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Rucaparib in Combination With Nivolumab in Patients With Advanced or Metastatic Biliary Tract Cancer Following Platinum Therapy

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Phase II Multi-Center Study of PARP inhibitor Rucaparib in Combination with Anti-PD-1 Antibody Nivolumab in Patients with Advanced or Metastatic Biliary Tract Cancer Following Platinum Therapy

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NOTE: To effectively manage the COVID-19 pandemic restrictions, 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). These changes are listed in **Appendix V** of the protocol (**Study Management during COVID-19**).

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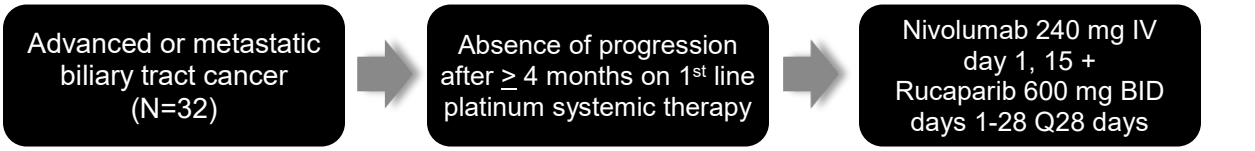
ABBREVIATIONS:

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
IDH	Isocitrate dehydrogenase
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
SAE	Serious Adverse Event
SD	Stable Disease
TIL	Tumor Infiltrating Leukocytes
UaP	Unanticipated Problem
WBC	White Blood Cells

STUDY SCHEMA



1° endpoint - PFS rate 4 months
2° endpoints – ORR, median PFS & OS

STUDY SYNOPSIS

Title	Phase II Multi-center Study of PARP inhibitor Rucaparib in Combination with Anti-PD-1 Antibody Nivolumab in Patients with Advanced or Metastatic Biliary Tract Cancer Following Platinum Therapy.
Phase	Phase II
Methodology	Single arm, open-label
Study Duration	3 years
Study Center(s)	Multi-Center: 3 sites total including lead site: University of Michigan
Objectives	Primary objective: 1. Determine the PFS rate at 4 months in patients with advanced BTC treated with rucaparib and nivolumab following 1st line platinum based therapy. Secondary objectives: 1. Evaluate the ORR and median PFS and OS as measured from start of study treatment and start of initial platinum therapy in patients with advanced BTC. 2. Evaluate the safety of rucaparib and nivolumab in this patient population. 3. Evaluate the ORR, median PFS and OS in patients with and without DNA damage response (DDR) and isocitrate dehydrogenase (IDH) signatures. Exploratory objectives: 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, 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.
Number of Subjects	32 patients meeting intent-to-treatment guidelines. Up to 35 patients may be enrolled to allow for a small number of patients to be replaced, if necessary.
Eligibility Criteria	1. Patients must have a pathologically confirmed adenocarcinoma 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 of mixed histology are excluded. 2. Patients must have received 1st line platinum-based chemotherapy for advanced BTC for 4-6 months (16-24 weeks) without radiologic or clinical progression. Last systemic infusion of 1st line platinum-based therapy may not be more than 4 weeks from study informed consent. Prior peri-operative chemotherapy is permitted provided it was completed > 6 months from start

	of platinum-based therapy for advanced disease. 3. Prior surgical resection, radiation, chemoembolization, radioembolization or other local ablative therapies are permitted if completed ≥ 4 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity. 4. Patients must have radiographically measurable disease (as per RECISTv1.1) in at least one site not previously treated with radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation) either within the liver or in a metastatic site unless the patient has had complete response to 1st line platinum-based therapy. 5. Age ≥18 years 6. Child-Pugh score of A or B7 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 obtained ≤2 weeks prior to registration (absolute neutrophil count $\geq$1500/mm^3, hemoglobin $\geq$9 g/dL, platelets $\geq$100,000/mm^3, serum creatinine $\leq$ 1.5 x upper limit normal (ULN), creatinine clearance >= 50 mL/min, albumin $\geq$3.0 g/dL, AST/ALT $\leq$3.0 x ULN ($\leq$5 x ULN if liver metastasis), total bilirubin ≤ 1.5 x upper limit normal. 12. Must not have a diagnosis of immunodeficiency, or received systemic steroid therapy, or any other form of immunosuppressive therapy within 14 days prior to trial treatment. 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 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 planned start of the study therapy. 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 rucaparib 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 blood or urine test to rule out pregnancy 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 6 months (for women) and 7 months (for men) following completion of study therapy. 21. Participants must not have an active, known or suspected autoimmune disease which may affect vital organ function, or has/may require systemic immunosuppressive therapy for management. 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 must not have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease. 23. Patients may not have previously received anti PD1/PDL1 antibodies or PARP inhibitor for treatment of this cancer.
Study Product(s), Dose, Route, Regimen	Rucaparib 600 mg PO BID days 1-28 Nivolumab 240 mg IV days 1 and 15
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 with stable or responding advanced disease after at least 4 months of 1st line platinum therapy, and expect a large majority of those patients to have previously received between 4 to 6 months of platinum therapy. The sample size of this trial is based on the hypothesis that the expected proportion of patients surviving without progression after 4 months of study treatment will be improved with investigational therapy. We will accrue 32 evaluable patients to this trial. Evaluable patients are compliant with study treatment and observed for progression-free survival events, progression, death, or lack of events following up to 4 months of study treatment. Patients non-complaint with treatment or lost to follow-up will be replaced. Based on the ABC-02 trial, PFS was estimated to be 72% and 60% at 4 and 6 months after first line gemcitabine and cisplatin, similar to the initiation point of our study and PFS was 51% and 32% at 8 and 10 months, similar to the end of the treatment period for the primary outcome assessment in this trial. Using a conditional probability argument, combined with the assumption that patient accrual to this study will follow an approximate uniform distribution over the 4 to 6 months of primary therapy for the patients accrued, we can accept the average of the PFS estimates for each period (4-6 months (66%) and 8-10 months (41.5%)) to correspond to our trial time period. We can then standardize the ABC-02 PFS data so that the 4-6 month estimate is 100% and the estimate for 4 months thereafter is 63%. For our trial, we hope to improve the PFS rate from 63% for these patients to 85%. With our proposed sample size of 32 patients this trial will have 80% power to detect this difference significantly using a 1-sided test.

1.0 BACKGROUND AND RATIONALE

1.1 Biliary Tract Cancer - Disease Overview

Biliary tract cancer (BTC) develops as a result of malignant transformation of the biliary tract mucosa and is anatomically classified as intra-hepatic, extra-hepatic (hilar and distal) and gall bladder adenocarcinoma. BTC accounts for 10-15% of all primary liver cancer cases worldwide, and its incidence is rising[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.

1.2 Role of PARP inhibitors in BTC

DNA damage response (DDR) is a broad term describing several complex pathways responsible for repairing damaged DNA. These known pathways include base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), recombinational repair including homologous recombination (HR) and non-homologous end-joining (NHEJ), and direct repair mechanisms. BER, NER and MMR are mechanisms responsible for repairing single strand breaks (SSB), whereas HR and NHEJ pathways are mechanisms involved in repairing double strand breaks (DSB)[4–7].

Poly (ADP ribose) polymerase 1 or PARP1 is an abundant nuclear protein heavily involved in the repair of SSB[8]. In the presence of SSB, PARP1 binds to the damaged DNA, undergoes conformational change and catalyzes the production of PAR which acts as a signal for recruitment of DNA repair factors[9]. Under normal conditions the dissociation of PARP1 from DNA is required prior to DNA repair completion. In the presence of inhibitors, PARP1 remains bound to SSB generating trapped PARP-DNA complexes, thus blocking repair and replication[9]. Unrepaired SSB can produce deleterious DSB at the replication forks. In replicating cells, DSB are repaired via HR and NHEJ pathways. However, in cancer cells that are HR deficient (HRD), repair mechanisms for DSB fall to more error prone NHEJ pathways which can lead to cell death[10]. Bryant and Farmer separately demonstrated that BRCA1/2 deficient cells, where the homologous recombination mechanism is defective, were exquisitely sensitive to PARP inhibitors[11,12]. This has led to many studies investigating the efficacy of PARP inhibitors, both as a single agent and in combination with chemotherapy, in various solid tumors including ovarian, breast, brain, pancreatic and NSCLC[13–20]. However, to date, HRD signaling and the use of PARPi has not been extensively investigated in BTCs.

