UMCC 2018.101

Phase Ib/II Trial of Nal-Irinotecan and Nivolumab as Second-Line Treatment in Patients With Advanced Biliary Tract Cancer

NCT03785873

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A Single Arm Phase Ib/II Multi-Center Study of Nivolumab in Combination with nanoliposomal-Irinotecan, 5-Fluorouracil, and Leucovorin as Second Line Therapy for Patients with Advanced Biliary Tract Cancer [CA209-8LF]

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Coordinating Center University of Michigan

Experimental Drugs: Nanoliposomal-Irinotecan (Onivyde□)
Nivolumab (Opdivo®)

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NOTE: To effectively manage the COVID-19 pandemic restrictions, changes to protocol-required item were made to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19). These changes are listed in **Appendix V** of the protocol (**Study Management during COVID-19**).

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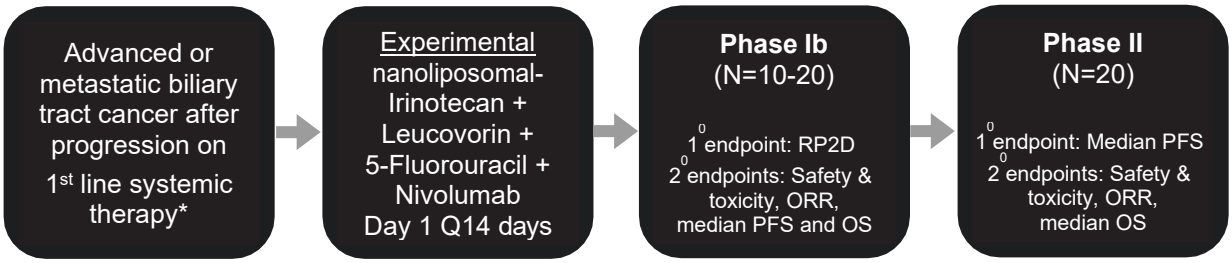
ABBREVIATIONS:

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
APC	Antigen Presenting Cells
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
DDR	DNA Damage Response
DILI	Drug-Induced Liver Injury
DLT	Dose Limiting Toxicity
DSMC	Data and Safety Monitoring Committee
H&P	History & Physical Exam
HRPP	Human Research Protections Program
IHC	Immunohistochemistry
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
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SD	Stable Disease
TIL	Tumor Infiltrating Leukocytes
UaP	Unanticipated Problem
WBC	White Blood Cells

STUDY SCHEMA



**No prior Irinotecan or PD-1 Ab*

STUDY SYNOPSIS

Title	A Single Arm Phase Ib/II Multi-Center Study of Nivolumab in Combination with nanoliposomal-Irinotecan, 5-Fluorouracil, and Leucovorin as Second Line Therapy for Patients with Advanced Biliary Tract Cancer
Phase	Phase Ib/II
Methodology	Single arm, open-label
Study Duration	3 years
Study Center(s)	Multi-Center: up to 6 sites total including lead site University of Michigan
Objectives	Primary objective: 1. Phase Ib: Determine the recommended phase 2 dose (RP2D) and dose-limiting toxicities (DLTs) of nanoliposomal-Irinotecan, 5-Fluorouracil, Leucovorin and Nivolumab 2. Phase II: Determine the median PFS Secondary objectives: 1. Evaluate the safety and toxicity of this drug combination in this patient population. 2. Evaluate the ORR and median OS Exploratory objectives: To explore biomarkers of 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 only). b) Whole exome genomic and transcriptomic (RNAseq) analysis for tumor biology, DDR and immune signature profiling at baseline and progression. c) PBMC collection for immune cell subset analysis including serum for future biomarker analysis (for patients enrolled at University of Michigan only).
Number of Subjects	30-40 evaluable
Eligibility Criteria	1. Patients must have a pathologically confirmed carcinoma of the biliary tract (intra-hepatic, extra-hepatic (hilar, distal) or gall bladder) that is not eligible for curative resection, transplantation, or ablative therapies. Tumors with mixed hepatocellular and cholangiocarcinoma histology are excluded.

	2. Patients must have received one and only one prior systemic therapy for advanced disease. Prior therapies must have not included Irinotecan or PD-1/PD-L1 antibody. Patient should have either progressed on or within 6 months of first-line systemic therapy or deemed intolerant of that therapy. 3. Prior surgical resection, radiation, chemoembolization, radioembolization or other local ablative therapies are permitted if completed ≥ 4 weeks prior to registration 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 lesion. 5. Age ≥18 years 6. Child-Pugh score less than 7 7. ECOG performance status of 0-1 8. Ability to understand and willingness to sign IRB-approved informed consent 9. Available archived tissue (FFPE block or 20 unstained slides from prior core biopsy or surgery) 10. Must be able to tolerate CT and/or MRI with contrast 11. Adequate organ function assessed ≤2 weeks prior to registration (absolute neutrophil count ≥1500/mm^3, hemoglobin ≥9 g/dL, platelets ≥75,000/mm^3, serum creatinine ≤ 1.5 x upper limit normal (ULN), albumin ≥3.0 g/dL, AST/ALT ≤3.0 x ULN (≤5 x ULN if liver metastasis), total bilirubin ≤ 1.5 x upper limit normal. 12. Must not have received systemic steroid therapy, or any other form of immunosuppressive therapy within 14 days prior to registration. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed. 13. No prior history of solid organ transplantation or brain metastasis (unless treated, asymptomatic and stable). 14. Must not have undergone a major surgical procedure < 4 weeks prior to registration. 15. 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. 16. Must have no ongoing active, uncontrolled infections (afebrile for > 48 hours off antibiotics). 17. Must not have received a live vaccine within 30 days of registration. 18. 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. 19. Women must not be pregnant or breastfeeding since 5-Fluorouracil, nanoliposomal-Irinotecan and/or Nivolumab 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 pregnancy test (blood or urine) within 2 weeks prior to registration. 20. 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. 21. 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. 22. Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of registration are excluded. Inhaled, ocular, intra-articular, intra-nasal or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. 23. No known UGT1A1* variants or Gilbert's syndrome 24. Prisoners or subjects who are involuntarily incarcerated, or compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness would be excluded. 25. No known hypersensitivity to 5-Fluorouracil, Leucovorin, Irinotecan, and/or Nivolumab. 26. Must not have ongoing bowel obstruction. 27. No known HIV, Hepatitis B or Hepatitis C infection that is untreated and/or with a detectable viral load. 28. Patients must not have uncontrolled intercurrent illness including, but not limited to, interstitial lung disease, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia. 29. No known medical condition (e.g. a condition associated with uncontrolled diarrhea such as ulcerative colitis or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or interfere with the interpretation of safety results. 30. Patients must not be on warfarin, strong CYP3A4 inducers (such as phenytoin, phenobarbital, primidone, carbamazepine, rifampin, rifabutin, rifapentine or St. John's Wort), strong CYP3A4 inhibitors (such as ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole), and strong UGT1A1 inhibitors (such as atazanavir, gemfibrozil, indinavir and ketoconazole).
Study Product(s), Dose, Route, Regimen	Starting Dose Level (cycle length is 14 days) nanoliposomal-Irinotecan 70 mg/m^2 IV day 1 5-Fluorouracil 2400 mg/m^2 IV continuous infusion for 46 hours Leucovorin 400 mg/m^2 IV day 1 Nivolumab 240 mg IV day 1
Duration of Administration	Patients may continue treatment for 2 years in absence of disease progression or unacceptable toxicity.
Statistical Methodology	The investigators intend to enroll patients who have either progressed or are deemed intolerant of 1st line systemic therapy for advanced biliary tract cancer. A limited phase 1b trial will be implemented to assure that dose levels suggested for this combination are safe. Because toxicity across the combined agents is expected to be additive rather than synergistic and in light of the poor prognosis for this patients, we are willing to tolerate up to but not exceeding 30% DLT toxicity proportion during the first 4 weeks of therapy. To investigate this, we will enroll up to 10 patients to the phase Ib portion of this trial at dose level 0. If >4 patients of the first 5 to 10 patients enrolled into this cohort have a DLT during the first 4 weeks of therapy, then accrual at dose level 0 will halt if yet to reach 10. Dose level will be abandoned in favor of dose level -1. If the toxicity boundary of 4 is crossed at dose level 0, up to an additional 10 patients will be accrued at dose level -1 and the same rules applied. If at dose level -1 more than 4 patients experience DLT, then the trial will be stopped and the combination abandoned. However, if either the 10 patient cohort at dose level 0

	or level -1 conclude without tripping the toxicity rule, then that dose level will be declared the recommended phase 2 dose (RP2D) with an additional 20 patients enrolled at that dose level for the Phase 2 assessment of efficacy as measured by the median PFS. The median PFS of second line treatment of cholangiocarcinoma is expected to be 2.9 months (null) and we expect that the median PFS will be 5.0 months (alternate hypothesis) for this study's combination. We anticipate that we can accrue 1.7 patients per month for 18 months (between phase 1b and phase 2); we will follow all patients for progression and survival for 12 months following the accrual of the last patient. This will afford 83% power to detect the hypothesized difference in median PFS time, using a two-sided test with at most 5% type one error. Patients on the phase Ib portion of this trial treated at the RP2D will be included in the population for the analysis of the primary endpoint of the phase II portion of the trial.

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[1]. Advanced BTCs are aggressive tumors with median survival time from diagnosis of less than 12 months[2], and five-year overall survival (OS) of ~5% despite therapy[3]. The options for systemic chemotherapy for patients with advanced BTC remain limited with few meaningful improvements over the past 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[2]. 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. This result established the gemcitabine and cisplatin combination as a standard first line regimen for patients with advanced BTC. Durable response rates are infrequent however, and a substantial number of patients progress quickly. Additional strategies and subsequent lines of therapy remain largely investigational, with no clear standard at present.

