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Rucaparib and Pembrolizumab for Maintenance Therapy in Stage IV Non-Squamous Non-Small Cell Lung Cancer

TITLE: A Phase I/II Multi-site Study of Rucaparib and Pembrolizumab Maintenance Therapy in Stage IV Non-Squamous Non-Small Cell Lung Cancer after Initial Therapy with Carboplatin, Pemetrexed, and Pembrolizumab

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
ALK	Anaplastic Lymphoma Kinase
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CPP	Carboplatin/Pemetrexed/Pembrolizumab
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CTSU	Clinical Trials Support Unit
DLT	Dose Limiting Toxicity
DSB	Double-Stranded Breaks
DSMC	Data and Safety Monitoring Committee
ECI	Events of Clinical Interest
EGFR	Epidermal Growth Factor Receptor
ERC	Ethics Review Committee
GCP	Good Clinical Practice
H&P	History & Physical Exam
HRD	Homologous Recombination Deficiency/deficient
HRR	Homologous Recombinant Repair
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
irRECIST	Immune Response RECIST
ITIM	Immunoreceptor Tyrosine-Based Inhibition motif
ITSM	Immunoreceptor Tyrosine-Based Switch Motif
IV (or iv)	Intravenously
MSD	Merck Sharpe & Dohme
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PARP	Poly (ADP-Ribose) Polymerase
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1

PD-L1	Programmed Death-Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PO	per os/by mouth/orally
PR	Partial Response
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
SAE	Serious Adverse Event
SD	Stable Disease
SSB	Single Stranded Breaks
TCGA	The Cancer Genome Atlas
TEAE	Treatment-emergent Adverse Event
TMB	Tumor Mutational Burden
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cells

1.0 TRIAL SUMMARY

Abbreviated Title	Rucaparib and Pembrolizumab Maintenance Therapy in Stage IV Non-squamous NSCLC
Trial Phase	I/II
Trial Type	Interventional
Study Centers	Multi-Center: 3 sites total including the lead site: University of Michigan
Objectives	Primary: - To determine the progression free survival (PFS) of patients with stage IV non-squamous NSCLC on maintenance therapy with rucaparib and pembrolizumab after initial induction therapy with carboplatin/pemetrexed/pembrolizumab (CPP) Secondary: - To determine overall survival - To evaluate safety and tolerability of the combination of rucaparib and pembrolizumab as maintenance therapy - To evaluate response based on immune-related RECIST (ir-RECIST) criteria and compare to response rate as evaluated by RECIST v1.1. Exploratory: - To evaluate for genomic correlates that predict improved PFS to the combination of rucaparib and pembrolizumab maintenance therapy; these include tumor mutational burden, homologous repair deficiency, loss of heterozygosity, and PD-L1 expression - To evaluate the correlation between somatic mutations in the homologous repair pathway and association with improved PFS to the combination of rucaparib and pembrolizumab.
Type of control	Historical controls of patients treated with pembrolizumab +/- pemetrexed maintenance following induction therapy with carboplatin/pemetrexed/pembrolizumab
Study drugs: dose and administration	Rucaparib, PO, 600mg BID days 1-21 of a 21-day cycle Pembrolizumab, IV, 200mg day 1 of a 21-day cycle
Duration of administration	Until disease progression or intolerable toxicity, or after completing 2 years of therapy
Inclusion Criteria	• Stage IV NSCLC whose tumors do not have a mutation in epidermal sensitizing growth factor (EGFR) or BRAF or rearrangements in ALK (anaplastic lymphoma kinase) or ROS-1 • Non-squamous histology • Presence of measurable disease according to RECIST v1.1 • ECOG performance status 0-1 • Adequate organ function defined as AST and ALT $\leq 2.5 \times$ ULN, bilirubin $\leq 1.5 \times$ ULN, and creatinine clearance ≥ 50 ml/min • Adequate hematologic parameters • Sufficient tissue sample of adequate quality for correlative studies
Exclusion Criteria	• Presence of significant comorbidities precluding participation in a clinical study as determined by investigator

	• Has active autoimmune disease that has required systemic treatment in the past 2 years • Daily oral corticosteroid use >10mg of prednisone (or its equivalent) • ECOG performance status 2-4 • Prior systemic treatment for stage IIIB/IV NSCLC • Pregnancy or lactation
Number of trial subjects	38 (stage I), 17 (stage II), 55 total, with a 6-12 patient safety lead-in for stage 1
Statistical design	Bayesian two-stage design with phase I safety run-in
Estimated duration of trial	46 months (maximum)
Estimated average length of treatment per patient	12 months

2.0 TRIAL DESIGN

2.1 Trial Design

This study is a multicenter, Phase I/II, single arm trial to assess the safety and efficacy of the combination of oral rucaparib plus intravenous pembrolizumab as maintenance therapy in patients with stage IV non-squamous non-small cell lung cancer (NSCLC) without progressive disease (PD), as confirmed on CT scans, after induction therapy with carboplatin/pemetrexed/pembrolizumab (CPP) triplet therapy. Approximately 55 patients whose tumors who do not have an epidermal sensitizing growth factor (EGFR) mutation or rearrangements in ALK (anaplastic lymphoma kinase) or ROS-1 will be enrolled.

A small safety-run in will be conducted to assess the safety of the combination of rucaparib and pembrolizumab at the proposed dose of rucaparib 600mg PO BID d1-21 and pembrolizumab 200mg IV on day 1 every 21 days. While there have not been any studies specifically with the combination of rucaparib and pembrolizumab, the phase I study of durvalumab (a PD-L1 inhibitor) and olaparib (a PARP inhibitor) did not have any DLTs. The only grade 3 adverse events observed were lymphopenia and anemia and all other toxicities were ≤Grade 2.[1] However, if ≥2 DLTs occur within the DLT timeframe (Cycle 1) after enrolling the first 6 patients, then there will be a dose reduction of rucaparib. Specific details are available in section 11.1.