Using whole exome-transcriptome sequencing, our pre-clinical data of 53 patients with BTCs revealed 14 pts (26.4%) had biallelic DNA damage repair pathway mutations (ATM, BAP1, MSH2, BRCA1, BRCA2). Of these, 11 had somatic mutations and 3 had germline (MSH2, BRCA1, BRCA2) mutations. Four additional patients were found to have mono-allelic mutations with BRCA1 (somatic), PALB2 (somatic) and ATM (familial). These monoallelic mutations have been shown to increase the risk of cancer development and are involved in DNA DSB repair[21–24].

BRCA1 associated protein (BAP1), is a deubiquitinase of histone H2A involved in chromatin remodeling and is recruited to DSB sites. BAP1-/- cells are strikingly sensitive

to ionizing radiation and PARP inhibition (olaparib) relative to BAP1+/- and BAP1+/+ cell[25].

In addition, 8 patients had isocitrate dehydrogenase (IDH)1 mutations. Pre-clinical data with IDH1 mutant cells demonstrates reduced capacity to repair DSBs which renders them highly sensitive to PARP inhibition[26,27]. This concept is currently being evaluated in clinical trial (NCT03212274).

In total, 26 patients (49%) in our cohort had either biallelic somatic and germline (n=14) mutations, or monoallelic somatic or germline (n=4) DDR mutations, or IDH1 mutations (n=8) and may have potentially benefitted from the use of PARPi.

Rucaparib is a small oral inhibitor of PARP1, PARP2, and PARP3, currently FDA-approved in patients with ovarian cancer treated with two or more chemotherapy regimen[28]. A phase II ARIEL2 trial evaluating the efficacy of rucaparib at 600 mg twice daily, demonstrated greatest response in patients harboring germline or somatic BRCA mutations (PFS 12.8 months; 95% CI 9.0-14.7), reduced response rate in those with HRD status by high loss of heterozygosity (PFS 5.7 months; 95% CI 5.3-7.6), and least response in low loss of heterozygosity (PFS 5.2 months; 95% CI 3.6-5.5)[29]. Grade ≥3 adverse events included anemia, elevated ALT or AST, and fatigue. A recent phase III clinical trial ARIEL3 of 564 patients demonstrated promising disease control in patients with BRCA mutant ovarian cancer[30]. Median PFS in BRCA mutant arm was 16.6 months (95% 13.4-22.9) compared to 5.4 months (95% CI 3.4-6.7) in placebo arm. In patients with HRD status, median PFS was 13.6 months (95% CI 10.9-16.2) versus 5.4 months (95% CI 5.1-5.6). Similar adverse events were reported in each arm. Rucaparib is currently being evaluated in breast, ovarian, as well as prostate cancer with HRD status (NCT02505048, NCT02952534, NCT02975934).

1.3 Role of Checkpoint Inhibitors in BTC

The role of cytotoxic immune response against a tumor requires a complex and evolving interaction between immune cell subsets. T-cell activation requires dual signaling from the T-cell receptor and an additional co-stimulatory molecule[31,32]. The first signal includes binding of the T-cell receptor to antigens presented by antigen presenting cells (APCs). Subsequently, the B7 (CD80, CD86) ligand binds to CD28 which is a co-stimulatory receptor. This signaling leads to T-cell proliferation, cytokine release and upregulation of the immune response. As a result, cytotoxic T lymphocyte antigen 4 (CTLA-4) is upregulated and competes with the CD28 receptor for B7 binding. CTLA-4 has higher affinity than the CD28 receptor and therefore T-cell response is ultimately down-regulated. PD-1 is a member of the CD28/CTLA-4 family of T-cell costimulatory receptors that includes CD28, CTLA-4, ICOS and BTLA[33]. PD-1 is expressed on activated T cells, B cells and myeloid cells[34]. 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[35,36]. When the PD-1 ligand binds to the PD-1 receptor, T-cell activation is blocked. CTLA-4 and PD-1 are negative regulators of T-cell response that prevent autoimmunity and allows tolerance to self-antigens[31]. If these interactions are interrupted, the 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[37]. 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%. 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[37]. 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[38–42]. There is an ongoing phase II clinical trial evaluating the efficacy of single agent Nivolumab in advanced biliary tract cancers (NCT02829918), the results of which has not been reported yet. Other checkpoint inhibitors currently being investigated in this disease group include combination checkpoint inhibitors with chemotherapy (NCT03101566) as frontline therapy.

1.4 Rationale

Patients with advanced, unresectable or metastatic BTC have a poor prognosis despite systemic chemotherapy. The median PFS with first-line gemcitabine and cisplatin is expected to be 8 months[2]. PARP inhibitors have been shown to be effective when used as a single maintenance agent or in combination with conventional chemotherapy in patients with BRCA mutations[19,20,29,30]. PARP inhibitors affect the cells ability to repair single strand breaks and also increase frequency of double strand breaks[8]. Disruption of the DNA damage repair pathways results in increased mutational burden, neoantigens[43] and therefore immunogenicity[8] (see Figure 1). This provides a rationale for combining the use of PARPi such as rucaparib with a checkpoint inhibitor, nivolumab. Preclinical data using combination rucaparib with anti-PD1/ PD-L1 antibodies resulted in greater survival benefit and greater tumor response in BRCA1 null syngeneic model as compared to monotherapy[44]. In a separate study, while the use of PARPi in animal models showed increased PD-L1 expression, the combination of PARPi with PD-L1/PD-1 checkpoint inhibitors showed increased therapeutic efficacy in comparison to each therapy alone[45].

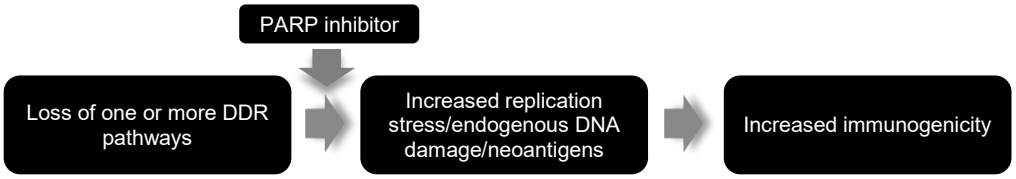


Figure 1. Potential Synergism of PARP and Immune Checkpoint Inhibition

We therefore hypothesize that following first-line platinum based chemotherapy, rucaparib in combination with nivolumab, will improve progression-free survival and overall survival in BTC patients. We expect greater efficacy in patients with DDR and IDH signatures. These results are expected to have an important positive impact because they will provide evidence guided understanding for further evaluation of the use of PARP inhibitors with an immune check point inhibitor in BTCs.

1.5 Correlative Studies

We will study the BTC tumor biology, 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, IDH and/or immune signatures) that may have clinical efficacy from rucaparib 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 Determine the PFS rate at 4 months in patients with advanced BTC treated with rucaparib and nivolumab following 1st line platinum based therapy

2.2 Secondary Objectives

2.2.1 Evaluate the ORR and the median PFS and OS from start of study treatment and start of 1st line platinum therapy in patients with advanced BTC.
2.2.2 Evaluate the safety of rucaparib and nivolumab in this patient population.
2.2.3 Evaluate the ORR, median PFS and OS in patients with and without DDR and IDH signatures.

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 Endpoint Assessment: For the intent-to-treat population the progression-free survival (PFS) rate will be defined as the proportion of patients alive and without radiological or clinical progression (leading to withdrawal from the study) at 4 months and patient replacement as specified in section 5.10.

2.4.2 Secondary Endpoint Assessment: Overall response rate (ORR) will be determined as per the combined RECISTv1.1 and irRECIST criteria. 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. PFS1 will be from start of study treatment and will be the primary study endpoint. PFS2 will be from start of 1st line platinum therapy. Overall survival (OS) will be defined from the date of treatment to either date of death or censoring. OS1 will be from start of study treatment. OS2 will be from start of 1st line platinum therapy. Follow-up time will be censored at the date of last disease evaluation. Adverse events and reportable serious events are defined by the study protocol (NCI Common Toxicity Criteria for Adverse Events (CTCAE) v5.0).