1.2 Role of Irinotecan in BTC

Irinotecan (Camptosar©, CPT-11) is a camptothecin derivative that inhibits topoisomerase I, an enzyme that induces reversible single-stranded DNA breaks to relieve torsional strain in DNA through its active metabolite, SN-38. The combination of Irinotecan plus 5-Fluorouracil (5-FU)/Leucovorin (LV) (FOLFIRI) has shown activity in the first and second line settings in multiple GI cancers. Studies in biliary cancer have revealed modest activity, although these are small studies (Table 1).

Table 1. Use of Irinotecan and/or 5-FU/capecitabine in 2nd line management of biliary tract cancer

No.	Regimen	N	Overall response rate, N (%)	Progression free survival, months	Overall survival, months
1	FOLFIRI[4]	24	NA	2.9	NR
2	Irinotecan[5]	13	1 (7.7)	1.8	6.7
3	Irinotecan[6]	25	2 (8%)	NR	10
4	Capecitabine or 5-FU/LV[7]	26	2 (10%)	2.8	8.0

Nanoliposomal-Irinotecan (nanoliposomal-IRI) is a nanoliposomal encapsulated form of Irinotecan that Drummond et al. demonstrated in animal studies to have significantly longer circulation times when bound to triethylammonium salts or polyphosphates when compared to free drug formulations. At 24 hours, 23.2% of an injected dose of nanoliposomal-IRI remained without detectable conversion of the encapsulated prodrug to its inactive or active metabolite form as compared to only 2% of the free drug formulation remaining after 30 minutes with 35% of injected free drug present in the inactive carboxylate form. Antitumor activity in breast and colon xenografts were significantly higher with nanoliposomal-IRI as compared to free Irinotecan with a fourfold reduction of drug toxicity in mice without reaching the maximum tolerated dose (MTD)[8,9]. Maximum tolerated doses of nanoliposomal-IRI have been established in several phase I studies in advanced solid tumors refractory to chemotherapy with recommended dosing of 120 mg/m^2 every 3 weeks as monotherapy and 70 mg/m^2 combined with 5-FU/LV every two weeks[10].

The combination of nanoliposomal-IRI plus 5-FU/LV has been shown to be both safe and effective following gemcitabine-based treatment in advanced pancreatic cancer in the NAPOLI-1 trial. The combination of nanoliposomal-IRI demonstrated improvements in progression free (PFS) (3.1 vs 1.5 months; P<0.001) and OS (6.2 vs 4.1 months; P=0.038) as compared to 5-FU/LV[10].

1.3 Role of Immune Checkpoint Inhibitors in BTC

Programmed death (PD)-1 is a member of the CD28/CTLA-4 family of T-cell costimulatory receptors that includes CD28, CTLA 4, ICOS and BTLA[11]. PD-1 is expressed on activated T cells, B cells and myeloid cells[12]. 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[,13,14]. When a PD-1 ligand binds to the PD-1 receptor, T-cell activation is blocked. PD-1 is a negative regulator of T-cell response that prevents autoimmunity and allows tolerance to self-antigens. If PD-1/ligand interactions are interrupted, this checkpoint is turned off which can lead to enhanced antitumor T-cell activation.

One of the first agents studied in this disease group was pembrolizumab, a humanized monoclonal antibody against PD-1 that is designed to block the interaction between PD-1 and its ligands PD-L1 and PD-L2. Twenty-three PD-L1 positive patients with advanced BTC were enrolled in the KEYNOTE-028 phase 1b trial of pembrolizumab 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%[15]. Adverse events were generally consistent with previously reported safety data for pembrolizumab. There were no treatment-related deaths. Five patients, including all responders, remained on treatment more than 40 weeks[15]. Nivolumab is an anti-PD1 antibody that is currently FDA-approved as a single agent and in combination with other agents in multiple solid tumors at 240 mg dose every 2 weeks, and more recently at 480 mg dose every 4 weeks. A few ongoing studies utilizing PD-1 blockade in advanced BTCs refractory to 1st line therapy include Nivolumab monotherapy (NCT02829918), pembrolizumab plus capecitabine and oxaliplatin (NCT03111732), and atezolizumab plus cobimetinib (NCT03201458)[16].

1.4 Role of Chemotherapy in Conjunction with Immune Checkpoint Inhibitors in BTC

Chemotherapy has been demonstrated to lead to upregulation of PD-L1 expression[17]. 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[18]. 5-FU, a pyrimidine analog antimetabolite which works by inhibition of thymidylate synthase, has demonstrated in vivo a major decrease in myeloid-derived suppressor cells (MDSCs) and induction of MDSC apoptotic death with net increase in IFNγ (interferon gamma) production by tumor-specific CD8(+) T Cells[19]. Irinotecan is also an example of an immunomodulatory chemotherapeutic agent with pleiotropic immune effects, and when combined with 5-FU/LV (FOLFIRI), demonstrated increased T-helper 1 and cytotoxic T-cell response, including secretion of IL-2 and IFNγ through down regulation of MDSCs and regulatory T-cells (TREG)[20]. The immunomodulatory properties of conventional chemotherapy and properties of these specific agents provide a good rationale for combining 5-FU and nanoliposomal-IRI with immunotherapy, particularly immune checkpoint inhibitors.

The PembroPlus trial (NCT02331251), a phase Ib, multicohort study, evaluated the safety and efficacy of pembrolizumab with gemcitabine (G), G+Docetaxel, G+nab-paclitaxel, G+vinorelbine, Irinotecan, or liposomal doxorubicin in advanced solid tumors. Forty-nine patients were enrolled. Specific to our study, pembrolizumab (2 mg/kg) was given in combination with Irinotecan (300mg/m2) every 21 days with an acceptable safety profile. All patients experienced grade 1-4 treatment-emergent adverse events (AEs), although only 3 of 12 enrolled patients experienced grade 3-4 toxicity, only one of which required a dose reduction[21].

1.5 Rationale

There is a clear and urgent need for an effective second line treatment in BTC. The immunomodulatory properties of conventional cytotoxic therapy, particularly in regard to the upregulation of PD-L1 expression[17] rendering tumor cells more sensitive to T cell-mediated lysis and neoantigen production[18], rapid emergence of chemotherapy resistance, and known modest efficacy of single agent PDL1 antibody in BTC provides a rationale for combining chemotherapy and immunotherapy.

We hypothesize that the combination of a PD-1 targeted antibody with 5-FU and nanoliposomal-Irinotecan chemotherapy will increase objective response rates. Nanoliposomal-Irinotecan with 5-FU/LV is an attractive cytotoxic option based upon favorable side effect profile and proven effectiveness following gemcitabine based therapy in advanced pancreas cancer. In colon and pancreatic ductal adenocarcinoma, the combination of Nivolumab plus capecitabine and Irinotecan is currently being investigated in a phase Ib/II (NCT02423954) study with phase I results suggesting an acceptable safety profile[22]. We anticipate the combination of nanoliposomal-Irinotecan with 5FU/LV and Nivolumab will be well tolerated. Additionally, we hypothesize that this combination of nanoliposomal-IRI, 5-FU/LV, and Nivolumab will prolong PFS in patients with advanced biliary tract cancer treated previously with systemic chemotherapy with commensurate improvements in survival and other meaningful patient outcomes.

1.6 Correlative Studies

We will study the BTC tumor biology, DNA damage response (DDR) and immune signatures 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 (such as DDR and/or immune signatures) that may have clinical efficacy from nanoliposomal-Irinotecan and Nivolumab will be the overarching goal of these translational studies along with developing biologic insights for future therapeutic development. Biologic readouts for PD-1 and other immune 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 Phase Ib: Determine the recommended phase 2 dose (RP2D) and dose limiting toxicities (DLTs) of nanoliposomal-Irinotecan, 5-Fluorouracil, Leucovorin and Nivolumab in subjects with advanced biliary cancer

2.1.2 Phase II: Determine the median PFS

2.2 Secondary Objectives

2.2.1 Evaluate the safety and toxicity of this drug combination in this patient population

2.2.2 Evaluate the ORR and median OS

2.3 Exploratory Objectives

2.3.1 To explore biomarkers of 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, DDR 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 Endpoints Assessment: The primary endpoint of the phase 1b portion of this trial is to evaluate the incidence of DLTs at different dose levels to identify the RP2D. 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 Endpoints Assessment: Adverse events and reportable serious events are defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events (CTCAE) v5.0). 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. Follow-up time will be censored at the date of last disease evaluation.

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 carcinoma of the biliary tract (intra-hepatic, extra-hepatic (hilar, distal) or gall bladder) that is not eligible for curative resection, transplantation, or ablative therapies. Tumors with mixed hepatocellular and cholangiocarcinoma histology are excluded.

3.1.2 Patients must have received one and only one prior systemic therapy for advanced disease. Prior therapies must have not included Irinotecan or PD-1/PD-L1 antibody. Patient should have either progressed on or within 6 months of first-line systemic therapy or deemed intolerant of that therapy.

3.1.3 Prior surgical resection, radiation, chemoembolization, radioembolization or other local ablative therapies are permitted if completed ≥ 4 weeks prior to registration 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 lesion.

3.1.5 Age ≥18 years

3.1.6 Child-Pugh score of less than 7.

3.1.7 ECOG performance status of 0-1.

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

3.1.9 Available archived tissue (FFPE block or 20 unstained slides from prior core biopsy or surgery).

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

3.1.11 Adequate organ function assessed ≤2 weeks prior to registration:

absolute neutrophil count	≥ 1500/mm^3
hemoglobin	> 9 g/dL
platelets	> 75,000/mm^3
serum creatinine	≤ 1.5 x upper limit of normal (ULN)
albumin	≥ 3.0 g/dL
AST/ALT	≤ 3.0 x ULN (< 5 x ULN if liver metastasis)
total bilirubin	≤ 1.5 x ULN

3.1.12 Must not have received systemic steroid therapy, or any other form of immunosuppressive therapy within 14 days prior to registration. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed.

3.1.13 No prior history of solid organ transplantation or brain metastasis (unless treated, asymptomatic and stable).

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

3.1.15 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.