The patients will be assessed using cross-sectional imaging obtained every 6 weeks (42 +/- 7 days) for the first 18 weeks, every 9 weeks through the first 12 months, and every 12 weeks thereafter. All imaging obtained will be submitted to an independent radiology review committee at the University of Michigan and will be assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). To minimize the number of patients to be treated, this study will use a Bayesian two-stage design with planned analysis to compare to historical controls of patients treated with pembrolizumab +/- pemetrexed maintenance after receiving four cycles of CPP. Adverse event (AE) monitoring will occur prior to each cycle (21 days) and events will be graded according to the NCI Common

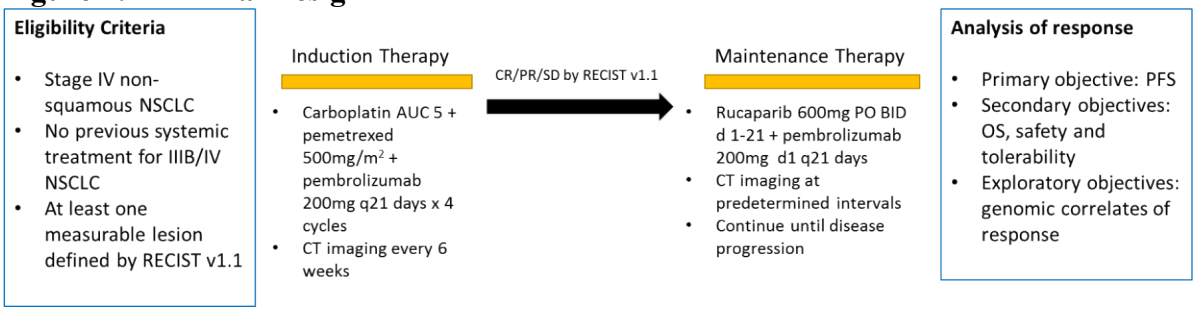
Terminology Criteria for Adverse Events (CTCAE) version 4.03. Patients will continue on trial until confirmed progression as defined by RECIST v1.1, develops unacceptable toxicity or intercurrent illness that prevents further administration of treatment, withdrawal from study, removal by the investigator, becomes pregnant, demonstrates noncompliance with trial requirements, or has received 24 months of treatment with rucaparib and pembrolizumab. Patients may continue on treatment despite RECIST v1.1-defined progression if the subject is felt to be continuing to derive clinical benefit as determined by the investigator. Additional information including the irRC[2] (immune-related response criteria) may be used by the investigator in deciding continuing treatment beyond RECIST v1.1-defined progression.

At the end of treatment, all patients will continue to be followed for a minimum of 30 days for AE monitoring. Subjects will have post-treatment follow-up for disease status for 5 years, including initiation of non-study cancer therapy until death, withdrawal of consent, or becoming lost to follow-up.

2.2 Trial Diagram

The trial design is depicted below in **Figure 1**.

Figure 1: Trial Design



3.0 OBJECTIVES

3.1 Primary Objective & Hypothesis

(1) **Objective:** To determine the progression free survival (PFS) of the combination of rucaparib and pembrolizumab maintenance therapy in patients with stage IV non-squamous NSCLC with CR, PR, or SD after completing induction therapy with four cycles of CPP. Response will be measured by RECIST v1.1.

Hypothesis: The combination of pembrolizumab and rucaparib maintenance therapy is superior to historical controls in NSCLC patients who received maintenance therapy with pembrolizumab +/- pemetrexed.

3.2 Secondary Objectives & Hypotheses

(1) **Objective**: To evaluate the safety and tolerability profile of pembrolizumab and rucaparib.

(2) **Objective:** To evaluate the OS in patients treated with maintenance pembrolizumab and rucaparib following induction therapy with CPP.

(3) **Objective:** Evaluate response based on immune response RECIST (irRECIST) as proposed by Wolchok *et al*[2] and compare with response as calculated by RECIST v1.1.

3.3 Exploratory Objectives

(1) **Objective:** To evaluate genomic correlates of response to combination maintenance therapy with rucaparib and pembrolizumab. Markers will include PD-L1 expression, tumor mutational burden (TMB), homologous repair deficiency (HRD), and loss of heterozygosity (LOH). We will also evaluate serial circulating tumor DNA (ct-DNA) as a genomic correlate of response, while on therapy to determine if there is a correlation with response to therapy.

(2) **Objective:** To evaluate the correlation between germline and somatic mutations in genes in the homologous repair pathway and association with improved PFS to the combination of rucaparib and pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

Disease Under Treatment

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-associated mortality worldwide. The prognosis for stage IV NSCLC remains dismal, with a 5-year survival rate of 1-2%. In addition to standard first-line platinum-based chemotherapy, other therapeutic options include tyrosine kinase inhibitors for patients with eligible mutations in the EGFR, ALK, or ROS-1 genes, and immune checkpoint inhibitors. Currently, both PD-1 (programmed cell death protein 1) and PD-L1 inhibitors are approved for the treatment of advanced NSCLC, irrespective of histology. Multiple phase II/III trials have demonstrated their superiority in terms of response rate and overall survival compared to docetaxel chemotherapy.[3–5]

Study Drugs

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. It is approved in the United States for the treatment of stage IV NSCLC with PD-L1 ≥50% in the front-line setting or for metastatic disease with PD-L1 ≥1% after progression on platinum-based chemotherapy. It also recently received accelerated approval by the FDA to be used in conjunction with carboplatin and pemetrexed as upfront therapy followed pembrolizumab +/- pemetrexed maintenance irrespective of PD-L1 expression in non-squamous etiologies.[6]