3.0 PATIENT ELIGIBILITY

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

3.1 Eligibility Criteria

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

3.1.2 Patients must have received 1st line platinum-based systemic chemotherapy for advanced BTC for 4-6 months (16-24 weeks) without radiologic or clinical progression. Last systemic infusion of 1st line platinum-based therapy may not be more than 4 weeks from study informed consent. Prior peri-operative chemotherapy is permitted provided it was completed > 6 months from start of platinum-based therapy for advanced disease.

3.1.3 Prior surgical resection, radiation, chemoembolization, radioembolization or other local ablative therapies are permitted if completed ≥ 4 weeks prior to enrollment AND if patient has recovered to ≤ grade 1 toxicity.

3.1.4 Patients must have measurable disease (as per RECISTv1.1) in at least one site not previously treated with radiation or liver directed therapy (including bland, chemo- or radio-embolization, or ablation) either within the liver or in a metastatic site unless the patient has had complete response to 1st line platinum-based therapy.

3.1.5 Age≥18 years

3.1.6 Child-Pugh score of A or B7

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 obtained ≤ 2 weeks prior to registration

absolute neutrophil count	≥ 1500/mm^3
hemoglobin	≥ 9 g/dL
platelets	≥ 100,000/mm^3
serum creatinine	≤ 1.5 x ULN
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 a diagnosis of immunodeficiency, or received systemic steroid therapy, or any other form of immunosuppressive therapy within 14 days prior to trial treatment. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed.

3.1.13 No prior history of solid organ transplantation or brain metastasis (unless treated 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 planned start of the study therapy.

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 rucaparib 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 blood or urine test to rule out pregnancy 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 6 months (for women) and 7 months (for men) following completion of study therapy

3.1.21 Participants must not have an active, known or suspected autoimmune disease which may affect vital organ function, or has/may require systemic immunosuppressive therapy for management. 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 must not have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of start of study treatment. Inhaled or topical steroids, and adrenal replacement steroid doses >10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.1.23 Patients may not have previously received anti PD1/PDL1 antibodies or PARP inhibitor for treatment of this cancer.

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. 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 PARP inhibitor Rucaparib and anti-PD1 antibody Nivolumab. The safety profile of both agents has been previously evaluated individually.

Table 1. Treatment Plan

Days	Treatment	Dose
Day 1 every 2 weeks	Nivolumab	240 mg IV
Days 1-28 every 28 days	Rucaparib	600 mg PO BID

Rucaparib may be taken with or without food. Patients should take rucaparib doses as close as possible to 12 hours apart, preferably at the same times every day. If a patient misses a dose (i.e., does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose Missed or vomited doses should not be made up. Patients may continue treatment for 2 years in absence of disease progression or unacceptable toxicity.

5.2 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed for the development of toxicity according to the Time and Events Table (Section 6.2). 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 2. Dose Modifications

Drug	Current Dose	Percentage Decrease	Modified Dose
Rucaparib	600 mg PO BID	~20%	500 mg PO BID
	500 mg PO BID	20%	400 mg PO BID
	400 mg PO BID	~20%	300 mg PO BID
	300 mg PO BID	100%	Discontinue
Nivolumab	240 mg IV	100%	Discontinue

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

- Treatment delay of more than 21 days from last intended therapy will result in discontinuation from trial, unless otherwise agreed and documented between the investigator and the sponsor.

- 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.

- Nivolumab cannot be dose reduced and can only be discontinued as per detailed algorithms for immune-therapy toxicity management in Appendix III.

Rucaparib Dose Modification Criteria
Treatment with rucaparib should be held if any of the following are observed and a dose reduction should be considered or implemented.

- Grade 3 or 4 hematologic toxicity. Anemia should be managed as described below

- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below

- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for unremitting Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

- For patients who meet treatment interruption guidelines above, treatment with rucaparib should be held until the toxicity improves to ≤ CTCAE Grade 2. Twice daily dosing may then be **resumed at either the same dose or a lower dose, per investigator discretion**. If treatment is resumed at the same dose, and the patient experiences the same toxicity, treatment should be interrupted, then resumed at a reduced dose following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted; however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID. If a patient continues to experience toxicity despite dose reduction steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 21 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed and documented between the investigator and the sponsor.

Management of Anemia including Evaluation for MDS/AML and Follow-up of Patients who Discontinue Treatment with Ongoing Anemia:

- If the patient develops anemia CTCAE Grade ≥ 3, rucaparib treatment should be held until the anemia improves to CTCAE Grade ≤ 2 whereupon daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion.
- If the duration of dosing is interrupted for > 21 consecutive days due to anemia CTCAE Grade ≥ 3, treatment should be permanently discontinued, unless otherwise agreed and documented between the investigator and the sponsor or designee.

- In addition, if anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusion occurs, then weekly complete blood counts should be performed until resolution of the event.
- If, after 42 days of interruption of rucaparib, the anemia has not improved to CTCAE Grade ≤ 1 then the patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice.
- The bone marrow analysis may include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

Management of Rucaparib Treatment-Emergent ALT/AST Elevations:

- Grade 4 ALT/AST elevations: hold rucaparib until values have improved to Grade 2 or better, then resume rucaparib with a dose reduction. If toxicity is ascribed to nivolumab alone then you may resume without a dose reduction. Monitor liver function tests weekly for 3 weeks after rucaparib has been restarted.
- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:
    - Monitor liver function tests weekly until improvement to ≤ Grade 2.
    - Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN.
    - If patient has Grade 3 ALT/AST elevation and continues on rucaparib, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose.

Management of Creatinine Elevation:

- Rucaparib can cause creatinine elevation of any grade in 92% of the patients (1% grade 3-4) possibly due to potent inhibition of the MATE1, MATE2-K and OCT1 transporters[49]. The majority of reported grade 1-2 creatinine elevations stabilize with continued rucaparib treatment without dose modification. However, grade 2 elevation of creatinine can also be due to autoimmune nephritis from nivolumab. To help identify whether rucaparib or nivolumab is the underlying etiology for the creatinine elevation all subjects will undergo repeat CMP on cycle 1 day 8.
    - Grade 2 creatinine elevation on cycle 1 day 8: Hold rucaparib and re-check on cycle 1 day 15. If creatinine is improved to grade 1 (≤1.5 x ULN) on day 15, then resume rucaparib at full dose.
    - Grade 3-4 creatinine elevation: Hold rucaparib and consider a dose reduction.

Rucaparib Re-treatment Criteria

Treatment may resume if:

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 75 x 10^9/L
- Non-hematologic toxicities have returned to baseline or ≤ CTCAE Grade 1 severity (or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient). Grade 3 or Grade 4 ALT/AST elevations should be managed as described above.

5.3 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.

5.4 Concomitant Medications/Treatments

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

- Other investigational agents
- Concurrent radiation

Effect of Other Drugs on Rucaparib
Rucaparib is primarily metabolized by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers.

Effect of Rucaparib on Other Drugs
Rucaparib reversibly inhibits CYP1A2, CYP2C19, CYP2C9 and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UGT1A1. It is also a potent inhibitor of MATE1 and MATE2-K, and a moderate inhibitor of OCT1. Caution should be used for concomitant use of CYP substrates with narrow therapeutic index as listed below.

CYP Enzyme	Substrates with Narrow Therapeutic Index
CYP1A2	Tizanidine, theophylline
CYP2C9	Warfarin, phenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus and terfenadine

5.5 Other Modalities or Procedures

None

5.6 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
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Patient voluntarily withdraws from treatment **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

5.7 Off Treatment Criteria

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

5.8 Duration of Follow-Up

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

5.9 Off Study Criteria

Patients can be taken off study 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:

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

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

5.9.3 Patient is unable to comply with protocol requirements;

5.9.4 Treating physician judges continuation on the study would not be in the patients best interest;

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

5.9.6 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;

5.9.7 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;

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

5.9.9 Patient completes protocol treatment and follow-up criteria;

5.9.10 Treatment delay of more than 28 days from last intended therapy;

5.9.11 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.

5.10 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 (IIT) population.