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

3.1.17 Must not have received a live vaccine within 30 days of registration.

3.1.18 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.

3.1.19 Women must not be pregnant or breastfeeding since 5-Fluorouracil, nanoliposomal-Irinotecan and/or Nivolumab 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 pregnancy test (blood or urine) within 2 weeks prior to registration.

3.1.20 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.

3.1.21 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.

3.1.22 Participants with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of registration are excluded. Inhaled, ocular, intra-articular, intra-nasal or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.1.23 No known UGT1A1* variants or Gilbert's syndrome

3.1.24 Prisoners or subjects who are involuntarily incarcerated, or compulsorily detained for treatment of either a psychiatric or physical (e.g. infectious disease) illness would be excluded.

3.1.25 No known hypersensitivity to 5-Fluorouracil, Leucovorin, Irinotecan, and/or Nivolumab.

3.1.26 Must not have ongoing bowel obstruction.

3.1.27 No known HIV, Hepatitis B or Hepatitis C infection that is untreated and/or with a detectable viral load.

3.1.28 Patients must not have uncontrolled intercurrent illness including, but not limited to, interstitial lung disease, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia.

3.1.29 No known medical condition (e.g. a condition associated with uncontrolled diarrhea such as ulcerative colitis or acute diverticulitis) that, in the investigator's opinion, would increase the risk associated with study participation or interfere with the interpretation of safety results.

3.1.30 Patients must not be on warfarin, strong CYP3A4 inducers (such as phenytoin, phenobarbital, primidone, carbamazepine, rifampin, rifabutin, rifapentine or St.

John's Wort), strong CYP3A4 inhibitors (such as ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole), and strong UGT1A1 inhibitors (such as atazanavir, gemfibrozil, indinavir and ketoconazole).

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Patient registration for this trial will be centrally managed by the Oncology Clinical Trials Support Unit (i.e. the Coordinating Center) of the University of Michigan Rogel 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 a Screening and Enrollment Log.

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 CTSU-Oncology-Multisite@med.umich.edu.

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. EST 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 to provide the study identification 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 enrollment to the study otherwise the patient will be taken off-study. Re-screening is allowed.

Patients will receive combination therapy with nanoliposomal-Irinotecan, 5-Fluorouracil, Leucovorin and Nivolumab. Prophylaxis/pre-medications per institutional policy. The safety profile of nanoliposomal-Irinotecan, 5-Fluorouracil, Leucovorin agents in combination has been previously evaluated. The safety profile of Nivolumab has been previously evaluated as well.

Patients will begin phase Ib dosing at dose level 0 and up to 10 patients will be treated at this level. If toxicity limits are not exceeded as per section 11.2, dose level 0 will be declared the recommended phase 2 dose and 20 additional patients will be treated on the phase II study.

Table 2. Treatment Plan (Day 1 Q14 days)				
Dose Level	**Leucovorin (IV over 90 min)**	**nanoliposomal-Irinotecan (IV over 90 min)**	**5-FU continuous infusion (IV over 46 hours)**	**Nivolumab (IV over 30 min)**
0	400 mg/m^2	70 mg/m^2	2400 mg/m^2	240 mg
-1	200 mg/m^2	70 mg/m^2	2000 mg/m^2	240 mg

Infusion times (+/- 10 min except 5-FU pump which would be per manufacturer guidelines) may be extended as needed for safety (e.g. infusion reaction occurs) but these instances should be documented in the patient medical records. The Leucovorin and nanoliposomal-Irinotecan will be infused concurrently, followed by Nivolumab and then the 5-FU continuous infusion. Pre-medications per institutional policy. Patients may continue treatment for 2 years in absence of disease progression or unacceptable toxicity.

5.2 Dose Limiting Toxicities (DLTs)

A DLT will be any of the following occurring during the first 4 weeks of therapy attributed (possibly, probably, or definitely) to the drug combination following day 1 treatment and occurring in the 28-day interval as assessed using the NCI CTCAE v5.0.

1. Grade 4 or greater hematological toxicity with the exception of uncomplicated grade 4 leukopenia/ neutropenia lasting <7 days)
2. Grade 3 or higher thrombocytopenia with bleeding
3. Grade 3 or greater febrile neutropenia per CTCAE v5.0 criteria.
4. Grade 3 or greater non-hematological toxicity, except nausea, vomiting, diarrhea, (lasting <3 days or without supportive care measures), hyperbilirubinemia (secondary to biliary obstruction), alopecia, fatigue, and hypersensitivity reaction
5. Any death not clearly due to the underlying disease or extraneous causes.
6. Any hepatic adverse event meeting the criteria for Hy's Law
7. Grade 3 or higher electrolyte abnormality that lasts >72 hours, or is clinically complicated, or does not resolve spontaneously or with conventional medical interventions.

With completion of cycle 1 and 2, and following DLT determination (**yes vs. no**), cycle 3 may begin.

5.3 Toxicities and Dosing Delays/Dose Modifications

General Considerations

1. Subsequent cycles of therapy may begin when ANC $\geq$ 1,000, platelets $\geq$ 75K and all toxicity attributable to treatment has resolved to $\leq$ grade 1 (except as noted in section 5.3.3).
2. Doses will not be modified for cholangitis attributable to biliary obstruction/stent occlusion unless this occurs in the setting of $\geq$ grade 3 neutropenia.
3. 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.
4. Efforts to attribute toxicity experienced to a single component or some combination of the cytotoxic agents will be made by treating investigator and doses of the accountable agent(s) will be modified or held according to that judgment. Dose adjustments for toxicity will be described in the clinical record.
5. Doses that are reduced for toxicity will not be subsequently increased.
6. If a patient experiences neutropenic fever at any point in the treatment cycle, chemotherapy will be delayed until ANC $\geq$ 1,000 and antibiotic treatment of the event

is completed. When treatment resumes, consider one dose level reduction as per Table 2 for one/more agents.

7. If a chemotherapy treatment is not given on day 1 of any cycle due to toxicity per Table 4 or5, one or more drugs will require dose modification as per Table 3.
8. Treatment delay of more than 28 days from last intended therapy will result in discontinuation from trial, unless otherwise agreed and documented between the investigator and the sponsor-investigator.
9. Investigators should consider dose re-calculation 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.
10. If more than one toxicity occurs requiring dose reduction, the dose administered should be based on the most severe toxicity.
11. If one of the drugs is held or discontinued due to toxicity attributed to that agent, the patient will be allowed to continue the rest of the combination therapy.
12. Nivolumab cannot be dose reduced and can only be held or discontinued as per detailed algorithms for immune-therapy toxicity management in Appendix III.
13. If the regimen held or missed was to be given on Day 1 then that cycle will not be considered to start until the day the first dose is actually administered.

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/Study Calendar (Section 6.2).

Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

Table 3. Dose Modifications

Drug	Current Dose	Percentage Decrease	Modified Dose
nanoliposomal-Irinotecan	70 mg/m^2	20%	55 mg/m^2
	55 mg/m^2	20%	45 mg/m^2
	45 mg/m^2	100%	Discontinue
Leucovorin	400 mg/m^2	50%	200 mg/m^2
	200 mg/m^2	100%	Discontinue
5-Fluorouracil	2400 mg/m^2	20%	2000 mg/m^2
	2000 mg/m^2	20%	1600 mg/m^2
	1600 mg/m^2	100%	Discontinue
Nivolumab	240 mg IV	100%	Discontinue

Table 4. Dose Modifications for Hematologic Toxicity for 5-Fluorouracil, Leucovorin and nanoliposomal-Irinotecan	
Hematologic Toxicity	**Dose Adjustment for 5-Fluorouracil, Leucovorin and nanoliposomal-Irinotecan**
ANC[1] ≥ 1000/mm^3 AND Platelets ≥ 75,000/mm^3	Treat as scheduled
ANC[1] < 1000/mm^3 OR/AND Platelets < 75,000/mm^3	Hold all drugs up to a maximum of 28 days from expected date of treatment until ANC ≥ 1000/mm^3 AND platelets ≥ 75,000/mm^3 then resume at next lower dose level for either or all drugs 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: Dose Modifications for Non-Hematologic Toxicity for 5-Fluorouracil, Leucovorin and nanoliposomal-Irinotecan		
Non-Hematologic Toxicity	**Dose Adjustment for 5-Fluorouracil/Leucovorin**	**Dose Adjustment for nanoliposomal-Irinotecan**
Alopecia, anemia, venous thromboembolism	No modification to doses	
Grade ≥3 nausea and vomiting (ongoing after maximal anti-emetic therapy)	Consider decrease	Consider decrease
Grade ≥2 hyperbilirubinemia	Hold 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 of one or more drugs.	

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 will be described in the clinical record.

5.4 Management Algorithms for Immuno-Oncology Agents

Nivolumab is 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 and consider the following criteria.

- Dosing delays to allow for prolonged steroid tapers to manage Nivolumab-related AEs are allowed. Prior to initiating treatment in a subject with a dosing delay lasting >4 weeks starting from date of missed/due dose, the sponsor-investigator must be consulted.
- Delay Nivolumab dosing for grade 2 non-skin, drug-related AE, with the exception of fatigue, constipation, hypertension
- Delay Nivolumab dosing for grade 3 drug-related laboratory abnormality, with the exception of lymphopenia, asymptomatic amylase or lipase.
- Discontinue Nivolumab for grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to grade 2 severity within the re-treatment period, or requires systemic treatment.
- Discontinue Nivolumab for any grade 3 non-skin, drug-related AE lasting >7 days or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, hypersensitivity reactions, infusions reactions and endocrinopathies.
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, neurologic toxicity, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
    - Grade 3 drug-related laboratory abnormalities do not require discontinuation except:
        - Grade 3 drug-related thrombocytopenia lasting >7 days or associated with bleeding requires discontinuation
        - Grade >3 or higher drug-related AST, ALT or total bilirubin management as per Hepatic AE Management Algorithm in Appendix III.
- Discontinue Nivolumab for any grade 4 drug-related AE or laboratory abnormality (including, but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
    - Grade 4 neutropenia $\leq$ 7 days
    - Grade 4 lymphopenia, leukopenia, asymptomatic amylase or lipase

  - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of onset
  - Grade 4 drug-related endocrinopathy AE, such as hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones, or glucose-controlling agents, respectively, may not require discontinuation after discussion with the sponsor-investigator.
- Discontinue Nivolumab for any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator present a substantial clinical risk to the subject with continued Nivolumab dosing.