Rucaparib is a small molecule inhibitor of the poly (ADP-ribose) polymerase (PARP) enzymes PARP-1, PARP-2, and PARP-3. It is FDA-approved for the treatment of BRCA mutant (germline/somatic) advanced ovarian cancer who have been treated with two or more previous chemotherapy regimens. It is also being explored in other solid tumors associated with

homologous recombination deficiency (HRD). Recently published results of a phase III randomized, placebo-controlled study showed that rucaparib maintenance therapy significantly improved progression free survival in women with platinum-sensitive high-grade ovarian, fallopian tube, and primary peritoneal cancer in all patients (including those that were BRCA wt and HRD-negative).[7] The benefit was greater for patients whose tumors carried the BRCA mutation or were found to possess HRD.

Refer to the Investigator's Brochures (IB)/approved labeling for detailed background information on pembrolizumab and rucaparib.

4.1.1 Immune surveillance of malignancy and the PD-1/PD-L1 pathway

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells[8] and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells[9] seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor, including

NSCLC. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.2 Homologous recombinant repair and PARP inhibitors

The homologous recombinant repair (HRR) pathway is critical for error-free repair of DNA double-stranded breaks (DSBs). Key genes in this pathway include BRCA1 and BRCA2, which when mutated are involved in the pathogenesis of hereditary breast and ovarian cancers, among others. Poly (ADP-ribose) polymerases (PARP) are a group of proteins that are crucial to the repair of single-stranded breaks (SSB). Upon formation of SSB, PARP binds at the end of broken DNA strands, a process which activates its enzymatic activity. Activated PARP catalyzes addition of long polymers of ADP-ribose on several proteins associated with chromatin, including histones and various DNA repair proteins. Therefore, PARP plays a key role in sensing DNA damage and converting it into intracellular signals that activate the base-excision-repair (BER) and SSB repair pathways.

Inhibition of PARP allows the propagation of SSBs which are converted to DSBs as the cell progresses through the S phase; the DSBs would normally then be repaired by the HRR pathway. The concept of synthetic lethality is demonstrated by the use of PARP inhibitors in homologous repair deficient (HRD) cells which are unable to repair DSBs, ultimately resulting in cell death. PARP inhibitors have been approved in the United States for treatment of refractory germline BRCA-mutated ovarian cancer.

There is increasing data to support that some sporadic tumors also harbor somatic mutations in other genes involved in the HRR pathway (*i.e.* ATM, RAD51, etc.), which result in a similar phenotype as germline BRCA mutant cells. These cells are considered to possess "BRCAness" which are also thought to render sensitivity to PARP inhibition.[10] Examination of cancer genomic data sets through The Cancer Genome Atlas (TCGA) reveal that 11% of all NSCLC sequenced possessed mutations in BRCA1 or BRCA2 with up to 38% of cases having mutations in genes involved in DNA damage response.[11]

4.1.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for both pembrolizumab and rucaparib for Preclinical and Clinical data.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

A new standard of care for patients with stage IIIB/IV non-squamous NSCLC without driver mutations is upfront carboplatin, pemetrexed, and pembrolizumab followed by pembrolizumab with or without pemetrexed maintenance therapy, irrespective of tumoral PD-L1 expression. In the KEYNOTE-021 cohort G, pemetrexed maintenance was not required, and 85% of patients in the pembrolizumab group received both drugs as maintenance therapy.[6] Previous trials with the combination of platinum-pemetrexed doublet chemotherapy followed by pemetrexed maintenance lead to a PFS of 4-6 months.[7,12] The median PFS of 13.0 months with

pembrolizumab +/- pemetrexed seen on the KEYNOTE-021 trial is therefore a significant improvement compared to pemetrexed maintenance alone. However, there is data that suggests that the combination of a PARP inhibitor and pembrolizumab may lead to further improvements in PFS.

Rizvi *et al*. have demonstrated through whole exome sequencing of patients with NSCLC treated with pembrolizumab that possess higher nonsynonymous tumor mutational burden (TMB) was associated with improved objective response, durable clinical benefit (DCB), and PFS.[13] Furthermore, in this study, 50% of patients who experienced DCB had a mutation or mutations in genes involved in DNA repair including BRCA2 and RAD51, suggesting a possible association between increased TMB, "BRCAness", and improved response to checkpoint inhibitors.[14] In cell models, deficiencies in proteins of other members involved in the HR pathway such as RAD51, ATM, and FANCA did convey sensitivity to PARP inhibitors.[10] This is also seen in BRCA wild-type (wt) but HR-deficient high grade serous ovarian carcinoma cells which have a higher neoantigen load compared to those that are BRCA-wt/HR-proficient.[15] There is also data to suggest that increased TMB correlates with loss of heterozygosity (LOH), which is another surrogate marker for HRD; this was seen through exploration of the TCGA data for lung adenocarcinoma. The recently published ARIEL2 trial showed that treatment with rucaparib lead to an improved progression free survival and a higher response rate in BRCA-wt/LOH high ovarian carcinomas compared to BRCAwt/LOH low tumors.[16]

Elevated tumoral PD-L1 expression appears to predict response to pembrolizumab. Compared to a response rate of 45% in patients with tumoral PD-L1 ≥50%, the response rate for tumoral PD-L1 1-49% is 16.5% and 10.7% with PD-L1 <1%.[17] Treatment with a PARP inhibitor was seen to lead upregulate PD-L1 expression in cancer cell lines and animal models.[18] This is supported by sequencing data from Dr. Arul Chinnaiyan's lab at the University of Michigan shows that there is increased PD-L1 expression in HR deficient lung tumors.