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

1. Patients who did not receive even one dose of 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 5.9.1 and/or 5.9.3 not secondary to toxicity.
4. Patients meeting off study criteria 5.9.2 and/or 5.9.5

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 to 35 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 4. Study Calendar								
Procedures	**Screening[1]**	**Cycle 1**			**Cycle X**		**EOT Visit[10]**	**Follow-Up Q3 months +/- 1 week[11]**
		Day 1	**Day 8**	**Day 15**	**Day 1**	**Day 15**		
Informed Consent	X							
History, Physical Examination	X	X		X	X		X	X
Weight, BSA	X	X			X		X	
Vital Signs	X	X		X	X	X	X	
Performance Status	X	X			X		X	
Toxicity Evaluations[12]		X	X	X	X	X	X	X
CBC with differential	X	X		X	X	X		
CMP[2]	X	X	X	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			
Scans with Tumor Measurements[6]	X				X			
Research Blood[7]		X			X		X	
Tissue[8]	X				X		X	
Study Drug Administration[9]		X		X	X	X		
Survival Follow-up								X

1. All screening procedures to be completed within 2 weeks of registration, except imaging and informed consent 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 and total protein.
3. Amylase, lipase, random cortisol, TSH, free T4 and 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 8 weeks, if patient is known to express these tumor markers.

5. Required for females of childbearing potential. Blood or urine pregnancy test per site investigator discretion. Required on C1D1 within 24 hours prior to treatment initiation and prior to study drug administration on Day 1 for each subsequent Cycle.
6. MRI or CT (abdomen/pelvis) with contrast along with CT chest with/without contrast will be assessed every 8 ± 1 weeks. Imaging assessment of scans at the site should be completed by either a radiologist or an imaging core, and not by the oncologist nor via abstraction of data from the subjective/clinical radiology report.
7. Collect 10 ml x 2 Streck® DNA tubes (must be shipped within 48 hours of collection) 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 3 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 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
11. Patients will be followed every 3 months +/- 1 week after completion of (or early withdrawal from) study treatment until death, withdrawal from protocol or 2 years whichever is the earliest.
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.

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 treatment with study drug.

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 and/or randomized 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 the treatment started, or appearance of new lesions since the last evaluation.

7.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

7.1.4.3 Evaluation of Best Overall Response

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

Table 5. 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, are not considered 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, or the administration of other drug(s) known to be hepatotoxic.

While treatment is interrupted, the patient should be evaluated for the presence of confounding factors including malignant disease in the liver, co-administration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as international normalized ratio (INR) should be implemented as indicated. If no alternative cause is identified, rucaparib must be permanently discontinued.

All cases of possible DILI should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin.

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.

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:

- Myelodysplastic Syndrome and Acute Myeloid Leukemia
- Pneumonitis

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 Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.2.7 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 must also be reported within 24 hours of receipt of the information by the investigator.

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

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

8.4.2 Reporting procedures to BMS

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

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to BMS Worldwide Safety (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 Clovis

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 Clovis. 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 Clovis. All AESIs will be collected and reported to Clovis throughout the subject's participation in the study.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to Clovis (drugsafety@clovisoncology.com; Fax: 303-261-8319).

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 Clovis 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 assist the Sponsor in submitting 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 must report it to the IRB within 14 calendar days of the study team becoming aware of the problem.

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 Clovis Oncology (drugsafety@clovisoncology.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@clovisoncology.com. The data elements listed on the reconciliation report will be used for identification purposes. If the Investigator determines a report was not transmitted to BMS GPV&E, and/or Clovis the report should be sent immediately as appropriate.

8.8 Stopping Rules

See section 11.5 for Early Stopping Rules Due to Toxicity. In addition, 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 Rucaparib camsylate

9.1.1 Other Names

Rubraca, CO-338; formerly known as PF-01368338-BW and AG-014447

9.1.2 Classification

RUBRACA is a poly (ADP-ribose) polymerase (PARP) inhibitor.

9.1.3 Mechanism of Action

Rucaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. In vitro studies have shown that rucaparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Increased rucaparib-induced cytotoxicity was observed in tumor cell lines with deficiencies in BRCA1/2 and other DNA repair genes. Rucaparib has been shown to decrease tumor growth in mouse xenograft models of human cancer with or without deficiencies in BRCA.

9.1.4 Pharmacokinetics

All pharmacokinetics of rucaparib were characterized in patients with cancer. Rucaparib demonstrated linear pharmacokinetics over a dose range from 240 to 840 mg twice daily with time-independence and dose-proportionality. The mean steady-state rucaparib Cmax was 1940 ng/mL (54% coefficient of variation [CV]) and AUC0-12h was 16900 h·ng/mL (54% CV) at the approved recommended dosage. Accumulation was 3.5 to 6.2 fold. Median terminal half-life ($T_{1/2}$) was 17 hours following a single intravenous dose of 12 to 40 mg rucaparib.

1. Absorption: The median Tmax at steady state was 1.9 hours at the approved recommended dosage (600 mg BID). The mean absolute bioavailability of rucaparib immediate release tablet was 36% with a range from 30% to 45%. Following a high-fat meal, the Cmax was increased by 20% and AUC 0-24h was increased by 38%, and Tmax was delayed by 2.5 hours, as compared to dosing under fasted conditions.

2. Distribution: Rucaparib had a steady-state volume of distribution of 113L to 262L following a single intravenous dose of 12 mg to 40 mg rucaparib. In vitro, the protein binding of rucaparib was 70% in human plasma at therapeutic concentrations. Rucaparib was preferentially distributed to red blood cells with a blood-to-plasma concentration ratio of 1.83.

3. Metabolism: In vitro, rucaparib was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4.

4. Elimination: The mean terminal $T_{1/2}$ of rucaparib was 17-19 hours, following a single oral dose of 600 mg rucaparib. The apparent clearance ranged from 15.3 to 79.2 L/hour, following continuous 600 mg rucaparib orally twice daily.

The clearance ranged from 13.9 to 18.4 L/hour, following a single intravenous dose of rucaparib 12 mg to 40 mg.

9.1.5 Storage, Preparation and Stability

Refer to the current FDA-approved package insert for storage, stability and special handling information. Rucaparib is supplied as 200, 250 and 300 mg strength tablets. All tablets are provided in high-density polyethylene (HDPE) bottles (or equivalent) with child-resistant caps and should be stored in the provided containers between 20°-25° C (68° to 77° F); excursion permitted between 15° to 30° C (59° to 86° F) (see USP Controlled Room Temperature). Patients may be dispensed 1 or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 28 days of treatment (plus a 2-day overage) until the next rucaparib dispensation visit. Bottles containing rucaparib tablets will be labeled according to national regulations for investigational products.

9.1.6 Dosing and Administration

See Section 5.1

The starting dose of rucaparib as a continually administrated oral monotherapy will be 600 mg twice daily.

Patients may take rucaparib with or without food. Each dose should be taken with approximately 8 oz (240 mL) of room temperature water. Tablets should be swallowed whole without crushing or chewing.

Patients should take rucaparib doses as close as possible to 12 hours apart, preferably at the same times every day. If a patient misses a dose (i.e., does not take it within 4 hours of the scheduled time), the patient should skip the missed dose and resume taking rucaparib with the next scheduled dose. Missed or vomited doses should not be made up.

9.1.7 Availability

Clovis Oncology will supply the study drug in 200 mg, 250 mg and 300 mg tablets with 60 tablets per bottle.

9.1.8 Handling and Disposal

Handling and disposal of rucaparib should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents.

9.1.9 Adverse Effects

1. Side Effects: Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions. Most common adverse reactions (≥ 20%) were nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea. Most common laboratory abnormalities (≥ 35%) were increase in creatinine, increase in ALT, increase in AST, decrease in hemoglobin, decrease in lymphocytes, increase in cholesterol, decrease in platelets, and decrease in absolute neutrophil count. The following adverse reactions have been identified in < 20% of the 377 patients treated with Rubraca 600 mg twice daily: dizziness (17%), neutropenia (15%), rash (includes rash, rash erythematous, rash maculopapular and dermatitis) (13%), pyrexia (11%), photosensitivity reaction (10%), pruritus (includes pruritus and pruritus

generalized) (9%), Palmar-plantar erythrodysesthesia syndrome (2%), and febrile neutropenia (1%).

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs), as these events have been observed in patients exposed to cytotoxic chemotherapy (e.g., platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation (8, 9). Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib. Clovis has added these potential risks to all Informed Consent Forms (ICFs) / Patient Information Sheets (PISs). AESI's (both serious and non-serious) will be reported to Clovis within 48 hours of awareness and will continue to be reported to Clovis under SAE reporting requirements. More information on AESIs for rucaparib is provided in the rucaparib IB.

