight, but no dose adjustment is required with dosing on a mg/kg basis. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. The mean value (% coefficient of variation) generated through population pharmacokinetic analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for CL was 16.8 mL/h (38%).

9.4.5 Storage, Preparation and Stability

Ipilimumab injection is supplied as 200 mg/40 mL (5 mg/mL). It is formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, non-pyrogenic, single-use, isotonic aqueous solution that may contain particles. Each vial is a Type I flint glass vial with gray butyl stoppers and sealed with aluminum seals.

1. Store intact vials of ipilimumab refrigerated at (2 to 8 °C), protected from light. Do not freeze.
2. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in a polyvinyl chloride(PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container up to 24 hours refrigerated at (2 to 8 °C) or at room temperature/room light.
3. The product may be infused using a pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-proteinbinding filter (pore size of 0.2 micrometer to 1.2 micrometer).
4. Do not administer ipilimumab as an IV push or bolus injection.
5. Stability of prepared IV ipilimumab solution is stable up to 24 hours refrigerated at (2 to 8 °C) or at room temperature/ room light.
6. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

9.4.6 Dose and Administration

See Section 5.1
Ipilimumab injection is to be administered as an infusion with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not administer as IV push or bolus injection.

9.4.7 Availability

Bristol Myers Squibb (BMS) will provide the study drug.

9.4.8 Handling and Disposal

Handling and disposal of ipilimumab should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Recommended safety measures for preparation and handling of ipilimumab include laboratory coats and gloves.

9.4.9 Adverse Effects

1. Side Effects: The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2678 patients. Below is the CAEPR for Ipilimumab (MDX-010). NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

   Please refer to the Investigator Brochure Addendum for the Comprehensive Adverse Events and Potential Risks (CAEPR) List.

2. Pregnancy and Lactation: There are no adequate and well controlled studies of Ipilimumab in pregnant women. Use of Ipilimumab during pregnancy only if the potential benefit justifies the potential risk to the fetus. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus. It is not known whether ipilimumab is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from ipilimumab, a decision should be made whether to discontinue nursing or to discontinue ipilimumab, taking into account the importance of ipilimumab to the mother.

3. Drug Interactions: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes

10.0 CORRELATIVES/TRANSLATIONAL STUDIES

We will study the BTC tumor microenvironment through the use of pre-treatment tissue collection (at all sites) as well as on-treatment (for patients at University of Michigan) and post-treatment (optional for patients enrolled at all sites) tumor biopsies. Identification of important biologic subsets of BTC patients that may have clinical efficacy from nivolumab and ipilimumab will be the overarching goal of this translational science. Tumor from core biopsies will be examined histologically by immunohistochemistry (IHC), immunofluorescence (IF), and RNA analysis. Post-treatment biopsy tissue will be separated into sections for paraffin embedding, fresh frozen in OTC, and fresh frozen in RNAlater. Whole genomic DNA will be evaluated for mutational analysis). Biologic readouts for PD-1 and CTLA4 response biomarkers will be assessed along with specific markers of tumor infiltrating leukocytes (TILs). TILs and their subsets will be assessed using markers by IHC (e.g. CD4, CD8, FoxP3 (Treg), CD14 or CD68 (TAMs), CD11c (DCs)). Response biomarkers will be determined by IHC or IF (e.g. B7-H1 (PD-1L), CD80, CD86, B7-H4, B7-HDC (PD-L2), CTLA4, CD28, LAG3, Tim-3, CD40, OX40) (Wu, Kryczek et al. 2009, Lou, Diao et al. 2016). Cytokine signaling representative of Th1, Th2, and other immune pathway signature gene expression will be determined by transcriptomic assessment (RNAseq) and analyzed using Gene Set Enrichment Analysis software (GSEA) (Subramanian, Tamayo et al. 2005, Eichler 2012) at the University of Michigan. Furthermore, we will study peripheral blood for the presence of peripheral blood mononuclear cell subsets following Ficoll separation and multiplex FACS analysis for T cell subset markers and co-stimulatory/inhibitory markers (Wu, Kryczek et al. 2009). Biologic markers and RNA expression will be examined in the context of patient efficacy.