Given the association between presence of HRD, increased PD-L1 expression, and increased TMB, the addition of a PARP inhibitor may enhance response to a PD-1 inhibitor. Furthermore, sensitivity to platinum chemotherapy is associated with sensitivity to PARP inhibitors.[19] We therefore propose to study the combination of rucaparib and pembrolizumab maintenance therapy in patients who have SD or PR after induction therapy with CPP.

4.2.2 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab

An open-label Phase I trial (KEYNOTE-001) has been conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. Recent data

from other clinical studies within the pembrolizumab program has shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provided the scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for pembrolizumab as shown in the melanoma indication. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

<u>Rucaparib</u>

A three-part, open-label, Phase 1/2 study of oral rucaparib monotherapy administered daily in continuous 21-day cycles is ongoing. Part 1 (Phase 1) evaluated PK and safety of escalating doses of rucaparib in patients with solid tumors dose (N = 56; enrollment complete) and identified 600 mg BID as the recommended starting for Phase 2 based on safety, PK, and the clinical activity profile.

There has been no phase I data that has specifically evaluated the combination of rucaparib and pembrolizumab. There are not any serious adverse events that appear to overlap between

the two agents based on review of published phase I/II/III and data. However, we will plan for a small phase I run-in for safety analysis. Details are described in Section 11.0.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The primary endpoint of this study is progression free survival. We chose PFS as the primary endpoint as we are studying the impact of a novel therapy combination in the maintenance setting. Response rate in this setting would not be an appropriate endpoint as all patients must respond or have SD to initial induction with CPP prior to starting maintenance therapy. We will assess OS as a secondary endpoint. In addition, we will evaluate safety and tolerability as the combination of rucaparib and pembrolizumab has not been exclusively studied in the past.

4.2.3.2 Biomarker Research

We anticipate that there will be a subset of patients who will remain without progressive disease on rucaparib and pembrolizumab maintenance therapy after induction CPP for >13 months (the median PFS seen in KEYNOTE-021). To interrogate genomic predictors of response, we will evaluate archived tissue samples for TMB, HRD, and LOH. Tumoral PD-L1 expression will also be assessed, which is currently considered standard of care in metastatic NSCLC. Finally, we will also measure serial ct-DNA for longitudinal monitoring of ctDNA as a measure of response to therapy and correlate with radiographic progression.

5.0 PATIENT ELIGIBILITY

5.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Have a life expectancy of at least 3 months.

4. Have a diagnosis of stage IV non-squamous NSCLC whose tumors do not have an epidermal sensitizing growth factor (EGFR) mutation or BRAF mutation or rearrangements in ALK (anaplastic lymphoma kinase) or ROS-1 and haveat least one measurable lesion based on RECIST v1.1.

5. Have a performance status of 0 or 1 on the ECOG Performance Scale (Appendix 15.1).

6. Demonstrate adequate organ function as defined in Table 1; all screening labs should be performed within 28 days of enrollment.

Table 1: Adequate organ function laboratory values

System	Laboratory Value
Hematologic	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

7. Female subject of childbearing potential should have a serum pregnancy test within -28 daysof enrollment and 72 hours prior to receiving the first dose of study medications.

8. Female subjects of childbearing potential must be willing to use a highly effective method of contraception as outlined in Section 6.3.3 for the course of the study through 180 days after the last dose of study medications.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 6.3.3, starting with the first dose of study therapy through 180 days after the last dose of study therapy.

   Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

10. If the patient has archival tissue, this should be collected for correlative studies. If archival tissue does not exist, a new biopsy is not required

5.2 Exclusion Criteria

The first dose of trial treatment is considered to be first dose of carboplatin, pemetrexed, and pembrolizumab. The subject must be excluded from participating in the trial if the subject:

1. Received previous systemic therapy for stage IV NSCLC.
2. Received radiation to the lungs >30Gy ≤6 months of enrollment.
3. Received palliative radiation within 7 days of enrollment.
4. Had prior treatment with any other anti-PD-1, PD-L1, or PD-L2 agent or an antibody targeting other immune-regulatory receptors or mechanisms.
5. Received prior treatment with a PARP inhibitor.
6. Has a known history of prior malignancy except if the patient has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy. Note: the time requirement for no evidence of disease for 5 years does not apply to the NSCLC tumor for which a subject is enrolled in the study. The time requirement also does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.
7. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to enrollment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior enrollment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
8. Has active autoimmune disease that has required systemic treatment within the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

   Note: Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Subjects requiring daily corticosteroids >10mg of prednisone (or its equivalent) would be excluded from the study.

   Note: Subjects with asthma that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would NOT be excluded from the study.

10. Has evidence of interstitial lung disease or a history of non-infectious pneumonitis that required oral or intravenous glucocorticoids to assist with management.

    Note: Lymphangitic spread of the NSCLC is not exclusionary.

11. Has an active infection requiring systemic therapy.

12. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with informed consent through 180 days after the last dose of trial treatment.

14. Has a diagnosis of immunodeficiency (including Human Immunodeficiency Virus (HIV) or acquired immunodeficiency (AIDS-related illness) or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to enrollment.

15. Has a known history of active TB (Bacillus Tuberculosis).

16. Has known active Hepatitis B or Hepatitis C.

17. Has received a live vaccine within 30 days of enrollment.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

18. A medical condition that requires daily systemic corticosteroids, greater than the equivalent of 10mg of prednisone.

    Note: Corticosteroids administered as part of pre-medications or supportive medications (as in the case of dexamethasone as an anti-emetic administered with pemetrexed) are allowed.

6.0 TREATMENT PLAN

6.1 Drug Administration

6.1.1 Induction Phase

The drugs to be used in the Induction Phase are outlined in Table 2 below. The first dose of trial treatment is considered to be first dose of carboplatin, pemetrexed, and pembrolizumab. Trial treatment should begin within 14 days of enrollment.