Photosensitivity has been observed in patients treated with rucaparib. Patients should avoid spending time in direct sunlight because they burn more easily during treatment with rucaparib. When outdoors, patients should use typical precautions such as applying sunscreen (sun protection factor 50 or greater) and/or covering exposed skin with clothing and wearing a hat and sunglasses.

2. Pregnancy and Lactation: Based on findings from animal studies and its mechanism of action, Rubraca can cause fetal harm when administered to pregnant women. There are no available data in pregnant women to inform the drug-associated risk. In an animal reproduction study, administration of rucaparib to pregnant rats during organogenesis resulted in embryo-fetal death at maternal exposure that were 0.04 times the AUC 0-24h in patients receiving the recommended dose of 600 mg twice daily. Women of reproductive potential should use highly-effective contraception during therapy and for at least 6 months after treatment has been discontinued. Men receiving rucaparib and who are sexually active with women of child bearing potential should adhere to contraception for a period of 6 months after the last dose of nivolumab. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib. Patients should be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with rucaparib

   There is no information regarding the presence of rucaparib in human milk, or on its effects on milk production or the breast-fed infant. Because of the potential for serious adverse reactions in breast-fed infants from Rubraca, advise lactating women not to breastfeed during treatment with Rubraca and for 2 weeks after the final dose.

3. Drug Interactions:
   Effects of Other Drugs on Rucaparib: In vitro, rucaparib had a low metabolic turnover rate in human liver microsomes, and was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. In vitro, rucaparib was shown to be a substrate of P-gp and BCRP, but not a substrate of renal uptake transporters OAT1, OAT3, and OCT2, or hepatic transporters OATP1B1 and OATP1B3. Concomitant treatment with proton pump inhibitors has no clinically meaningful change in steady-state exposures.

Effect of Rucaparib on Other Drugs: Effect of rucaparib on other drugs has not been studied in humans. Rucaparib reversibly inhibited CYP1A2, CYP2C19, CYP2C9, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and UGT1A1. Rucaparib induced CYP1A2, and down regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib was a potent inhibitor of MATE1 and MATE2-K, and a moderate inhibitor of OCT1. Weak inhibition was observed at ultra-therapeutic concentration (300 µM) of rucaparib for MRP4, OATP1B1, OATP1B3, OAT1, and OAT3. No inhibition was observed for MRP2, MRP3, or BSEP. Rucaparib was an inhibitor of BCRP and P-gp efflux transporters with IC50 of 55 µM and 283 µM, respectively. Rucaparib is a weak inhibitor of CYP2C9 in vivo. Caution should be used for concomitant use of CYP substrates with narrow therapeutic index as listed below.

CYP Enzyme	Substrates with Narrow Therapeutic Index
CYP1A2	Tizanidine, theophylline
CYP2C9	Warfarin, phenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus and terfenadine

9.2 Nivolumab

9.2.1 Other Names

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

9.2.2 Classification

Immunomodulatory; checkpoint inhibitor

9.2.3 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.

9.2.4 Pharmacokinetics

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

9.2.5 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 (5 vials of 100 mg/10 mL).

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the Investigator Brochure section for “Recommended Storage and Use Conditions” and/or pharmacy reference sheets. Briefly, withdraw the required volume and transfer into an IV container. Dilute with either NS or D5W to a final concentration of 1 to 10 mg/mL. Mix by gentle inversion; do not shake.

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

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

9.2.6 Dose and Administration

See Section 5.1
Nivolumab is to be administered as a 30 (± 10 minute) intravenous infusion (or as per current standard of care), 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.

9.2.7 Availability

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

9.2.8 Handling and Disposal

Handling and disposal of nivolumab should be per institutional guidelines for the handling and disposal of biologic and cytotoxic agents. Nivolumab disposal will be conducted at individual sites and will not be returned to BMS. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

9.2.9 Adverse Effects

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

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 6 months after treatment has been discontinued. Men receiving nivolumab and who are sexually active with women of child bearing potential should adhere to contraception for a period of 7 months after the last dose of nivolumab.

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

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

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 rucaparib will be the overarching goal of this translational science. Tumor from core biopsies will be examined histologically by immunohistochemistry (IHC), immunofluorescence (IF), and RNA analysis. Post-treatment biopsy tissue will be separated into sections for paraffin embedding, fresh frozen in OTC, and fresh frozen in RNAlater. Whole genomic DNA will be evaluated for mutational analysis). Biologic readouts for PD-1 and CTLA4 response biomarkers will be assessed along with specific markers of tumor infiltrating leukocytes (TILs). TILs and their subsets will be assessed using markers by IHC (e.g. CD4, CD8, FoxP3 (Treg), CD14 or CD68 (TAMs), CD11c (DCs)). Response biomarkers will be determined by IHC or IF (e.g. B7-H1 (PD-1L), CD80, CD86, B7-H4, B7-HDC (PD-L2), CTLA4, CD28, LAG3, Tim-3, CD40, OX40)[46,47]. 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)[48] 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[46] 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:

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: Screening
2. On-treatment: Cycle 4 Day 1
3. Post-treatment: 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 3 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 samples collected for this study will be retained at University of Michigan. Specimens will be stored indefinitely or until they are used up. If future use is denied or withdrawn by the patient, best efforts will be made to stop any additional studies and to destroy the specimens.

All CT scans should be de-identified using trial patient and site IDs and shipped to the University of Michigan for banking and exploratory endpoint assessment.

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 at least 4 months of platinum-based front-line systemic chemotherapy with last dose within 4 weeks of informed consent. The primary endpoint is PFS rate at 4 months following the initiation of study treatment. Secondary endpoints include the calculation of the ORR, median PFS and OS (from start of study treatment and 1st line platinum-based therapy), and the incidence of adverse events.

11.2 Sample Size and Accrual

The investigators hope to enroll patients after 4-6 months of first line platinum therapy without progression. The sample size of this trial is based on the hypothesis that we will improve upon the expected proportion of patients surviving without progression after 4 months of investigational therapy. We will accrue 32 evaluable patients to this trial. Evaluable patients are compliant with study treatment and observed for progression-free survival events, progression (requiring study discontinuation), death, or lack of events at 4 months. Patients non-complaint with study treatment or lost to follow-up (either not secondary to toxicity) will be replaced. Based on the ABC-02 trial, PFS was estimated at 72% and 60% after 4 and 6 months of first line gemcitabine and cisplatin, similar to the initiation point of our study. PFS was 51% and 32% at 8 and 10 months, similar to the end of the treatment period for the primary outcome assessment in this trial. Using a conditional probability argument, combined with the assumption that patient accrual to this study will follow an approximate uniform distribution over the 4 to 6 months of primary therapy for the patients accrued, we can accept the average of the PFS estimates for each period (4-6 months (66%) and 8-10 months (41.5%)) to correspond to our trial time period. We can then standardize the ABC-02 PFS data so that the 4-6 month estimate is 100% to correspond to the start point for patients in this trial and the estimate for 4 months thereafter, 63% (0.415/0.66). For our trial, we hope to improve the PFS rate from 63% for these patients to 85%. With our proposed sample size of 32 patients this trial will have 80% power to detect this difference significantly, with 5% type 1 error, using a 1-sided test

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 5.10.

11.4 Data Analyses Plans

The primary endpoint is the progression-free survival proportion measured after 4 months of study treatment for patients in the IIT population. This endpoint is defined as the proportion of evaluable patients alive and progression-free after 4 months of study treatment in the event of no loss to follow-up and/or early patient discontinuation. The outcome is expected to be observed for each patient. In the event that either loss to follow-up or early discontinuation occurs (either not secondary to toxicity), the 4-month PFS will be estimated using the product-limit method of Kaplan and Meier. Follow-up time will be defined as time from the date of first study treatment (PFS1) and 1st line platinum-based therapy (PFS2) until the date of radiological (as per combined RECIST v1.1 and irRECIST criteria) or clinical progression (leading to withdrawal from the study treatment), or loss to follow-up due to toxicity or non-compliance with study procedures, 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. In order to adjust for the patient's exposure to primary platinum-based therapy, a secondary analysis will utilize the Cox proportional hazards model with exposure time entered as an adjustment covariate as either a continuous covariate or as 4 months of exposure versus more than 4 months of exposure. OS will be similarly estimated and summarized with follow-up time calculated from the date of first study treatment (OS1) and 1st line platinum-based therapy (OS2) 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.