10.1 Tissue Collection

Tissue will be collected at the time points specified in section 6.2 Study Calendar. A FFPE block or 10 unstained and 1 H&E slide should be submitted as per the lab manual. Please refer to the lab manual for additional sample collection and processing details.

A CLIA certified targeted gene panel will be run on the post-treatment tissue without additional cost to the patient, and the report will be released to the treating investigator to inform future therapy options.

10.2 Blood Collection

Blood samples will be collected at the time points specified in section 6.2 Study Calendar. Please refer to the lab manual for sample collection and processing details.

10.3 Centralized Imaging

All baseline and response imaging studies will be de-identified and shipped to the University of Michigan for banking and exploratory endpoint assessment. Please see the lab manual for data format and shipping details.

10.4 Specimen Banking

Patient samples collected for this study will be retained at University of Michigan. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

Specimens being stored long-term for potential use not outlined in the protocol are subject to University Policy Governing Tissue Sample Collection, Ownership, Usage, and Disposition within all UMMS Research Repositories.

11.0 STATISTICAL CONSIDERATIONS

11.1 Study Design/Study Endpoints

This protocol will randomize patients with advanced unresectable BTC equally (1:1) to one of two novel treatment regimens. The randomization will be stratified for locally advanced versus metastatic cancers. The primary endpoint is PFS at 6 months following the initiation of treatment. Comparisons will be limited between each novel treatment regimen and the historical control value and not directly between treatments. Secondary endpoints include the calculation of the overall response rate, median PFS, overall survival, and the incidence of adverse events for each treatment regimen separately.

11.2 Sample Size and Accrual

The trial is sized to compare each randomized treatment arm to a historical value for PFS in this patient population receiving standard treatment. The PFS proportion in this patient population at 6 months is 59% (Valle, Wasan et al. 2010). Using this value as the null hypothesis, we hope to see an increase in the proportion of alive, progression-free patients to 80% or above in each of the combination arms. Thirty-two patients evaluable for the 6-month PFS endpoint are required to test this hypothesis with >80% power and at most 5% type I error (1-sided). A maximum of 64 evaluable patients (per Section 7.1.1) will be enrolled.

11.3 Data Analyses Plans

PFS will be estimated using the product-limit method of Kaplan and Meier. Follow-up time will be defined as time from date of first study treatment until the date of radiological or clinical progression (leading to withdrawal from the study), or death from any cause, whichever comes first. Follow-up time will be censored at the date of last disease evaluation. Estimates for the median and 75th percentiles with 95% confidence intervals will be reported. OS will be similarly estimated and summarized with follow-up time calculated from the date of first study treatment until date of death or censoring. Other safety data (e.g., laboratory safety parameters, vital signs, concomitant medications and new physical examination findings) will be summarized descriptively by reporting counts and percentages, with exact binomial confidence intervals where appropriate. ORR will be determined as per the RECISTv1.1 guidelines. Adverse events will be reported per the NCI CTCAE v4.03. There are no formal stopping rules for this study.

12.0 ADMINISTRATIVE PROCEDURES

12.1 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and be consistent with Good Clinical Practice (GCP), as defined by the International Conference on Harmonization (ICH), WHO and any local directives.

The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

12.2 Data Management

All information will be recorded locally and entered into Case Report Forms (CRFs) on the web-based electronic data capture (EDC) system of the University of Michigan. Online access will be provided to each site by the Coordinating Center.

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing

resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

- At the time of registration
  - Subject entry into the EDC
    - Subject Status
    - Demographics
- During study participation
  - All data should be entered online within 10 business days of data acquisition. *[Information on dose limiting toxicity events must be entered within one business day.]* Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 8.5 of the protocol.

All study information should be recorded in an appropriate source document (e.g. clinic chart).

12.3 Record Retention

The Investigators must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, whichever is longer.

13.0 DATA AND SAFETY MONITORING

The Data and Safety Monitoring Committee (DSMC) of The University of Michigan Comprehensive Cancer Center (UMCCC) is the DSMC for this study. This committee is responsible for monitoring the safety and data integrity of the trial.

At each site the study team is required to meet quarterly to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

These meetings are to be documented by the site data manager or study coordinator using the Protocol Specific Data and Safety Monitoring Report (DSMR), signed by the site principal investigator or co-investigator. Each site is required to submit the completed DSMR to the Multi-Site Coordinator at the University of Michigan Coordinating Center on a quarterly basis together with other pertinent documents.