Table 2: Induction phase drugs

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle; given first and at least 30 minutes prior to chemotherapy
Pemetrexed	500 mg/m^2	Q3W	IV infusion	Day 1 of each 21-day cycle; given after pembrolizumab and before carboplatin
Carboplatin	AUC 5	Q3W	IV infusion	Day 1 of each 21-day cycle; after pemetrexed

Pembrolizumab 200 mg will be administered as a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). Similarly, infusion times may be extended as needed for safety (e.g., infusion reaction occurs). These instances must be documented in the patient medical records. It must be administered first and at least 30 minutes prior to infusion of subsequent pemetrexed and carboplatin in the Induction Phase.

Pemetrexed 500mg/m^2 will be administered as an IV infusion over 10 minutes (+/- 5 minutes) Q3W during the Induction Phase. All subjects should receive appropriate supplementation of vitamin B12 and folic acid according to the approved product label and/or standard practice. In addition, all patients should receive the appropriate corticosteroid prophylaxis as per the local approved label. Additional prophylaxis should be administered as per standard practice.

Carboplatin AUC5 will be administered as an IV infusion over 15-60 minutes +/- 5 minutes Q3W during the Induction Phase immediately after pemetrexed. Additional pre-medications should be administered as per standard protocol.

6.1.2 Maintenance Phase

The drugs to be used in the Maintenance Phase are outlined in **Table 3** below.

Patients must have complete response (CR), partial response (PR), or stable disease (SD) after initial therapy with the 4 cycles of induction phase therapy to be permitted to proceed with the maintenance phase.

Table 3: Maintenance phase drugs

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 21-day cycle

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period
Rucaparib	600 mg	BID	PO	Day 1-21 of each 21 day cycle

All trial treatments will be administered on an outpatient basis.

Rucaparib 600mg (2 X 300mg rucaparib tablets) PO will be taken twice daily starting on day 1 of cycle 1 of the Maintenance Phase. Rucaparib should be taken with water, on an empty stomach or with food. Treatment is continuous and each cycle will comprise 21 days. Patients should take rucaparib doses as close to 12 hours apart as possible, 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 at the next scheduled dose. Vomited doses should not be replaced.

Subjects will be given a pill diary and instructed to complete for each day of administration of rucaparib. Missed and/or vomited doses should be recorded on the diary as such. Subjects will be asked to bring their pill diary to each study visit along with all used and unused study drug containers.

6.2 Dose Modification

In the event that one drug is discontinued for any reason, then the other drug will also be discontinued and the patient will come off study treatment. If one or both drugs are held for ≥6 consecutive weeks from intended cycle start, the patient must come off study treatment. The primary objective of this trial is to look at the efficacy of rucaparib and pembrolizumab in the maintenance setting and therefore patients on maintenance therapy with a single agent should not be evaluated for the primary endpoint; however, they will still be evaluable for toxicity.

6.2.1 Pembrolizumab Dose Modification

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in **Table 4**.

Table 4: Pembrolizumab infusion reaction dose modification and treatment guidelines

NCI CTCAE Grade	Treatment	Premedication and Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: - IV fluids -Antihistamines -NSAIDs -Acetaminophen -Narcotics -Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: -Epinephrine** -IV fluids -Antihistamines -NSAIDs -Acetaminophen -Narcotics -Oxygen -Pressors -Corticosteroids -Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. -Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0.3 (CTCAE) at http://ctep.cancer.gov		

For dose modification/management of immune-related adverse events, please see section 7.3 Table 7.

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor-Investigator. The reason for interruption should be documented in the patient's study record.

6.2.2 Rucaparib Dose Modification

Phase I Safety-Run In - Dose Limiting Toxicity (DLT)

The DLT for the phase I safety run in will be defined as in the phase I/II study of rucaparib in patients with germline BRCA 1/2 mutated solid tumors.[20] A DLT was defined as any of the following events that occurred in Cycle 1 and were assessed by investigators as related to rucaparib:

1) Absolute neutrophil count less than 0.5 x 10^9/L lasting for more than 5 days or febrile neutropenia (which is defined as a temperature >38.3ºC and an ANC < 1.0 x 10^9/L).

2) Platelets less than 25 x 10^9 or less than 50 x 10^9/L with bleeding requiring a platelet transfusion

3) Grade 4 anemia

4) Any non-hematologic adverse event ≥ CTCAE Grade 3 (except nausea, vomiting, and diarrhea, if well controlled by systemic medication, and alopecia)

Maintenance Phase Rucaparib Dose Modification

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

- 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)

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

Treatment with rucaparib should be held until the toxicity improves to ≤ CTCAE Grade 2. BID 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, the dose should be reduced following improvement of the event to ≤ CTCAE Grade 2.

At the discretion of the treating investigator, treatment may be discontinued:

- If a subject continues to experience toxicity despite dose reduction [as allowed per the phase I safety run-in] or,
- If upon rechallenge, dosing with rucaparib is interrupted for >14 consecutive days due to toxicity

Dose reduction steps are presented in **Table 5**.

Dose re-escalation upon resolution of toxicity to ≤ CTCAE Grade 1 is permitted, upon the investigator's discretion.

Table 5: Dose modification for rucaparib

Rucaparib (CO-338)	
Tablets	**300/250/200 mg**
Starting Dose	**600 mg BID**
Dose Level -1	500 mg BID

Criteria for Rucaparib Re-treatment

A new cycle of treatment may begin 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 in **Table 6**.