Subjects may resume treatment with Nivolumab when the drug-related AE(s) resolve to grade $\leq$1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of grade 2 fatigue
- Subjects who have not experienced a grade 3 drug-related skin AE may resume treatment in the presence of grade 2 skin toxicity
- Subjects with grade 2 AST, ALT and/or total bilirubin abnormalities, dosing may resume when laboratory values return to baseline, and management with corticosteroids (if needed) is complete.
- Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Participants with persistent grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by sponsor-investigator,
- Subjects with drug-related endocrinopathies controlled with only physiologic hormone replacement may resume treatment. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

5.5 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
- Concurrent radiation
- Warfarin
- Strong CYP3A4 inducers (such as phenytoin, phenobarbital, primidone, carbamazepine, rifampin, rifabutin, rifapentine or St. John's Wort) and inhibitors (such as ketoconazole, clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole). Please refer to the FDA package insert for nanoliposomal-Irinotecan for details.
- Strong UGT1A1 inhibitors (such as atazanavir, gemfibrozil, indinavir and ketoconazole). Please refer to the FDA package insert for nanoliposomal-Irinotecan for details.

5.6 Other Modalities or Procedures

None

5.7 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 2 years until one of the following criteria apply:

- Disease progression as defined in Section 7.0
- Treatment delay of more than 28 days from last intended therapy
- 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

5.8 Off-Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.7 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 5.9. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.9 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.

5.10 Off-Study Criteria

Patients can be taken off study treatment 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 treatment/study participation will be documented and may include:

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

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

5.10.3 Patient is unable to comply with protocol requirements;

5.10.4 Treating physician judges continuation on the study would not be in the patient's best interest;

5.10.5 Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);

5.10.6 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;

5.10.7 Lost to Follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented;

5.10.8 Termination of the study by the Sponsor, the University of Michigan or the FDA;

5.10.9 Patient completes protocol treatment and follow-up criteria;

5.10.10 Patient has confirmed progressive disease as per RECISTv1.1/irRECIST criteria and/or, at the discretion of the treating physician, exhibits clinical progression which warrants removal from the study.

5.11 Patient Replacement

All patients that receive at least one dose of study therapy will be considered evaluable for toxicity and will be considered a member of the intent-to-treat (ITT) population.

Patients enrolled on the study will be replaced and not considered a member of the ITT for the following reasons

1. Patients who received no investigational therapy on study.
2. Patients that withdraw consent for study therapy prior to first response evaluation not secondary to toxicity.
3. Patients meeting off-study criteria 5.10.1 and/or 5.10.3 not secondary to toxicity.
4. Patients meeting off-study criteria 5.10.2 and/or 5.10.5

We expect the proportion of patients needed to be replaced to be extremely small for this clinical trial, at or less than 10% of those enrolled. Maximum enrollment to this trial will be increased from 30 to 35 and from 40 to 44 patients if the necessity to replace patients is encountered.

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 6. Study Calendar					
Procedures	**Screening[1]**	***Cycle 1**	**Cycle 2+**	**EOT Visit[10]**	**Follow-Up Q3 months +/- 1 week[11]**
		Day 1	**Day 1**		
Informed Consent	X				
History, Physical Examination	X	X	X[13]	X	X
Weight, BSA	X	X	X	X	
Vital Signs	X	X	X	X	
Performance Status	X	X	X[13]	X	
Toxicity Evaluations[12]		X	X[13]	X	X
CBC with differential	X	X	X		
CMP[2]	X	X	X		
Other labs[3]		X	X		
CA 19-9 (or CEA)[4]	X	X	X	X	
PT, PTT	X				
Pregnancy Test[5]	X	X	X		
Concomitant Medication Review	X	X	X[13]		
Scans with Tumor Measurements[6]	X		X		
Research Blood[7]		X	X	X	
Tissue[8]	X		X	X	
Study Drug Administration[9]		X	X		
Survival Follow-up					X

*Cycle = 2 weeks

1. All screening procedures to be completed within 2 weeks of registration, except imaging which should be ≤ 4 weeks. Protocol treatment is to begin ≤14 calendar days of registration.
2. Comprehensive metabolic panel includes BUN/creatinine, sodium, potassium, chloride, glucose, calcium, alkaline phosphatase, AST, ALT, total bilirubin, total protein and albumin.
3. Amylase, lipase, random cortisol, TSH, free T4 and free T3 on cycle 1 day 1, and then day 1 of every odd-numbered cycle.
4. Check CA 19-9 (or CEA, if CA 19-9 not expressed) every odd-numbered cycle, if patient is known to express these tumor markers.

5. Required for females of childbearing potential. Serum or urine pregnancy test per site investigator discretion. Must be completed prior to every odd numbered cycle.
6. MRI or CT (abdomen/pelvis) with contrast along with CT chest with/without contrast will be assessed as follows: at Screening ≤4 weeks **prior** to study enrollment; C2 + performed at every 8 ± 1 week from C1D1. Subsequent scans should be performed 8 ±1 week from the date of last scan. 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.
7. See Section 10.1 for details. Cycle 1 Day 1 specimens will be collected pre-treatment and Cycle X Day 1 specimens will only be collected on Cycle 5 Day 1 prior to drug administration.
8. Pre-treatment, diagnostic pathology specimens obtained in the course of standard biopsy or surgery. Formalin-Fixed Paraffin-Embedded (FFPE) block(s) (preferred), or 20 FFPE slides plus H&E slide is required. Procurement of tissue is mandatory for enrollment. On-treatment biopsies will only be collected at/after cycle 4 day 1 for patients enrolled at the University of Michigan. Post-treatment biopsies on progression are optional (see Section 10.1).
9. See Section 5.1 for details. Study drug administration with associated labs will have a window of ± 3 days.
10. 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.
11. Patients will be followed every 3 months +/- 1 week after completion of (or early withdrawal from) study treatment 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.
12. 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.
13. Cycle 2, 3, and then every odd-numbered cycle

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect- Solid Tumors

Immunotherapy drugs such as Nivolumab 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 study treatment.

Evaluable for primary endpoint, PFS at 4 months. All patients that receive at least one dose of study therapy will be considered evaluable. Patients enrolled to therapy but that never receive study therapy will be replaced.

Evaluable for objective response. All enrolled patients who have measurable disease at registration, receive at least 1 cycle(s) of therapy, and have 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 be considered progressive disease.)

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 >10 mm 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 5 mm 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 disease progression per RECIST 1.1, 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.

Table 7. 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 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)
- Tumor markers are stable/improving, if expressed

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 6.2).

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 20% increase in tumor burden with a minimum 5 mm absolute increase from time of initial PD. 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 5.0 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. Adverse Events of Special Interest as defined in section 8.2.4 will be collected throughout the subject's participation in the study. 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.

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.

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 or vital sign finding which requires protocol treatment to be modified), 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.
- Anticipated fluctuations of pre-existing conditions, including the disease under study, that don't represent a clinically significant exacerbation or worsening, do not need to be reported as AEs.

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
  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 investigator], 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 $\geq$ 24 hours

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- 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.

Events or outcomes not qualifying as SAEs:

- 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.

- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period.

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, progression of liver metastasis, or the administration of other drug(s) known to be hepatotoxic.

8.2.4 Adverse Events of Special Interest (AESI)

AESIs (serious or non-serious) are defined as AEs of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

These events may differ from those caused by non-immunotherapies and may require immunosuppression as part of their management.

All AESIs must be reported as SAEs and will be collected throughout the subject's participation in the study.

The AESI(s) for this trial are:

- Demyelination,
- Encephalitis,
- Guillain-Barré syndrome,
- Myasthenic syndrome,
- Uveitis.

8.2.5 Pregnancy or drug exposure during pregnancy

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

All pregnancies occurring during study participation or within 6 months of last dosing must be reported to the Coordinating Center within the same timelines as for an SAE.

All pregnancies should be followed through to outcome whenever possible. The Coordinating Center should be notified once the outcome of a pregnancy is known.

The Coordinating Center will be responsible for reporting pregnancy information to the FDA and supporters, as appropriate (outlined below).

8.2.6 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 Inserts (Labels).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochures.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9 for the list of expected adverse events related to the drug under study.
- The "expectedness" of an event is defined only in relation to the study drug(s) and does not relate to it being "anticipated" due to the disease or population under study.

8.2.7 Unexpected Adverse Event

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

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 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 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.
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.
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 734-232-0744 or via email to CTSU-Oncology-Multisite@med.umich.edu within 24 hours of the site's knowledge of the event.

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

Participating sites should report all SAEs and UPs to their local IRB per current local 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 and events of pregnancy) 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. All AESIs will be collected and reported to BMS throughout the subject's participating in the study.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to BMS Worldwide Safety (Worldwide.Safety@bms.com; Fax: 609-818-3804).

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 Ipsen

All Serious Adverse Events (SAEs and events of pregnancy) 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 Ipsen. 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 Ipsen. All AESIs will be collected and reported to Ipsen throughout the subject's participating in the study.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to Ipsen (drugsafety.USA@ipsen.com).

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 Ipsen within 24 hours of receipt.

8.4.4 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. The Michigan IND/IDE

Assistance Program (MIAP) will be responsible for reporting SAEs to the FDA that meet the reporting requirements in 21 CFR 312.32.

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 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 should report it to the Coordinating Center within 24 hours of awareness and to their local IRB per local guidelines.