Similarly, protocol deviations are to be documented using the Notice of Protocol Deviation Form and requires the signatures of both the sites data manager or study coordinator and the site principal investigator or co-investigator. These reports are to be sent to the University of Michigan Coordinating Center within 7 calendar days of awareness of the event and on a quarterly basis with the Protocol Specific Data and Safety Monitoring Report.

The Coordinating Center is responsible for collating all the Data and Safety Monitoring Reports from all the participating sites, and providing the information to the Data Safety Monitoring Committee.

14.0 QUALITY ASSURANCE AND AUDITS

The Data and Safety Monitoring Committee can request a ‘for cause’ quality assurance audit of the trial if the committee identifies a need for a more rigorous evaluation of study-related issues.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the Coordinating Center that such a request has been made.

15.0 CLINICAL MONITORING PROCEDURES

Clinical studies coordinated by The University of Michigan Comprehensive Cancer Center (UMCCC) must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements.

This study will be monitored by a representative of the Coordinating Center of the UMCCC. Monitoring visits will be made during the conduct of the study and at study close-out.

Prior to subject recruitment, a participating site will undergo site initiation meeting to be conducted by the Coordinating Center. This will be done as an actual site visit; teleconference, videoconference, or web-based meeting after the site has been given access to the study database and assembled a study reference binder. The site's principal investigator and his study staff should make every effort in attending the site initiation meeting. Study–related questions or issues identified during the site initiation meeting will be followed-up by the appropriate UMCCC personnel until they have been answered and resolved.

Monitoring of this study will include both 'Centralized Monitoring', the review of source documents at the Coordinating Center and 'On-site Monitoring', an actual site visit. The first 'Centralized' visit should occur after the first subject enrolled completes [first treatment cycle/course]. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Proper storage, dispensing and inventory of study medication
- Compliance with regulations

During a monitoring visit to a site, access to relevant hospital and clinical records must be given by the site investigator to the Coordinating Center representative conducting the monitoring visit to verify consistency of data collected on the CRFs with the original source data. While most patient cases will be selected from patients accrued since the previous monitoring visit, any patient case has the potential for review. At least one or more unannounced cases will be reviewed, if the total accruals warrant selection of unannounced cases.

The Coordinating Center expects the relevant investigational staff to be available to facilitate the conduct of the visit, that source documents are available at the time of the visit, and that a suitable environment will be provided for review of study-related documents. Any issues identified during these visits will be communicated to the site and are expected to be resolved by the site in a timely manner. For review of study-related documents at the Coordinating Center, the site will be required to ship or fax documents to be reviewed.

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

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17.0 APPENDICES

Appendix I ECOG Performance Status
Appendix II Child-Pugh Status
Appendix III Management Algorithms for Immuno-Oncology Agents
Appendix IV Investigator's Statement

Appendix I ECOG Performance Status

	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Source: Eastern Cooperative Oncology Group

Appendix II Child-Pugh Score

Measure	1 point	2 points	3 points
Total Bilirubin mg/dL	<2	2-3	>3
Serum Albumin g/dL	>3.5	2.8-3.5	<2.8
PT Time • **PT** • **INR**	 1-3 <1.8	 4-6 1.8-2.3	 >6 >2.3
Ascites	Absent	Slight	Moderate to Severe
Hepatic Encephalopathy	None	Grade 1-2 (or suppressed with medication)	Grade 3-4 (or refractory)

Source: R.N.H. Pugh, I.M. Murray-Lyon, J.L. Dawson, M.C. Pietroni, Roger Williams. Transection of the esophagus for bleeding esophageal varices. British Journal of Surgery. Volume 60. Issue 8, pages 646-649, August 1973.