6.2.3 Overlapping Expected or Potential Hepatotoxicity

Elevated ALT/AST is among the most frequently reported treatment-related adverse events reported for rucaparib monotherapy. Immune-mediated hepatitis has been associated with the administration of pembrolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminase, and liver function will be monitored throughout study treatment. While on this study, patients presenting with right

upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose of study drug. If LFTs increase, neoplastic, concurrent medications, viral hepatitis, and toxic etiologies should be considered and addressed, as appropriate. Imaging of the liver, gall bladder and biliary tree should be performed to rule out neoplastic or other causes for increased LFTs. Anti-nuclear antibody, perinuclear anti-neutrophil cytoplasmic antibody, anti-liver kidney microsomal antibodies, and anti-smooth muscle antibody tests should be performed if an autoimmune etiology is considered. Recommended guidelines for managing LFT abnormalities are outlined in **Table 6**.

Table 6: Management Guidelines for Rucaparib-Pembrolizumab Combination Treatment-Emergent AST/ALT Elevations

Description	Management
AST/ALT > ULN to 3 x ULN	• Continue rucaparib and pembrolizumab with the standard monitoring plan
AST/ALT > 3 x ULN to 5 x ULN with total bilirubin ≤ULN	• Continue rucaparib and pembrolizumab • Monitor LFTs at least weekly
AST/ALT > 5 x ULN to 10 x ULN with total bilirubin ≤ ULN OR AST/ALT > 3 x ULN to 5 x ULN with bilirubin > ULN	• Hold rucaparib and pembrolizumab • Monitor LFTs every 48-72 hours; if incremental increases observed after 72 hours of initial > 5 x ULN observation, follow the guidelines below for AST/ALT>10 x ULN (even if it is ≤10 x ULN) • Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary • If resolves to ≤5 x ULN in ≤7 days, restart rucaparib and pembrolizumab • If persists > 7 days, follow guidelines for AST/ALT > 10 x ULN
AST/ALT > 10 x ULN	• Permanently discontinue rucaparib and pembrolizumab • Consider GI consult and liver biopsy to establish etiology of hepatic injury if necessary • Start 60mg prednisone or equivalent per day • Monitor LFTs every 48 hours • If LFT results do not decrease within 48 hours after initiation of systemic steroids, addition of an alternative immunosuppressive agent (e.g. mycophenolate or TNFα antagonist) may be considered

	• Continue monitoring LFTs every 48-72 hours until decreasing and then follow weekly until resolution to ≤ 5 X ULN • Taper steroids over >1 month

GI = gastrointestinal; LFT = liver function test; TNFα = tumor necrosis factor alpha; ULN = upper limit of normal.

6.2.4 Carboplatin and Pemetrexed Dose Modification

Dose reduction in carboplatin and pemetrexed will be done on an as needed basis as determined appropriate by the investigator.

6.3 Diet/Activity/Other Considerations

6.3.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

6.3.2 Photosensitivity

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.

6.3.3 Contraception and Pregnancy

Pembrolizumab and rucaparib may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab and rucaparib have transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 180 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

(2) use (or have their partner use) highly effective contraception during heterosexual activity.

Highly effective methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of **two** of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill) associated with inhibition of ovulation, contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Patients should be informed that taking the study medications may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement

(described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 180 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

If a patient inadvertently becomes pregnant while on study, the subject will immediately be removed from the study and the site should notify the Coordinating Center within 24 hours of knowledge. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Coordinating Center within 24 hours. The Coordinating Center will be responsible for notifying Merck and Clovis regarding pregnancies as described in Section 9.3.

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Coordinating Center within 24 hours of knowledge. The Coordinating Center will be responsible for notifying Merck and Clovis as described in Section 9.3.

6.3.4 Use in Nursing Women

It is unknown whether pembrolizumab or rucaparib is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment. In addition, subjects should not breastfeed for 180 days after the last dose of study medication.

6.4 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.5.

A subject must be discontinued from study treatment for any of the following reasons:

- The subject withdraws consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved at the discretion of the investigators.

- Unacceptable adverse experiences as described in Section 6.2 and 7.3
- Intercurrent illness that prevents further administration of treatment

- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab and rucaparib
- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 7. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 9.0). End of treatment and survival follow-up procedures are listed in section 7.2. Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed every 6 months through the medical record (up to 5 years) for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

6.4.1 Discontinuation of Study Therapy after Complete Response (CR)

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with the combination of pembrolizumab and rucaparib and had at least two treatments with the two drugs beyond the date when the initial CR was declared.

Discontinuation of therapy should occur if the patients have received 2 years of treatment with pembrolizumab (counting from C1 of induction phase).

6.5 Subject Replacement Strategy

Any subject that does not receive at least one dose of rucaparib and one dose of pembrolizumab will be replaced.

6.6 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Merck and Clovis decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

Patient registration for this trial will be centrally managed by 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 the Screening and Enrollment Log provided by the Coordinating Center.

It is the responsibility of the local site investigator to determine patient eligibility prior to submitting patient registration request to the Coordinating Center. After patient eligibility has been determined, a copy of the **completed** Eligibility Worksheet together with all the pertinent de-identified source documents will be submitted by the requesting site to the Coordinating Center, by email to CTSU-Oncology-Multisite@med.umich.edu.

The Multi-Site Coordinator, 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.

An email will be sent by the registrar to the requesting site registrar to confirm patient registration and to provide the study identification number that has been 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.

The Treatment Calendar - Section 7.2 summarizes the trial procedures to be performed at each visit. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigators and/or Merck/Clovis for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB requirements, applicable laws and regulations and Sponsor requirements.