11.5 Early Stopping Rules Due to Toxicity

In order to protect patients from potential undue severe toxicity of this regimen, we have implemented stopping rules for documented SAE events that are at least possibly attributable to the study regimen. Using data from study of rucaparib monotherapy as maintenance therapy in ovarian cancer (phase 3 ARIEL3 trial; Coleman RL et al. Lancet. 2017 Oct 28;390(10106):1949-1961) as a guide, which had a SAE rate of 21% - defined as the percentage of patients experiencing at least one SAE during study treatment. In addition, the investigation of nivolumab in hepatocellular carcinoma (CHECKMATE-040 trial; El-Khoueiry AB et al. Lancet. 2017 Jun 24;389(10088):2492-2502) had a SAE rate of 4%. During the conduct of this proposed study, if we become confident from accumulating study data that the SAE rate, defined in the same way, involves more than 30% patients, then we will halt accrual on the trial in order to convene the data safety monitoring board (DSMB). The DSMB will review types and outcome of toxicity events and to recommend study closure or changes that could improve the trial.

To operationalize this stopping rule we have used a Bayesian sequential stopping rule under the beta-binomial relationship between prior expectation of toxicity and accumulating toxicity data. We have used a pessimistic and slightly informative prior, the uniform, to suggest that prior to study data we believe the percentage of SAE is equally like between 0 and 100%, with an average of 50%. If the posterior probability after study data is 80% or greater that the SAE probability per patient is 30% or greater, we will halt the trial. The following table lists the number of patients accrued and the number of patients experiencing an SAE to trigger stopping the trial. The rule is implemented after 5 patients are accrued.

Number of patients on study treatment	Number experiencing SAE
1 – 5	No rule to apply –

	too early
6 – 10	6
11 – 12	7
13 – 14	8
15 – 16	9
17 – 18	10
19 – 20	11
20 – 22	12
23 – 24	13
25 – 26	14
27 – 28	15
29 – 30	16
31 – 32	17

Under this rule, if the true probability of SAE was 20%, 30%, 40%, 50%, or 60% the trial would stop early <1%, 8%, 30%, 62%, and 71%, respectively. And the expected sample size for the trial would be 32, 31, 27, 21, and 19 patients, respectively.

12.0 ADMINISTRATIVE PROCEDURES

12.1 Ethics and good clinical practice

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

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

12.2 Data Management

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

CRFs will be reviewed and source verified by the MSC during annual monitoring visits and prior to and between visits. Discrepant, unusual and incomplete data will be queried by the MSC. The investigator or study coordinator will be responsible for providing resolutions to the data queries, as appropriate. The investigator must ensure that all data queries are dealt with promptly.

The data submission schedule is as follows:

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

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

12.3 Record Retention

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

13.0 DATA AND SAFETY MONITORING

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 quarterly 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 quarterly 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 first treatment cycle. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

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

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

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

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

Participating site will also undergo a site close-out upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the conduct of the study, and that the site

Investigator is aware of his/her ongoing responsibilities. In general, a site close-out is conducted during a site visit; however, site close-out can occur without a site visit.

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17.0 APPENDICES

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

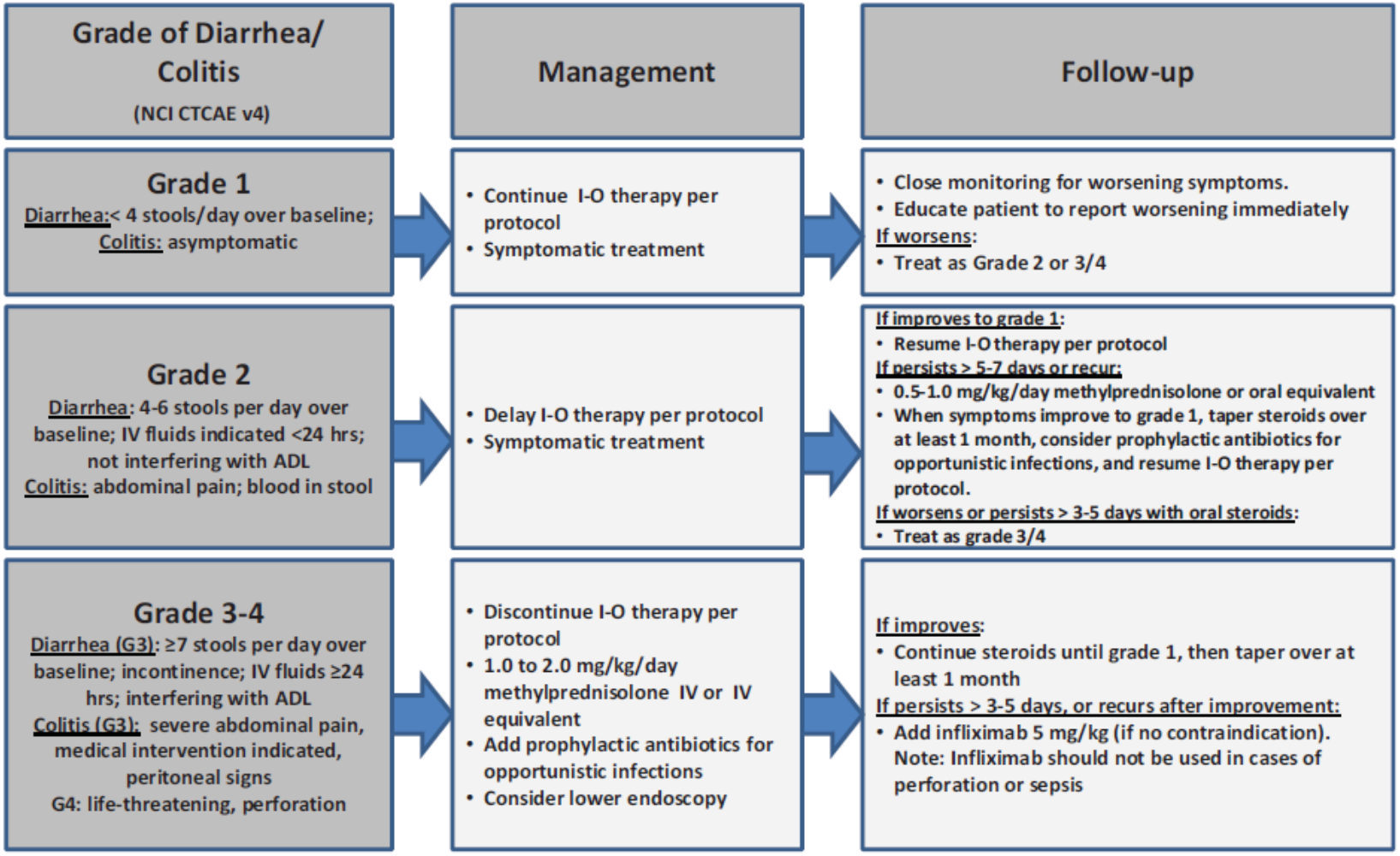
Appendix III Management Algorithms for Immuno-Oncology Agents