Appendix III Management Algorithms for Immuno-Oncology Agents

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

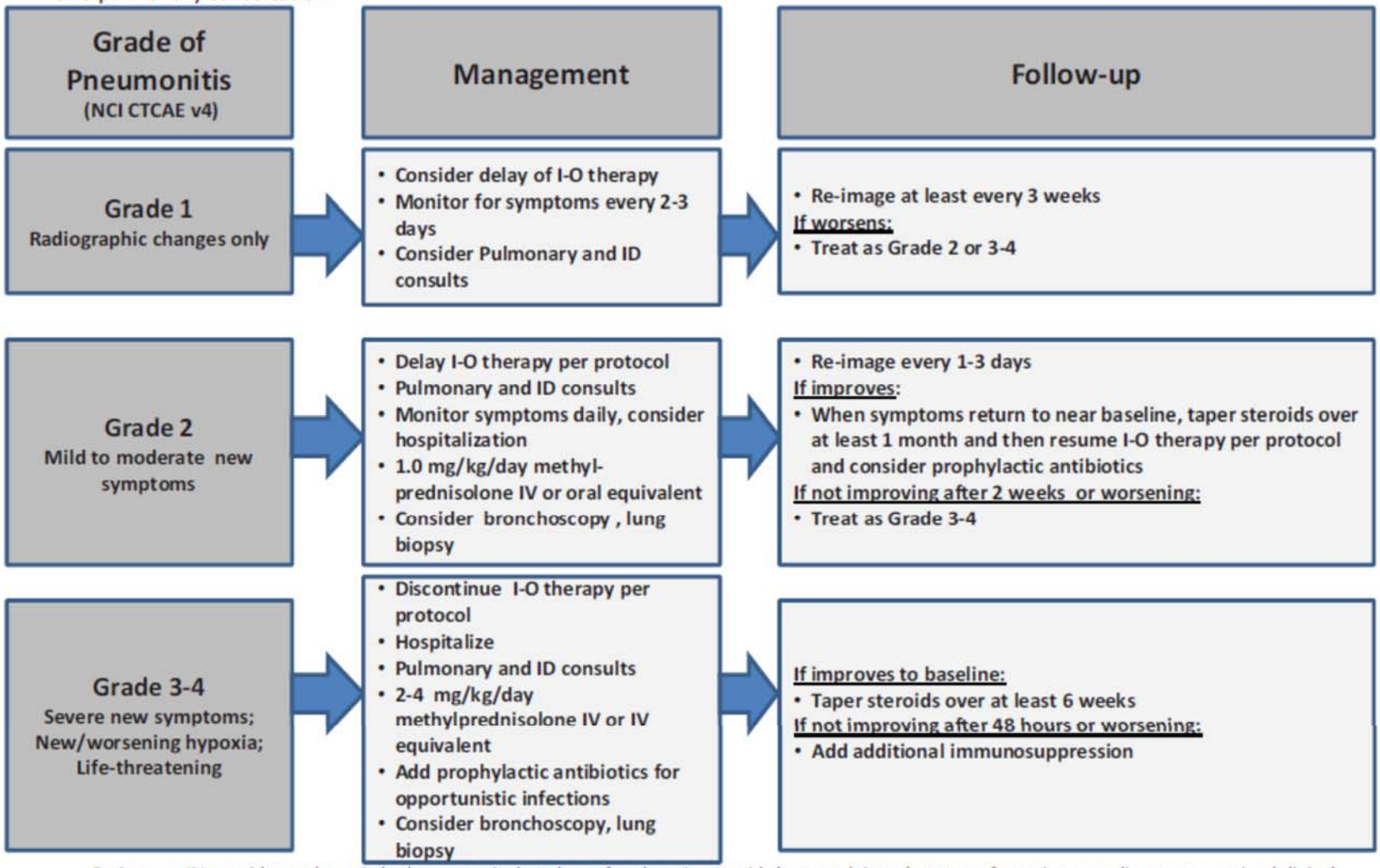
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	<u>If returns to baseline</u>: •Resume routine creatinine monitoring per protocol <u>If worsens:</u> •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	<u>If returns to Grade 1</u> : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