7.2 Treatment Calendar

	Screening Visit [1]	Induction Phase				Maintenance Phase						End of Treat-ment[2]	Progress-ion Free Follow-up [9]	Survival Follow-up [10]
	A ± 3-day window will be allowed for all treatment visits and assessments, unless otherwise specified. However, every effort must be made to follow the schedule outlined in the table below.													
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 and beyond			
	Day -28 to -1													
Informed Consent	X													
History, physical exam and medication review[3]	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse event monitoring[11]	X		X	X	X	X	X	X	X	X	X	X		
Complete blood count with differential	X		X	X	X	X	X	X	X	X	X	X		
Comprehensive metabolic panel[4]	X		X	X	X	X	X	X	X	X	X	X		
Lipid panel[5]	X													
PT/INR and aPTT	X											X		
Urinalysis	X											X		
TSH	X			X		X		X			X	X		
Pregnancy test – serum β-HCG[6]	X	X		X		X		X		X				
12-lead ECG	X											X		
CT of chest and other relevant sites of disease[7]	X		X (within 7 days prior to C3)		X (within 7 days prior to C1 of Maintenance)		X (within 7 days prior to C3)			X (within 7 days prior to C6)	X (within 7 days prior to C9, C12, C15)[7a]	X	X (q12 weeks)[7b]	

	Screening Visit [1]	Induction Phase				Maintenance Phase						End of Treat-ment[2]	Progress-ion Free Follow-up [9]	Survival Follow-up [10]
	A ± 3-day window will be allowed for all treatment visits and assessments, unless otherwise specified. However, every effort must be made to follow the schedule outlined in the table below.													
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 and beyond			
	Day -28 to -1													
Infusion of pembrolizumab 200mg		X	X	X	X	X	X	X	X	X	X			
Infusion of pemetrexed 500mg/m^2		X	X	X	X									
Infusion of carboplatin AUC 5		X	X	X	X									
Rucaparib 600mg PO BID						X	X	X	X	X	X			
Tissue sent and archived for correlative studies	X													
Whole blood sample collection to assess for ctDNA[8]		X				X				X		X		
Survival status														X

1. Assessment for eligibility, including blood tests and cross sectional imaging, must occur within 28 days of starting therapy. If complete blood count with differential and comprehensive metabolic panel was obtained within 7 days prior to initiation of therapy, it does not need to be repeated.
2. The end of treatment visit will occur 30days (+/-10 days) after the last dose of rucaparib [or last induction dose, for those who don't initiate maintenance therapy] or before the start of subsequent antineoplastic therapy if that occurs sooner.
3. Includes vital signs as well as evaluation of performance status
4. Comprehensive metabolic panel includes serum sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, protein, albumin, AST, ALT, alkaline phosphatase, and total bilirubin.
5. Lipid panel includes total cholesterol, triglycerides, HDL, and LDL.
6. Serum pregnancy testing will be performed every 6 weeks (i.e. every other cycle) throughout the duration of the study.

7. CT scan to assess response to be obtained every 6 weeks for the first 18 weeks (starting from Screening visit), every 9 weeks for the first 12 months (starting from Cycle 3 of Maintenance phase), and every 12 weeks (from last CT during treatment intervention) thereafter. There will be a scheduling leeway of 7 days prior to the next cycle. If treatment is held greater than 30 days after most recent scans, new scans should be obtained prior to restarting treatment, i.e., if scans were within 30 days, no new scan is needed.
   7a. Until after 52 weeks since starting induction.
   7b. Starting from last CT during treatment intervention.
8. Whole blood samples to assess for ctDNA will be obtained at start of induction phase, start of maintenance phase, and every 4 cycles (i.e. 12 weeks) on maintenance therapy until progression.
9. Progression Free follow-up: subjects who discontinue for reasons other than progressive disease will have follow-up for disease status every 12 weeks (+/- 2 weeks) until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up (limited to subjects who have received at least one dose of Rucaparib).
10. Survival follow-up (every 6 months =+/- 2 weeks) limited to subjects who have received at least one dose of rucaparib. After documented disease progression each subject will be followed every 6 months through the medical record for overall survival up to 5 years until death, withdrawal of consent, or the end of study, whichever occurs first.
11. Serious adverse events will be collected for 90 days after the last dose as described in Section 9.

7.3 Management of Adverse Events

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in **Table 7**.

Table 7: Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		

Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Please see section 6.2.3 regarding the management of overlapping hepatotoxicity with rucaparib and pembrolizumab.			
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine)	• Monitor for signs and symptoms of thyroid disorders.

			per standard of care	
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		
NOTES: 1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. 2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withholding of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)				

7.4 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

1. Antineoplastic systemic chemotherapy or biological therapy
2. Immunotherapy not specified in this protocol
3. Chemotherapy not specified in this protocol
4. Investigational agents
5. Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
6. Live vaccines within 30 days prior to enrollment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
7. Daily systemic glucocorticoids with dose >10mg of prednisone (or its equivalent) for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. Note that corticosteroids administered as part of pre-

medications or supportive medications (as in the case of dexamethasone as an anti-emetic administered with pemetrexed) is allowed.

8. Pegfilgrastim (Neulasta, Udenyca, etc. via any delivery method), unless used during Induction phase (with carboplatin/pemetrexed/pembrolizumab).

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

7.4.1 CYP450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on results of in vitro CYP interaction studies, *caution* should be used for concomitant medications with narrow therapeutic windows that are substrates of CYP2C19, CYP2C9, and/or CYP3A. Selection of an alternative concomitant medication is *recommended*.

Examples of CYP Substrates with Narrow Therapeutic Range

CYP Enzyme	Substrates with Narrow Therapeutic Range [a]
CYP2C9	Warfarin, phenytoin
CYP2C19	S-mephenytoin
CYP3A	Alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine

The table is based on the Draft FDA Guidance on Drug Interaction Studies — Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations, 2012.