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

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

GI Adverse Event Management Algorithm

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



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

Renal Adverse Event Management Algorithm

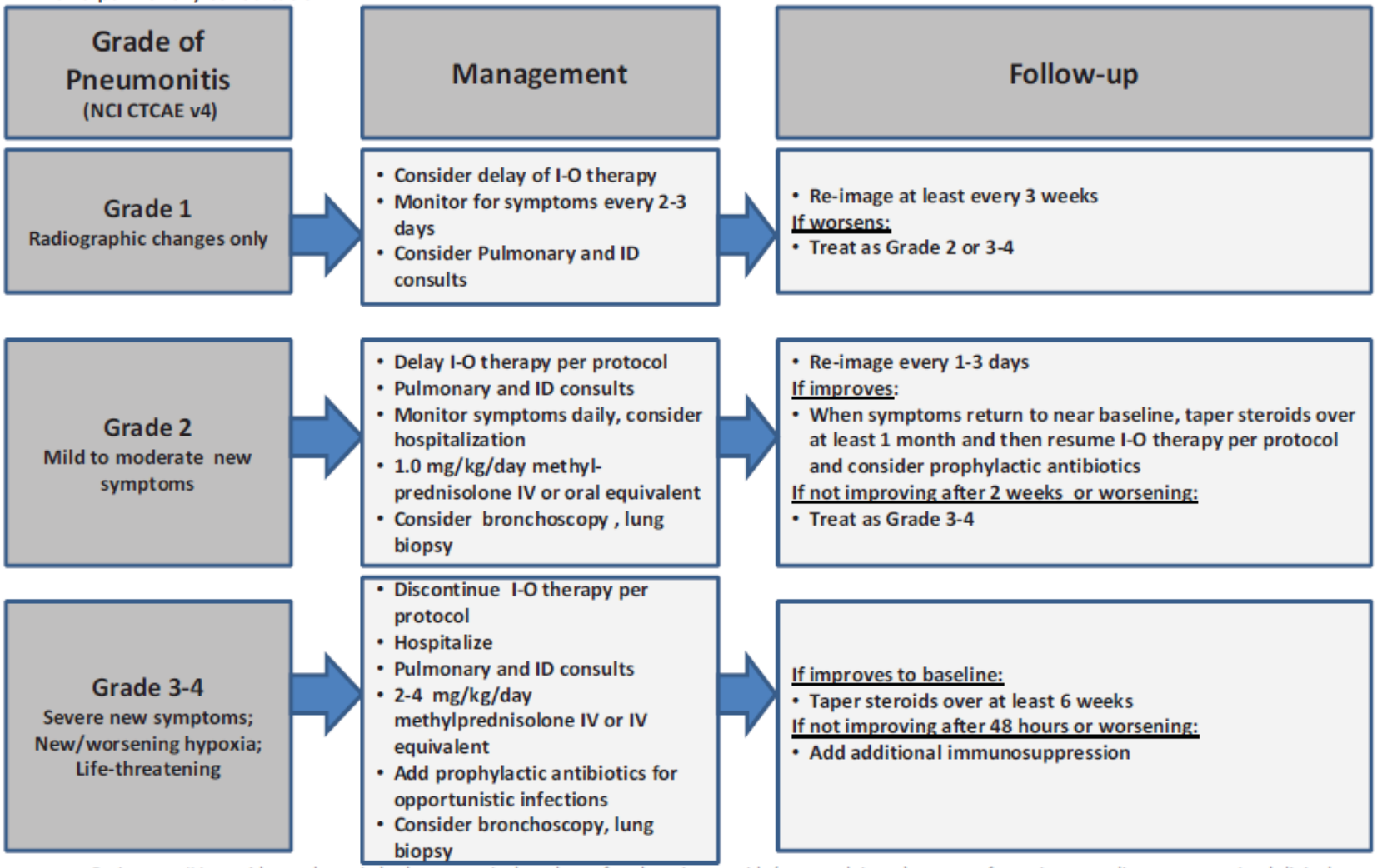
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

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

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

Pulmonary Adverse Event Management Algorithm

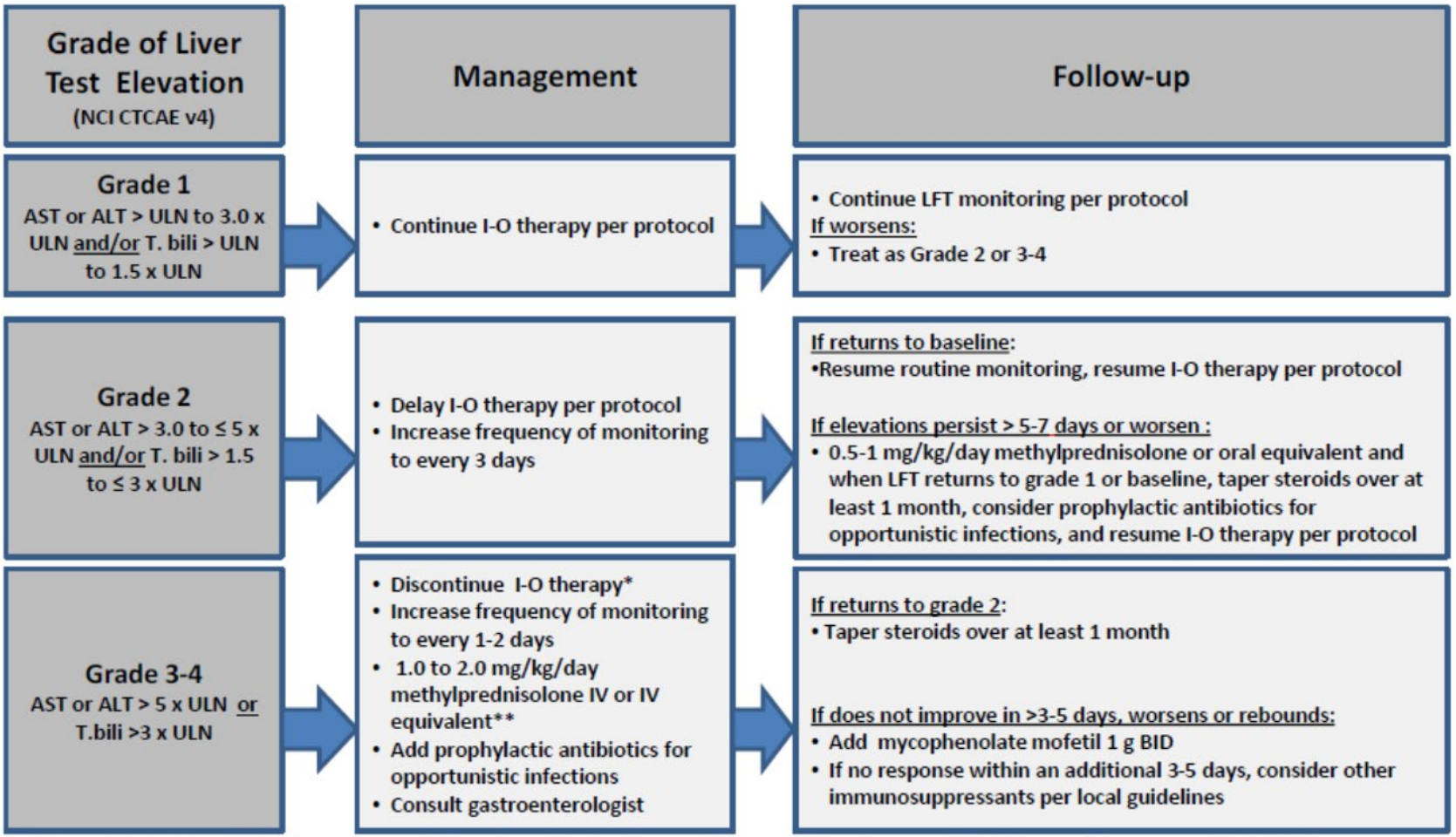
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