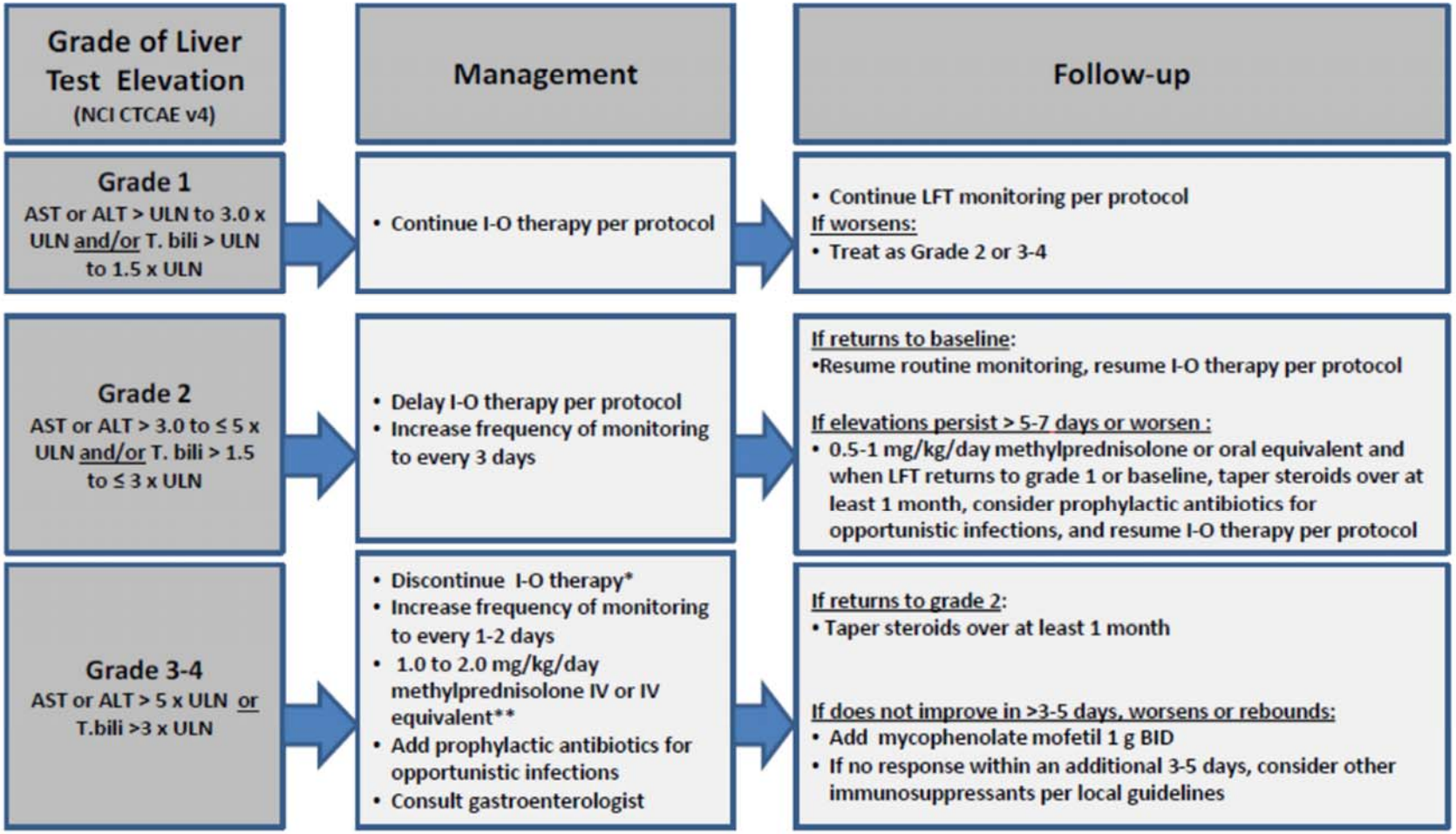
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