8.7 Safety Report Reconciliation

The Sponsor-Investigator, or designee will reconcile the clinical database SAE reports transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com and Ipsen Oncology (drugsafety.USA@ipsen.com). Frequency of reconciliation should be as outlined in the clinical study agreements. BMS GPV&E will email, upon request from the Sponsor-Investigator, or designee, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com and drugsafety.USA@ipsen.com. 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, and/or Ipsen the report should be sent immediately as appropriate.

8.8 Stopping Rules

There are no formal stopping rules for this study; however, the Data and Safety Monitoring Committee (DSMC) of the University of Michigan Rogel Cancer Center is the DSMC for this study and will be responsible for monitoring the safety and data integrity of the trial as outlined in Section 13.

9.0 DRUG INFORMATION

9.1 Nanoliposomal-Irinotecan

9.1.1 Other Names

Onivyde®

9.1.2 Classification

nanoliposomal-Irinotecan is formulated with Irinotecan hydrochloride trihydrate, a topoisomerase I inhibitor, into a liposomal dispersion for intravenous use.

9.1.3 Mechanism of Action

Irinotecan liposome injection is a topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome. Topoisomerase 1 relieves torsional strain in DNA by inducing single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase 1-DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. In mice bearing human tumor xenografts, Irinotecan liposome administered at Irinotecan HCl-equivalent doses 5-fold lower than Irinotecan HCl achieved similar intratumoral exposure of SN-38.

9.1.4 Pharmacokinetics

The pharmacokinetic parameters of total Irinotecan and total SN-38 following the administration of nanoliposomal-Irinotecan 70mg/m^2 as a single agent or part of combination chemotherapy are presented in Table 4 of the package insert. Over the dose range of 50 to 155 mg/m^2, the Cmax and AUC of total Irinotecan increases with dose. Additionally, the Cmax of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

1. Distribution:
   Direct measurement of Irinotecan liposome showed that 95% of Irinotecan remains liposome-encapsulated, and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose. The mean volume of distribution is summarized in Table 4 of the package insert. Plasma protein binding is <0.44% of the total Irinotecan in nanoliposomal-Irinotecan.

2. Metabolism:
   The metabolism of Irinotecan liposome has not been evaluated. Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. In the population pharmacokinetic analysis using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had total SN-38 average steady-state concentrations of 1.06 and 0.95 ng/mL, respectively.

3. Elimination:

The disposition of nanoliposomal-Irinotecan has not been elucidated in humans. Following administration of Irinotecan HCl, the urinary excretion of Irinotecan is 11 to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of Irinotecan and its metabolites (SN-38 and SN-38 glucuronide), over a period of 48 hours following administration of Irinotecan HCl in two patients, ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

9.1.5 Storage, Preparation and Stability

Refer to the current Investigator Brochure for storage, stability and special handling information.

9.1.6 Dosing and Administration

See Section 5.1
nanoliposomal-Irinotecan injection should be administered as a 90 (± 10 minute) intravenous infusion without the use of an in-line filter.

9.1.7 Availability

Ipsen pharmaceuticals will provide the study drug.

9.1.8 Handling and Disposal

The investigator will be instructed by the Coordinating Center on the return or destruction of unused nanoliposomal-Irinotecan. If any nanoliposomal-Irinotecan is lost or damaged, its disposition should be documented in the source documents. nanoliposomal-Irinotecan supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center.

If instructed to do so, unused supplies of nanoliposomal-Irinotecan should be destroyed according to institutional policies. Destruction will be documented in the drug accountability forms.

9.1.9 Drug accountability

The investigator or designee is responsible for taking an inventory of each shipment of nanoliposomal-Irinotecan received, and comparing it with the accompanying form. Accurate records will be kept in the source documentation of all drug administration (including dispensing and dosing).

9.1.10 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.
   The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of nanoliposomal-Irinotecan70 mg/m^2 with Leucovorin 400 mg/m^2 and Fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks (nanoliposomal-Irinotecan/5-FU/LV; N=117), nanoliposomal-Irinotecan 100 mg/m^2 every 3 weeks (N=147), or Leucovorin 200 mg/m2 and Fluorouracil 2000 mg/m^2 over 24 hours weekly for 4 weeks followed by 2-week rest (5-FU/LV; N=134). Serum bilirubin within the institutional normal range, albumin ≥ 3 g/dL, and Karnofsky Performance Status (KPS) ≥ 70 were required for study entry. The median duration of exposure was 9 weeks in the nanoliposomal-Irinotecan/5-FU/LV arm, 9 weeks in the nanoliposomal-Irinotecan monotherapy arm, and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥ 20%) of nanoliposomal-Irinotecan were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥ 2%) of nanoliposomal-Irinotecan were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of nanoliposomal-Irinotecan in 11% of patients receiving nanoliposomal-Irinotecan/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of nanoliposomal-Irinotecan were diarrhea, vomiting, and sepsis. Dose reductions of nanoliposomal-Irinotecan for adverse reactions occurred in 33% of patients receiving nanoliposomal-Irinotecan/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. nanoliposomal-Irinotecan was withheld or delayed for adverse reactions in 62% of patients receiving nanoliposomal-Irinotecan/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.

2. Pregnancy
Risk Summary - Based on animal data with Irinotecan HCl and the mechanism of action of nanoliposomal-Irinotecan, nanoliposomal-Irinotecan can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with Irinotecan HCl, at doses resulting in Irinotecan exposures lower than those achieved with nanoliposomal-Irinotecan 70 mg/m^2 in humans, administered to pregnant rats and rabbits during organogenesis [see Data]. Advise pregnant women of the potential risk to a fetus. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data - Animal Data No animal studies have been conducted to evaluate the effect of Irinotecan liposome on reproduction and fetal development; however, studies have been conducted with Irinotecan HCl. Irinotecan crosses the placenta of rats following intravenous administration. Intravenous administration of Irinotecan at a dose of 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose resulted in an Irinotecan exposure of approximately 0.002 times the exposure of Irinotecan based on area under the curve (AUC) in patients administered nanoliposomal-Irinotecan at the 70 mg/m^2 dose. Administration of Irinotecan HCl resulted in structural abnormalities and growth delays in rats at doses greater than 1.2 mg/kg/day (approximately 0.0002 times the clinical exposure to Irinotecan in nanoliposomal-Irinotecan based on AUC). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan HCl administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

3. Lactation:
   Risk Summary - There is no information regarding the presence of Irinotecan liposome, Irinotecan, or SN-38 (an active metabolite of Irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk [see Data below]. Because of the potential for serious adverse reactions in breastfed infants from nanoliposomal-Irinotecan, advise a nursing woman not to breastfeed during treatment with nanoliposomal-Irinotecan and for one month after the final dose.
   Data - Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled Irinotecan HCl and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

4. Drug Interactions:
   In a population pharmacokinetic analysis, the pharmacokinetics of total Irinotecan and total SN-38 were not altered by the co-administration of Fluorouracil/Leucovorin. Following administration of Irinotecan HCl, dexamethasone, a moderate CYP3A4 inducer, does not alter the pharmacokinetics of Irinotecan. In vitro studies indicate that Irinotecan, SN-38 and another metabolite, aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes.

   Strong CYP3A4 Inducers Following administration of non-liposomal Irinotecan (i.e., Irinotecan HCl), exposure to Irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's Wort) if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of Onivyde therapy. 7.2 Strong CYP3A4 or UGT1A1 Inhibitors Following administration of non-liposomal Irinotecan (i.e., Irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to Irinotecan and its active metabolite SN-38. Co-administration of nanoliposomal-Irinotecan with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to Irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible.

9.2 5-Fluorouracil (5-FU)

5-FU will be supplied from commercially available product obtained through the local hospital pharmacy or licensed distributor in accordance with local guidelines. For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, known precautions, warnings and adverse reactions please see the 5-FU package insert.

9.3 Leucovorin (LV)

Leucovorin will be supplied from commercially available product obtained through the local hospital pharmacy or licensed distributor in accordance with local guidelines. For complete details on drug preparation, administration, storage conditions, clinical pharmacology, pharmacokinetics, known precautions, warnings and adverse reactions please see the Leucovorin package insert. Note, Leucovorin should not be mixed in the same infusion as 5-Fluorouracil, since this may lead to the formation of a precipitate.

9.4 Nivolumab

9.4.1 Other Names

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

9.4.2 Classification

Immunomodulatory; checkpoint inhibitor

9.4.3 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.

9.4.4 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. 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.

9.4.5 Storage, Preparation and Stability

Nivolumab is supplied as 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. Do not freeze or shake.

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 or dilute with either NS or D5W to protein concentration as low as 0.35mg/mL. The total volume of infusion must not exceed 160mL and for patients with body weight of less than 40 kg it must not exceed 4mL/kg of body weight. 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), polyolefin containers and infusion sets, 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 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

9.4.6 Dose and Administration

See Section 5.1

Nivolumab is to be administered as a 30 (± 10 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.

9.4.7 Availability

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

9.4.8 Handling and Disposal

The investigator will be instructed by the Coordinating Center on the destruction of unused Nivolumab. If any Nivolumab is lost or damaged, its disposition should be documented in the source documents. Nivolumab disposal will be conducted at individual sites and will not be returned to BMS. Nivolumab supplies will be retained at the clinical site pending instructions for disposition by the Coordinating Center. Recommended safety measures for preparation and handling of Nivolumab include laboratory coats and gloves.

When instructed to do so, unused supplies of Nivolumab should be destroyed according to institutional policies. Destruction will be documented in the drug accountability forms.

9.4.9 Drug accountability

The investigator or designee is responsible for taking an inventory of each shipment of Nivolumab received, and comparing it with the accompanying form. Accurate records will be kept in the source documentation of all drug administration (including dispensing and dosing).

9.4.10 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).

   The most common adverse reaction (≥20%) in patients with melanoma was rash. The most common adverse reactions (≥20%) in patients with advanced squamous non-small cell lung cancer were fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation.