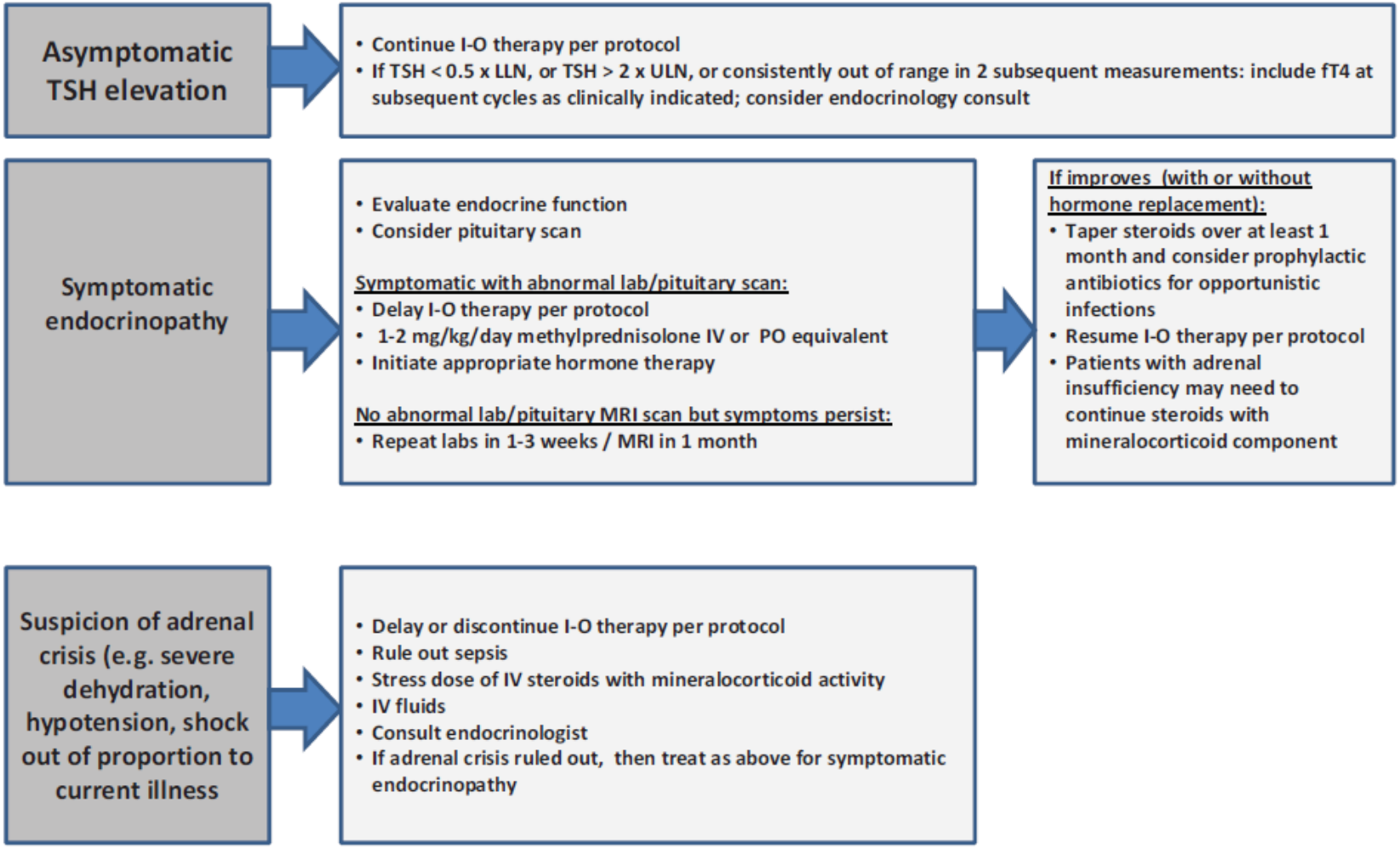
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

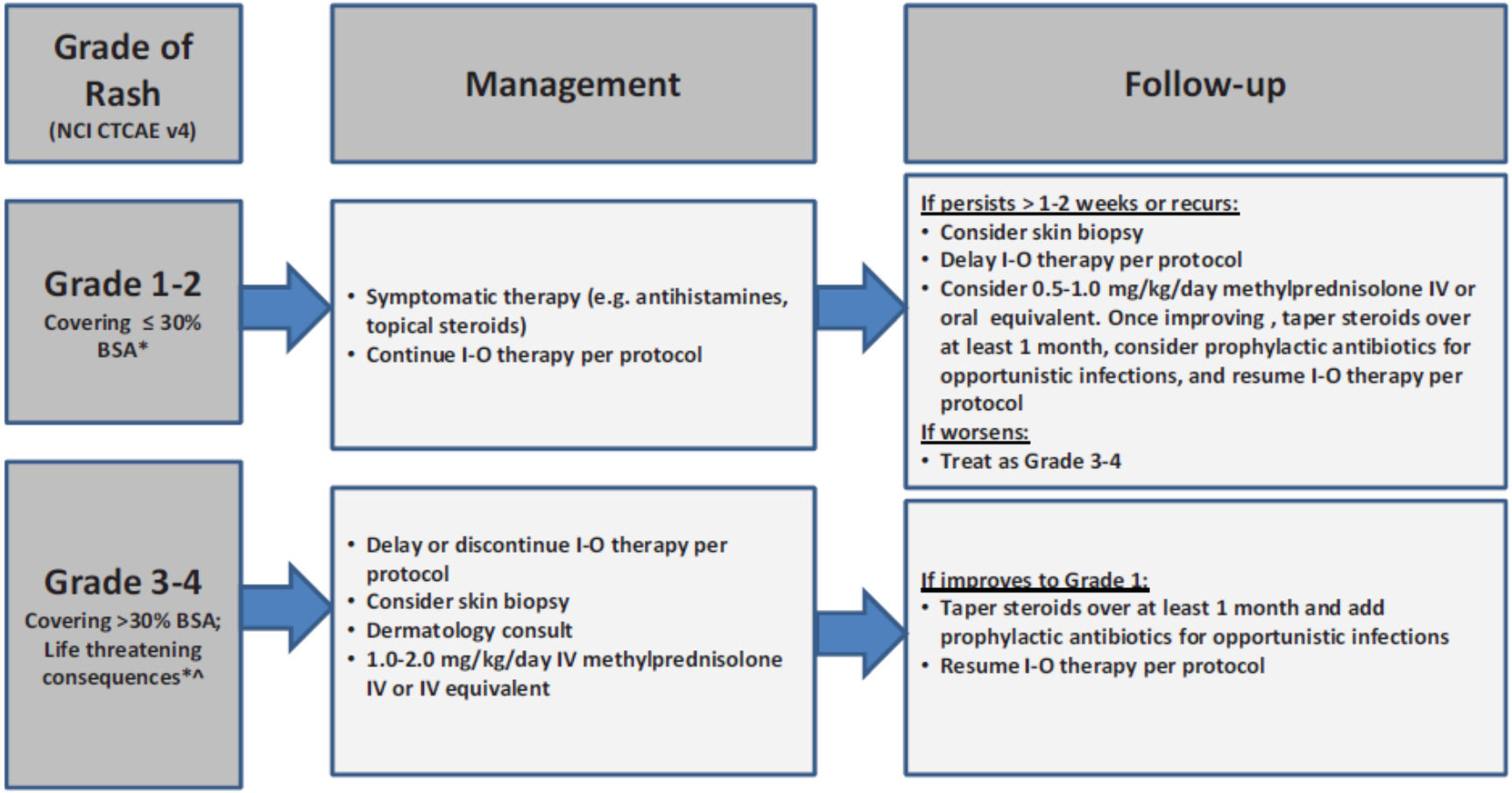
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm

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

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

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

Appendix IV Investigator's Statement

1. I have carefully read this protocol entitled "Phase II Study of PARP inhibitor Rucaparib in Combination with Anti-PD-1 Antibody Nivolumab in Patients with Advanced or Metastatic Biliary Tract Cancer Following Platinum Therapy", **Version 4.0 dated 11/24/2020** 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).

1. **COVID-19 Testing:**
    a. 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.
    b. 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.
    c. Per study Supporters [Clovis and Bristol-Myers Squibb] additional reporting requirements, it is requested that the Medical Monitor is to be immediately informed in the event that a trial participant exhibits or reports symptoms consistent with COVID-19 (whether or not confirmed by a positive test result). Depending on the investigational product being administered and the patient's clinical presentation, dosing may be withheld, until such time as symptoms resolve. This decision should be made by the site PI, determining what is the best course of action for the patient, in consultation with the Medical Monitor. In some cases, the PI and/or Medical Monitor may request a participant be retested before dosing of the investigational product is resumed.

2. **Study Visit Schedule:**
    a. 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).
    b. 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.
    c. Where participants cannot be seen at the site or by home visit, the use of telemedicine and adaptation of schedule of assessments can be implemented, where feasible to ensure patient safety.
    d. 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.

3. **Laboratory Assessments:**
    a. Pre-Treatment, Cycle 4 Day 1 (UM Only) & End of Treatment (EOT) biopsy samples will be obtained, if applicable/possible, and will be retained at site until further notification.
    b. Cycle 1 Day 1, Cycle 3 Day 1 and End of Treatment blood samples 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.

4. **Study Medications:**

a. Adjustments for alternate drug administration have been permitted by the Supporters (Clovis and Bristol-Myers Squibb) and Sponsor-Investigator. 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.

b. The patient may remain on study without receiving drug for more than 28 days if the drug(s) are held due to COVID-19.

c. If a patient does not receive investigational regimen (both Nivolumab and Rucaparib) 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.

d. Nivolumab or Rucaparib may be held independent of the other drug if drug infusion or intake not considered possible or safe due to COVID-19.

e. Sites may ship Rucaparib (Oral Medication) with drug diary directly to subjects via an overnight, traceable courier.