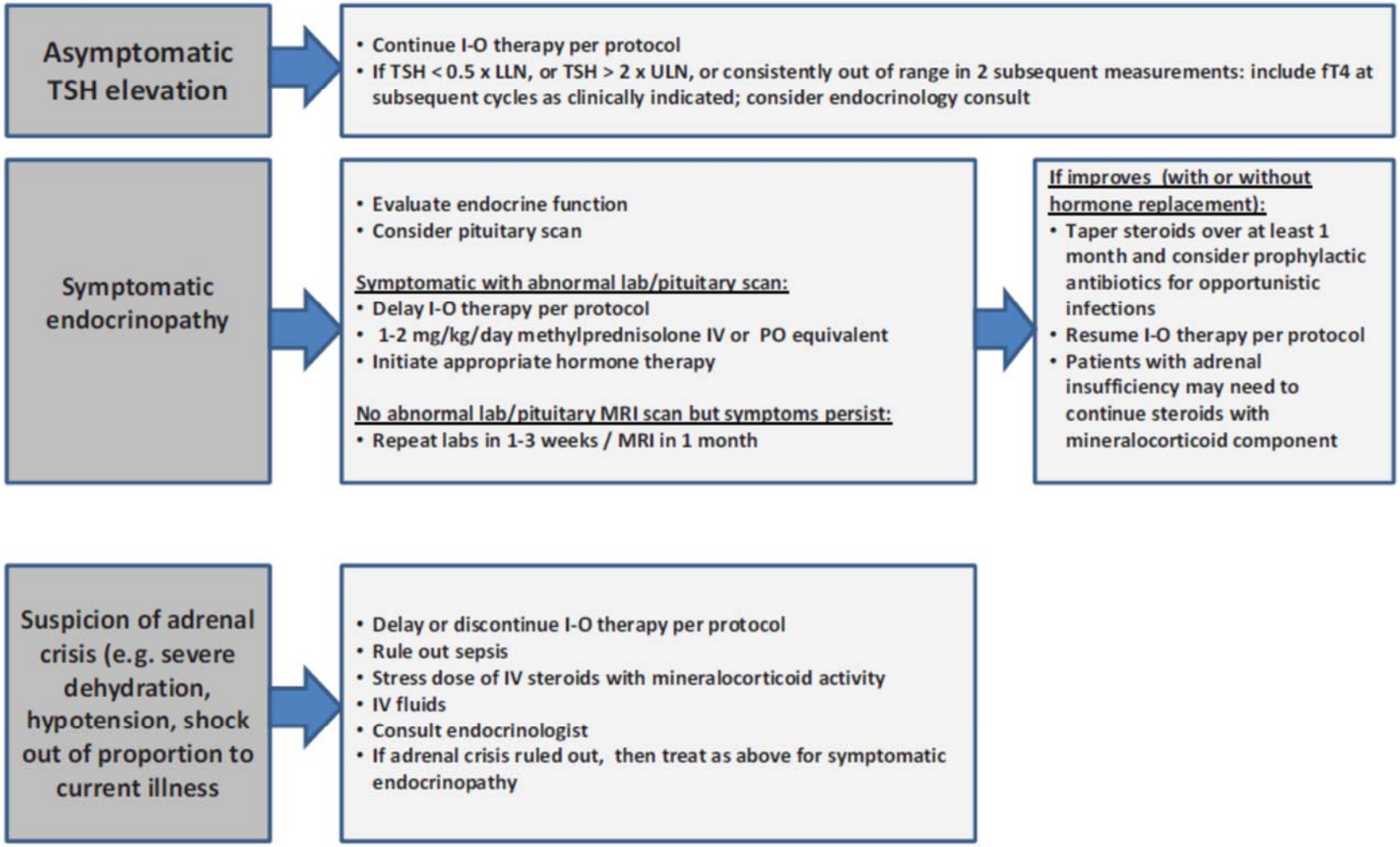
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Management Algorithm