   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 5 months (for women) and 7 months (for men) 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.

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 nanoliposomal-Irinotecan 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 RNA later. 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)[23,24]. 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)[25] 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[23] (for patients at University of Michigan). Biologic markers and RNA expression will be examined in the context of patient efficacy.

10.1 Tissue Collection Guidelines (See Laboratory Manual for details)

Pre- and Post-treatment (for patient at all sites excluding University of Michigan):

1. Pre-treatment: Screening:

Formalin-fixed paraffin-embedded (FFPE) diagnostic tumor tissue block(s) is preferred to allow IHC and genomic/immune profiling. If not, then up to 20 FFPE 5 micron slides plus a H&E slide from a core biopsy block will be required for IHC. Procurement of tissue is mandatory to complete correlative studies.

2. Post-treatment biopsy for research (optional):

Tissue should be collected, processed and shipped to University of Michigan as detailed in the lab manual.

Pre-, On- and Post-treatment (for patients enrolled at University of Michigan):

1. Pre-treatment tissue collection: Screening
2. On-treatment biopsy for research: Cycle 4 Day 1
3. Post-treatment biopsy for research (optional): EOT

Please refer to the lab manual for 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.

10.2 Blood Collection Guidelines

Blood samples will be collected at three different time-points for each patient as detailed below:

1. Pre-treatment: Cycle 1 Day 1
2. On-treatment: Cycle 5 Day 1
3. Post-treatment: EOT

Blood will be collected, processed and shipped to the University of Michigan as detailed in the lab manual.

10.3 Specimen Banking

Patient blood and tissue samples collected for this study will be retained at University of Michigan for optional unspecified future research. 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.

All CT scans should be de-identified and coded using trial patient and site IDs and submitted to the University of Michigan for banking and exploratory endpoint assessment. Refer to Lab Manual for details.

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 enroll patients with advanced unresectable BTC who have received one and only one prior systemic therapy (not including Irinotecan or PD-1 antibody) and have either progressed or deemed intolerant to at front-line systemic therapy. The primary endpoint of phase Ib portion of the trial is determination of RP2D and DLTs and the primary endpoint of the phase II portion is median PFS following the initiation of study treatment. Secondary endpoints include the calculation of the ORR, median OS (from start of study treatment and 1st line therapy), and the incidence of adverse events.

11.2 Sample Size and Accrual

A limited phase 1b trial will be implemented to assure that dose levels suggested for this combination are safe. Because toxicity across the combined agents is expected to be additive rather than synergistic and in light of the poor prognosis for this patients, we are willing to tolerate up to but not exceeding 30% DLT toxicity proportion during the first 4 weeks of therapy. To investigate this, we will enroll up to 10 patients to the phase Ib portion of this trial at dose level 0. If>4 patients of the first 5 to 10 patients enrolled into this cohort have a DLT during the first 4 weeks of therapy then accrual at dose level 0 will halt if yet to reach 10. Dose level will then be abandoned in favor of dose level -1. The operating characteristics for this schema for different values for the true probability of DLT are given in the table 3 below.

Table 8. Operating Characteristics for Trial Schema

Probability of DLT	Probability of early stopping	Probability declaring level not safe	Expected sample size	Expected number of patient experiencing DLT†
0.20	0.007	0.032	10	2.0
0.25	0.020	0.075	10	2,5
0.30	0.050	0.149	9.9	3.0
0.35	0.100	0.250	9.8	3.4
0.40	0.167	0.371	9.7	3.8
0.45	0.263	0.500	9.4	4.1
0.50	0.379	0.623	9.1	4.4

†Mean number of patients experiencing toxicity for each trial, whether stopped early or complete accrual.

If the toxicity boundary of 4 is crossed at dose level 0, up to an additional 10 patients will be accrued at dose level -1 and the same rules applied. If at dose level -1 more than 4 patients experience DLT, then the trial will be stopped and the combination abandoned. However, if either the 10-patient cohorts at dose level 0 or level -1 conclude without tripping the toxicity rule then that dose level will be declared the recommended phase 2 dose (RP2D) with an additional 20 patients enrolled at that dose level for the Phase 2 assessment of efficacy as measured by the median PFS. The median PFS of second line treatment of cholangiocarcinoma is expected to be 2.9 months (null) and we expect that the median PFS will be 5.0 months (alternate hypothesis) for this study's combination. We anticipate that we can accrue 1.7 patients per month for 18 months (between phase 1b and phase 2); we will follow all patients for progression and survival for 12 months following the accrual of the last patient. This will afford 83% power to detect the

hypothesized difference in median PFS time, using a two-sided test with at most 5% type one error. Patients on the phase Ib portion of this trial treated at the RP2D will be included in the population for the analysis of the primary endpoint of the phase II portion of the trial.

During the phase 2 portion of the trial, we will continue to monitor patients for toxicity, identically as during the first 4-weeks of therapy as for the phase I patients. If at any point during the conduct of the phase 2 portion of this trial, the observed proportion of first-cycle dose-limiting toxicity is 45% or above at the RP2D then we will halt new accrual to the trial. The DSMB for this trial will then reconsider the appropriate level for the RP2D in light of the proportion, type, severity, and reversibility of DLTs.

11.3 Study Populations

The evaluable population for the primary, secondary, and safety endpoints is the intent-to-treat (IIT) population as defined in section 5.11.

11.4 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 treatment), 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. ORR will be determined as per the irRECIST guidelines for the IIT population. Other safety data (e.g., laboratory safety parameters, vital signs, and new physical examination findings) will be summarized descriptively for the IIT population by reporting counts and percentages, with exact binomial confidence intervals where appropriate. Adverse events will be reported per the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0.

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 8.4 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

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan, with oversight by the Rogel Cancer Center Data and Safety Monitoring Committee (DSMC).

The Sponsor-Investigator (S-I)/Study Principal Investigator will provide ongoing monitoring of data and patient safety in this trial and conduct regular data review with participating sites.

The Sponsor-Investigator (S-I)/Study Principal Investigator and/or the Project Manager/Delegate will review data and patient safety issues with participating sites per a defined monthly meeting cadence. Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (SAE reporting, unanticipated problems)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Participating sites are required to ensure all pertinent data for the review period are available in the database at the time of the discussion.

Participating sites unable to participate in the data review meeting are required to provide written confirmation that their site has reviewed the relevant data and patient safety issues for the review period and their site's data are in alignment with the data reported in the database. Written confirmation is to be provided to the Project Manager/Delegate within the timeline requested to retain compliance with monitoring timelines.

Documentation of the teleconference or alternate mechanism utilized to review items above is to be retained in the Trial Master File.

The Project Manager/Delegate is responsible for collating the data from all participating sites and completing the Protocol Specific Data and Safety Monitoring Report (DSMR) form to document the data review meeting discussion.

The DSMR will be signed by the Sponsor-Investigator (S-I)/Study Principal Investigator or designated Co-Investigator and submitted to the DSMC on a monthly basis for independent review.

14.0 QUALITY ASSURANCE AND AUDITS

The DSMC 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 Rogel Cancer Center 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 University of Michigan Rogel Cancer Center. 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 Coordinating Center 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 Cycle 2. 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.

16.0 REFERENCES

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17.0 APPENDICES

Appendix I ECOG Performance Status
Appendix II Child-Pugh Score
Appendix III Management Algorithms for Immuno-Oncology Agents
Appendix IV Investigator's Statement
Appendix V Study Management during COVID-19

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
Prothrombin Time • **PT >ULN** • **INR**	 1-3 <1.7	 4-6 1.7-2.3	 >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: Child CG, Turcotte JG. Surgery and portal hypertension. In: Child CG, editor. The Liver and Portal Hypertension. Philadelphia: Saunders; 1964. pp. 50–58.

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 (I-O) 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

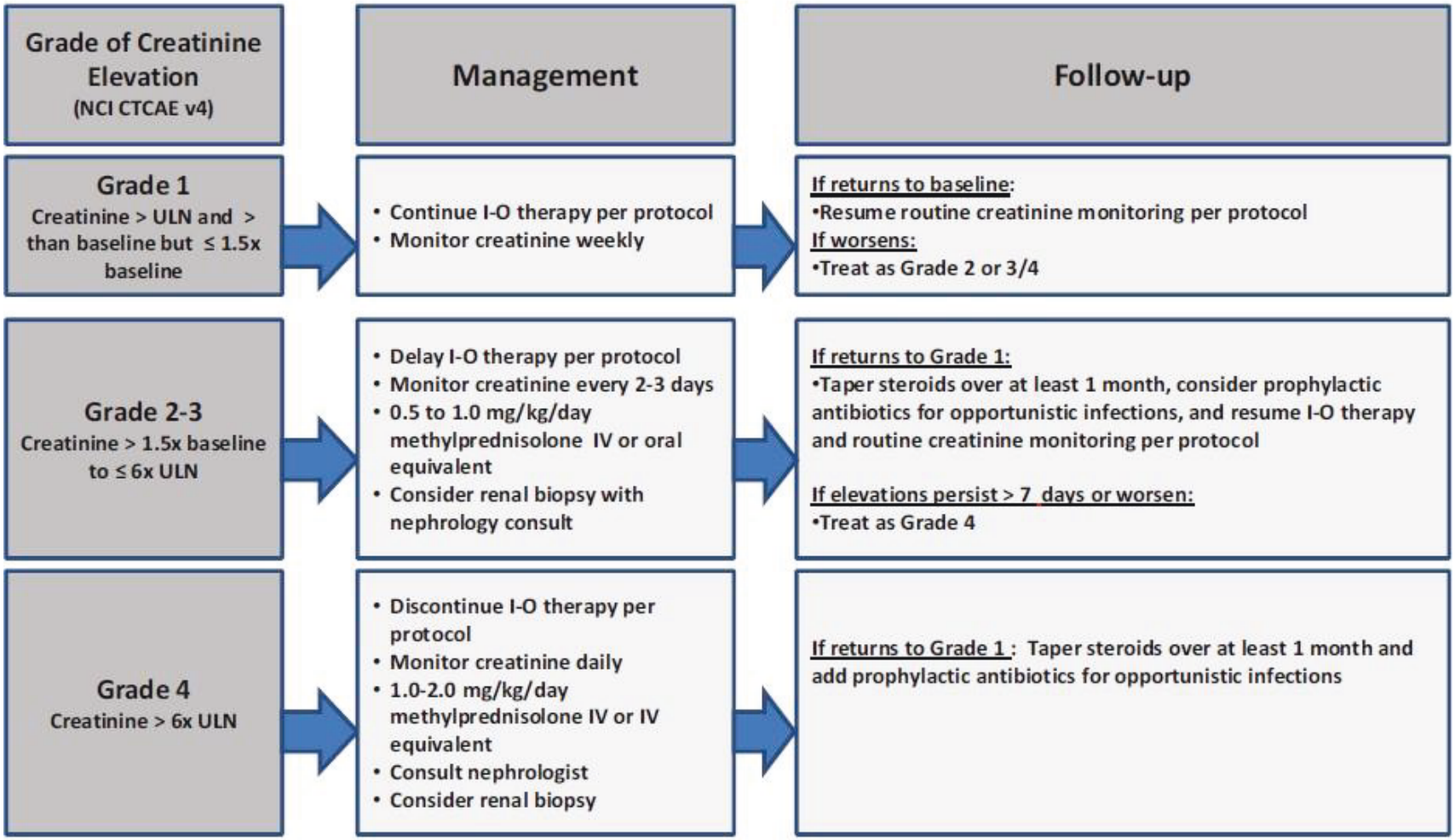
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

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

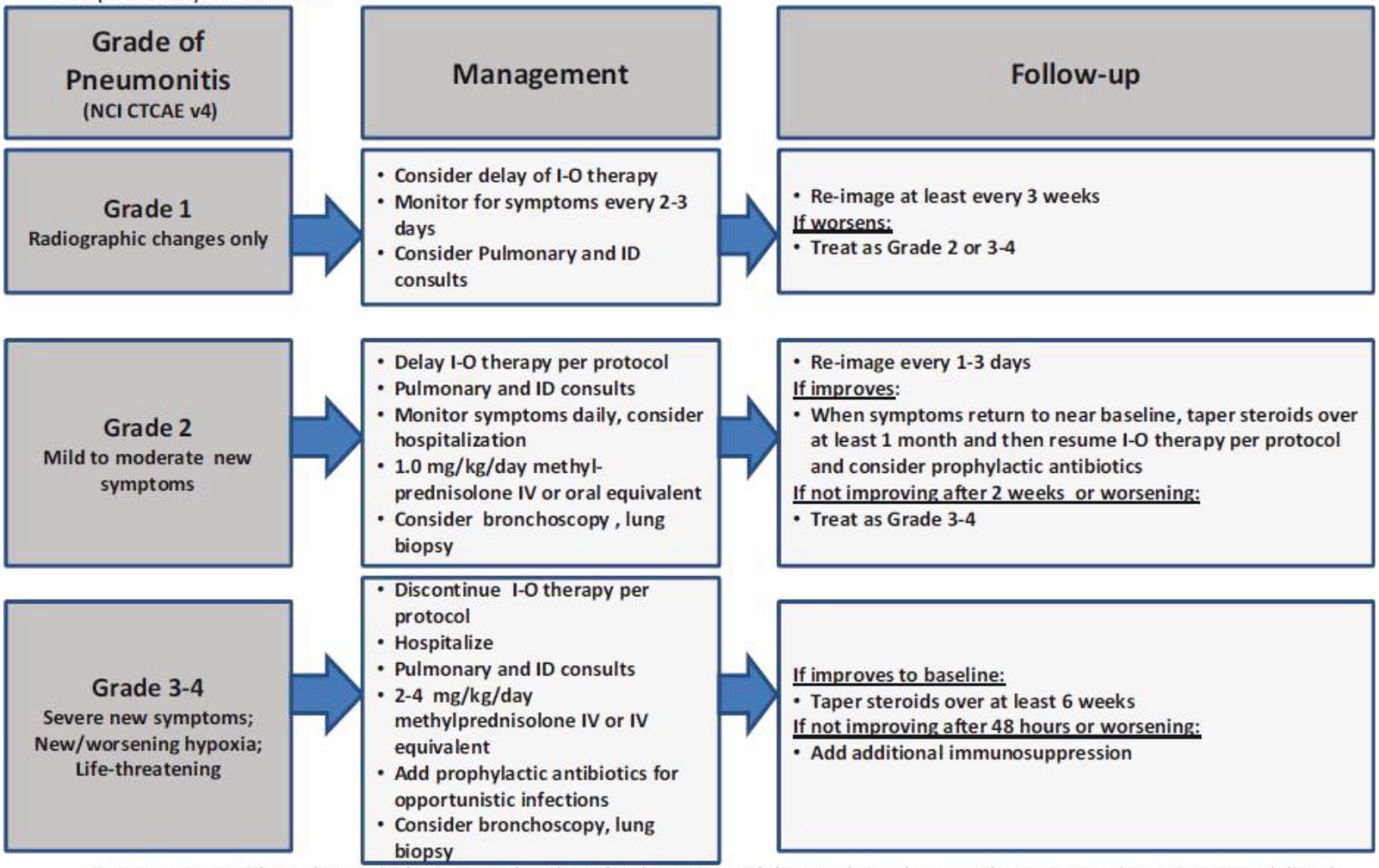
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

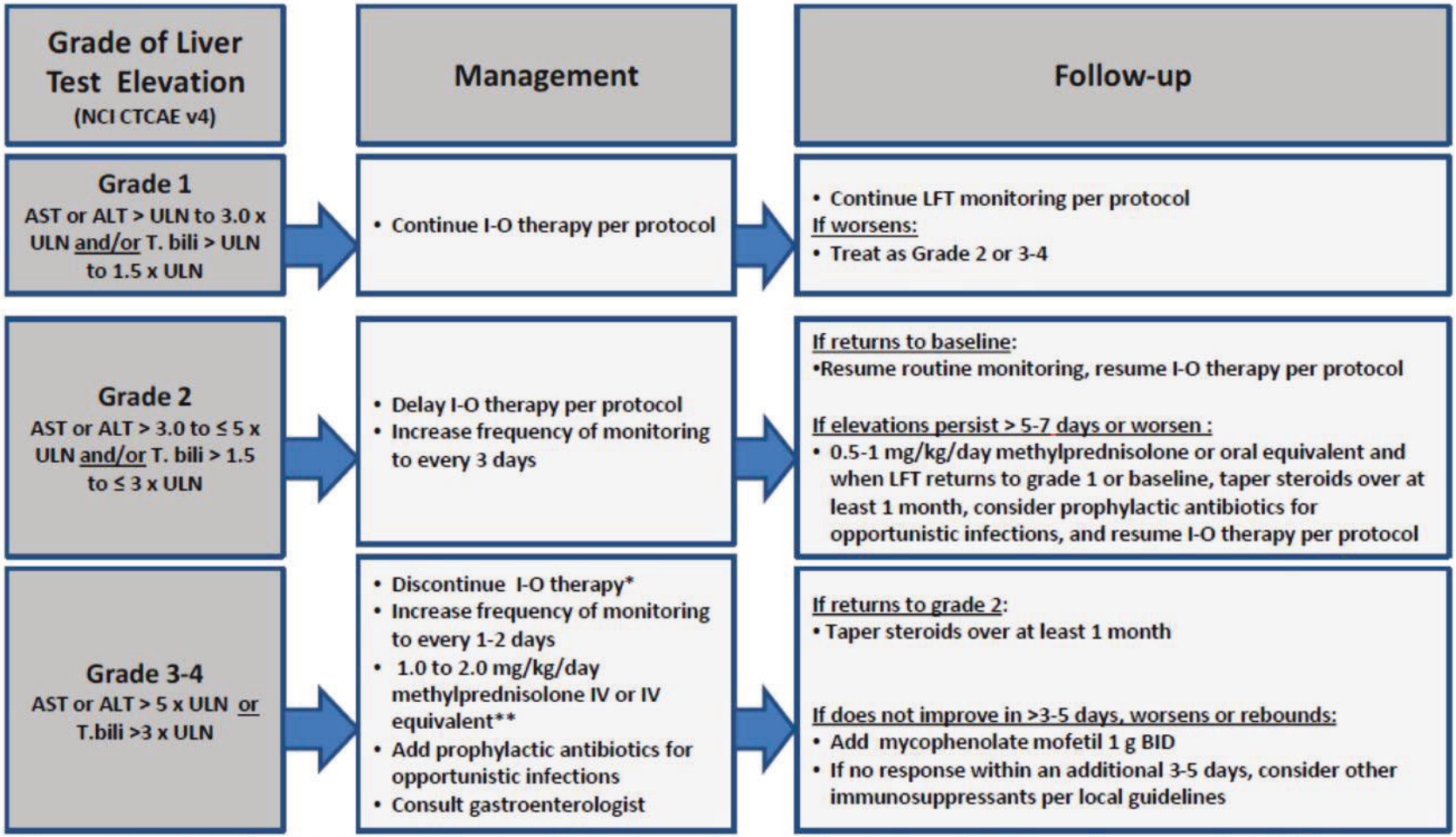
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.