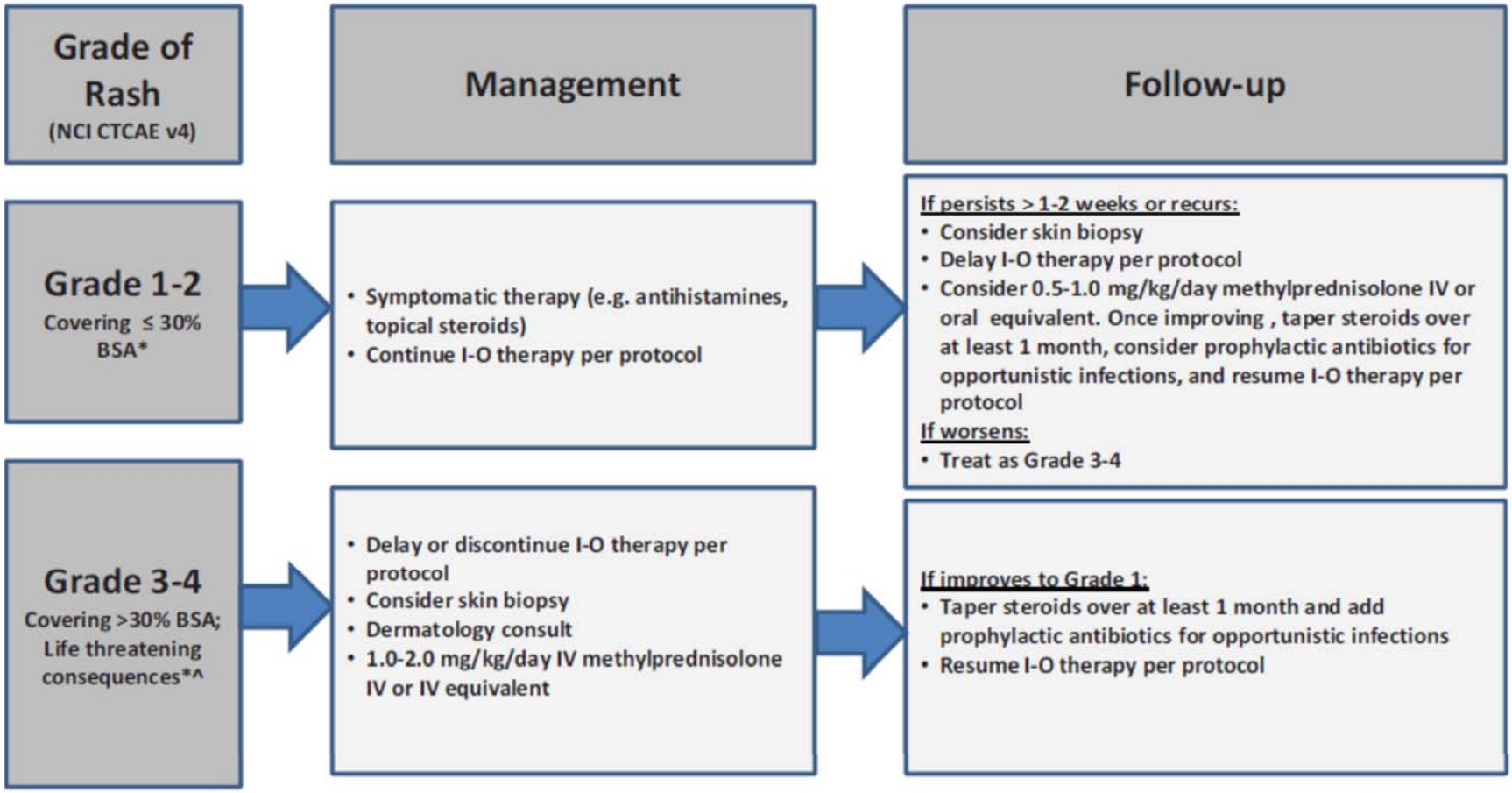
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Appendix IV Investigator's Statement

1. I have carefully read this protocol entitled "A Randomized Phase II Study of Nivolumab in Combination with either Gemcitabine/Cisplatin or Ipilimumab as First Line Therapy for Patients with Advanced Unresectable Biliary Tract Cancer", **Version dated 02/28/2018** and agree that it contains all the necessary information required to conduct the study. I agree to conduct the study as outlined in the protocol.

2. I agree to conduct this study according to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the principles of Good Clinical Practice (GCP) as described in 21 Code of Federal Regulations (CFR) and any applicable local requirements.

3. I understand that this trial and any subsequent changes to the trial will not be initiated without approval of the appropriate Institutional Review Board, and that all administrative requirements of the governing body of the institution will be complied with fully.

4. Informed written consent will be obtained from all participating patients in accordance with institutional and Food and Drug Administration (FDA) requirements as specified in Title 21, CFR, Part 50.

5. I understand that my signature on the electronic Case Report Form (eCRF) indicates that I have carefully reviewed each page and accept full responsibility for the contents thereof.

6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from University of Michigan unless this requirement is superseded by the FDA.

Site PI Name: _____

Site Name: _____

Signature of Site PI: _____

Date of Signature: _______________