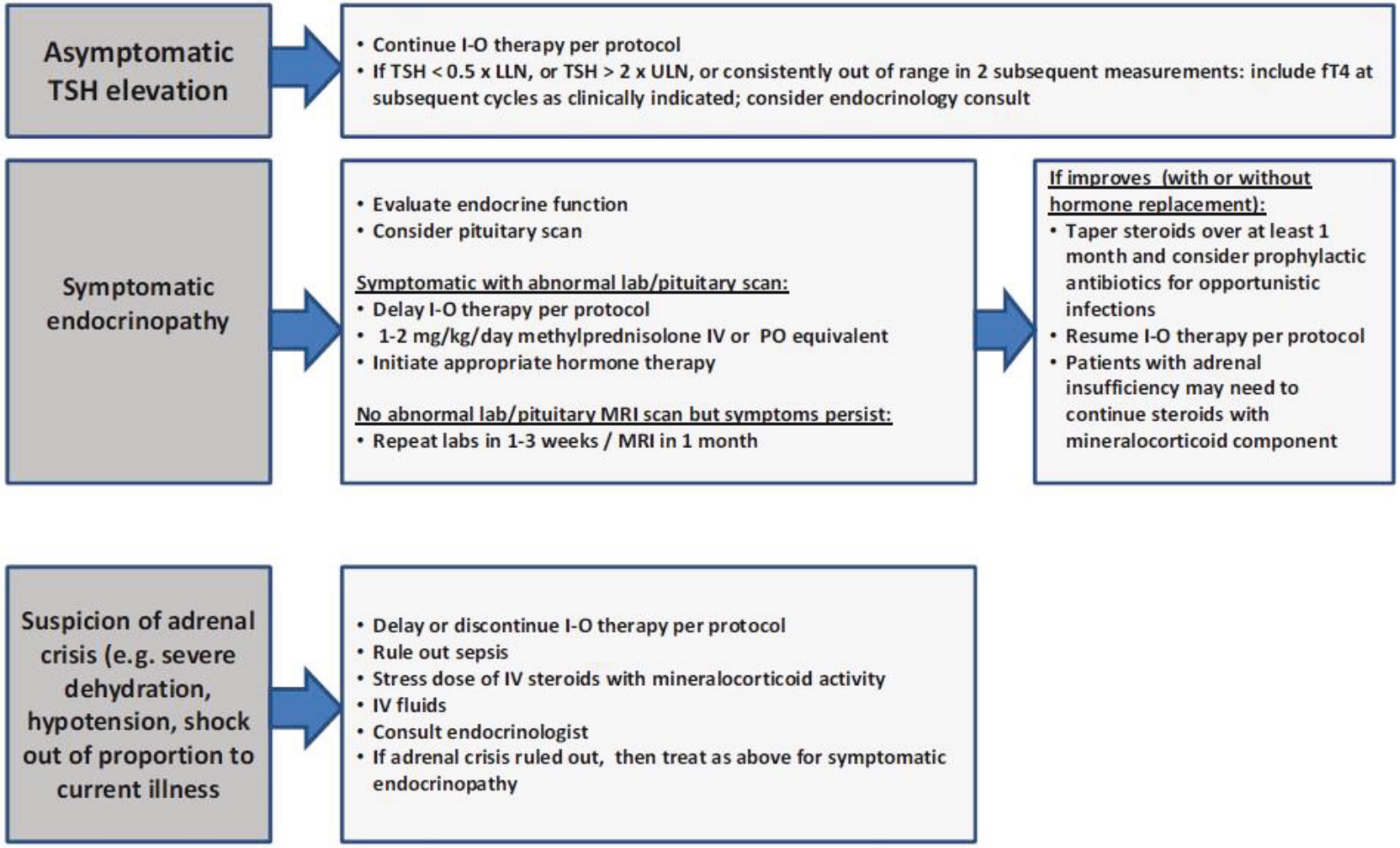
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

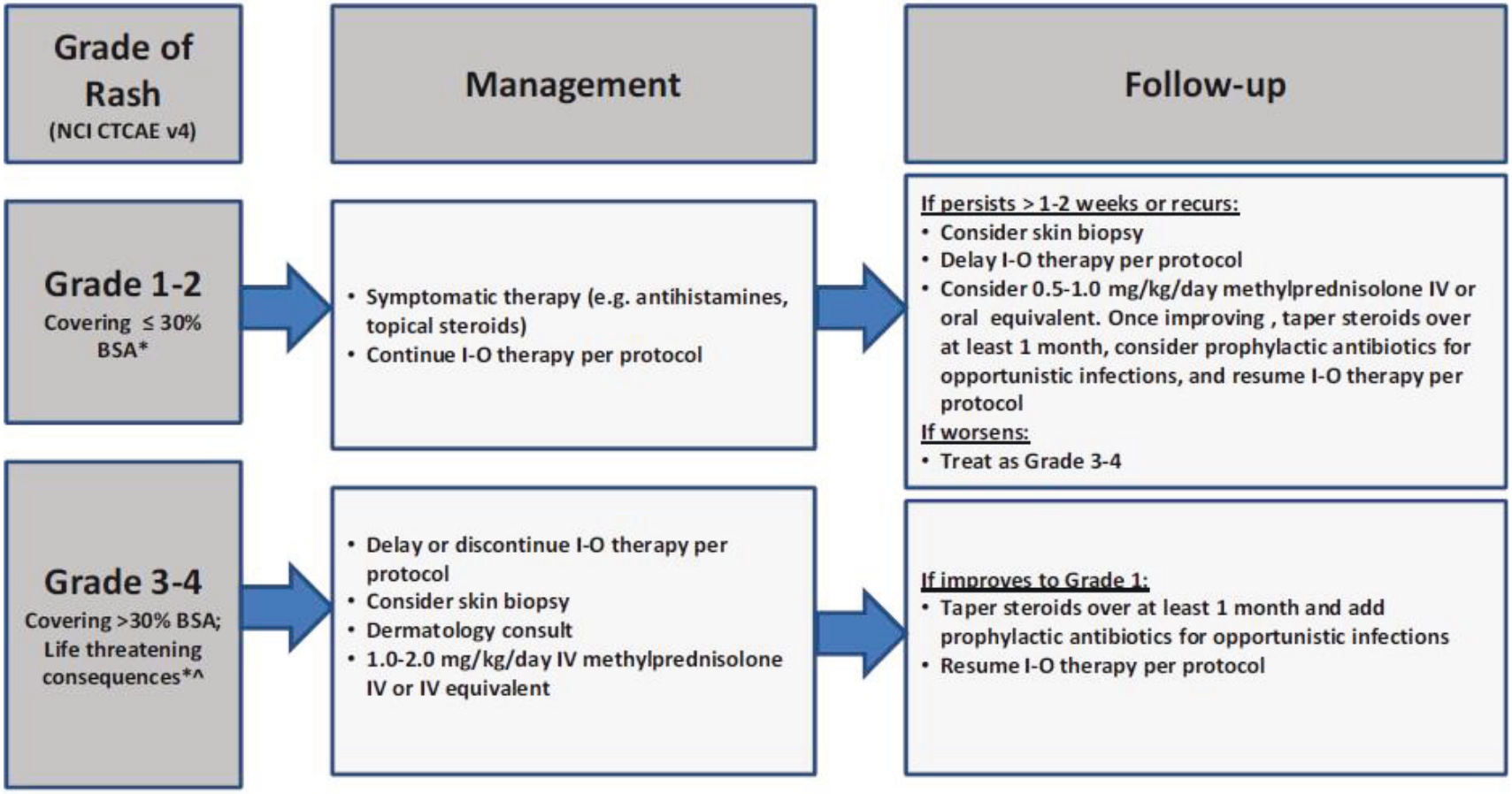
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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 Single Arm Phase Ib/II Multi-Center Study of Nivolumab in combination with nanoliposomal-Irinotecan, 5-Fluorouracil, and Leucovorin as Second Line Therapy for Patients with Advanced Biliary Tract Cancer", **version 5.0 dated 11Nov2020** 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: _______________

Appendix V Study Management during COVID-19

Due to ongoing government and clinical changes necessary to effectively manage the COVID-19 pandemic, the following changes to protocol-required items were made to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to COVID-19).

A. **COVID-19 Testing:**

- COVID-19 is not currently being added to the protocol as part of the screening requirements, but may be done as part of the clinical assessment, as needed during the course of the pandemic.
- COVID-19 tests/results will be recorded in the subject's source documents but will only be added as an Adverse/ Serious Adverse Event in the eCRF should the test yield a COVID-19 positive result.

B. **Study Visit Schedule:**

- For individual instances where assessments cannot be made and/or data are not able to be collected, the reasons for failing to obtain the data should be documented (e.g., identifying the specific limitation imposed by COVID-19 leading to the inability to perform the protocol-specified assessment).
- Ongoing participants who are unable or unwilling to attend protocol-specified trial visits and procedures, may continue in the trial if the Principal Investigator (PI) deems it appropriate and for as long as the patient continues to consent to participation and where patient safety can be monitored.
- Where participants cannot be seen at the site or by home visit, the use of telemedicine and adaptation of schedule of assessments will be implemented, where feasible to ensure patient safety.
- Adjustments to the protocol imaging visit window (8 ±1 week) are permitted by the Sponsor-Investigator if on-schedule visits are not possible due to COVID-19.

C. **Laboratory Assessments:**

- Screening tissue & End of Treatment (EOT) biopsy samples – will be obtained **only** at approved sites, if applicable/possible, and will be retained at site until further notification.
- Cycle 1 Day 1, Cycle 5 Day 1 and EOT – blood will be obtained if possible and will be processed and shipped per the study lab manual. If the research lab closes and is unavailable to accept samples, this will be communicated out to the study team.
- Cycle 4 Day 1 – biopsy sample will be obtained if possible. If the research lab closes and is unavailable to accept biopsy samples this will be communicated out to the study team.

D. **Study Medications:**

- Adjustments for alternate drug administration have been permitted by the Supporters (Ipsen and Bristol-Myers Squibb) and Sponsor-Investigator, stating that ongoing participants who are unable or unwilling to attend protocol-specified trial visits and procedures, may continue in the trial if the site PI deems it appropriate and for as long as the patient continues to consent to participation and where patient safety can be monitored.
- The patient may remain on study without receiving drug for more than 28 days if the drug(s) are held due to COVID-19.
- If a patient does not receive investigational regimen consecutively for 4 weeks from last intended dose between consecutive CT scans due to COVID-19, then the patient may continue on treatment despite progression on CT scan.