[a] CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

Anticoagulants

Caution should be exercised in patients receiving rucaparib and concomitant warfarin (Coumadin) as rucaparib showed a mixed inhibition of CYP2C9 *in vitro*. If appropriate, low molecular weight heparin should be considered as an alternative treatment. Patients taking warfarin should have international normalized ratio (INR) monitored regularly per standard clinical practice.

Other Medications

In vitro data showed that rucaparib is an inhibitor of P-gp and thus patients taking digoxin, a P-gp substrate, should have their digoxin levels monitored regularly via standard clinical practice. Caution should also be exercised for concomitant use of certain statin drugs (e.g., rosuvastatin and fluvastatin) due to potential increase in exposure from inhibition of BCRP and CYP2C9

7.5 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 9.0.

7.5.1 End of Treatment Follow-up Visits

The mandatory Safety Follow-Up Visit should be conducted within 30 +/- 10 days after the last dose of rucaparib. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever occurs first. Procedures should be conducted according to the Treatment Calendar in Section 7.2. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should be followed and recorded.

7.5.2 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject will be followed through his/her medical record and assessed for survival status until death or 5 years. Data will be collected every 6 months.

8.0 IMAGING AND MEASUREMENT OF DISEASE

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1.[21]

Immunotherapy drugs 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 thepatient 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.

Definitions

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least 2 cycle(s) of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

8.1 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 (or MRI) for studies with a slice thickness of ≤5mm, or twice the slice thickness
- 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 ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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 <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, 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 (lesions with the longest diameter), representative of all involved organs, and 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 which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as

measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm 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 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered nonpathological 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 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 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')

8.2 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 and never more than 4 weeks before enrollment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation 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 and 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.

8.3 Response Criteria

Evaluation of Target Lesions

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, 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 nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

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.

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 7.2).

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).

Duration of Response

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

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

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

Progression-Free Survival

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

9.0 ADVERSE AND OTHER REPORTABLE EVENTS

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 dose of pembrolizumab and rucaparib through 30 days after the last dose of rucaparib or pembrolizumab (whichever is later). Serious adverse events will be collected from the timeof the initial dose of pembrolizumab and rucaparib through 90 days after the last dose of rucaparib or pembrolizumab (whichever is later). Any serious adverse event that occurs morethan 90 days after the last dose of study treatment and is considered related to the study must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study drugs for the changes observed;
- The patient is lost to follow-up or withdraws consent; 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 enrollment onto study 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 9.1, occurring from the initial dose of pembrolizumab and rucaparib through 30 days following the last dose of rucaparib or pembrolizumab (whichever is later) 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 drugs.

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 is also considered an adverse event.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

Investigators are not obligated to actively seek AE or SAE or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Coordinating Center.

9.1 Definitions

9.1.1 Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or vital sign which requires protocol treatment to be modified, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drugs, is also an adverse event.

Progression of the cancer under study and/or symptoms related to progression of the underlying cancer are not considered an adverse event unless it resulted in death.

9.1.2 Serious Adverse Event

An adverse event is considered "serious" if, in the view of either the investigator or Sponsor 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 event is considered 'life-threatening' if, in the view of either the investigator or sponsors, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

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

- A congenital anomaly/birth defect

- 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.

9.1.3 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.

- For investigational new drugs or devices, those adverse events are described in the Reference Safety Information section of the Investigator's Brochure.

9.1.4 Unexpected Adverse Events

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

9.1.5 Events 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. *Progression of the cancer under study and/or symptoms related to progression of the underlying cancer are not considered a serious adverse event unless it resulted in death*.

9.2 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0.3 All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be down loaded from the CTEP web site (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

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

9.3 Reporting of Adverse Events

9.3.1 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 Clovis and Merck, as appropriate (outlined below).

9.3.2 Reporting procedures to Merck Global Safety

All Serious Adverse Events (SAEs) occurring from the initial study treatment administration through 90 days following the last dose of the study treatment will be reported by the Coordinating Center to Merck Global Safety. Any SAEs occurring after 90 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to Merck Global Safety.

The Coordinating Center will send the initial completed SAE Form and any other relevant safety information within 24 hours of receipt to the Merck Global safety facsimile number 1-215-993-1220.

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 Merck Global Safety within 24 hours of receipt.

9.3.3 Reporting procedures to Clovis

All Serious Adverse Events (SAEs) occurring from the initial study treatment administration through 90 days following the last dose of the study treatment will be reported by the Coordinating Center to Clovis. Any SAEs occurring after 90 days following the last dose of the study treatment that are believed to be related to study drug will also be reported to Clovis.

The Coordinating Center will send the initial completed SAE Form within 24 hours of receipt via email to Clovis (drugsafety@clovisoncology.com) or facsimile (1-303-261-8319).

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.

9.3.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) which are defined as AEs of scientific and medical concern specific to the drug product or program, for which ongoing monitoring and rapid communication by the investigator can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

All ECIs must be reported as SAEs as outlined above.

Events of clinical interest for this trial include:

1. An overdose of drugs (further detail can be found in Section 9.4).

2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testingor unscheduled laboratory testing.* This is in absence of any other explanation for the elevation in liver enzymes.

   *Note: These criteria are based upon available regulatory guidance documents. Thepurpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

3. Any AE of pneumonitis, or any of the following AEs, irrespective of causality assessment:

   - pneumonitis
   - interstitial lung disease
   - pulmonary fibrosis
   - acute interstitial pneumonitis
   - alveolitis necrotizing
   - alveolitis
   - hypersensitivity pneumonitis
   - organizing pneumonia

9.3.5 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck and Clovis as described in Section 9.3, unless there is evidence suggesting a causal relationship between the drugs and the event. should be.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be considered an SAE and reported as outlined above.

Hospitalization related to convenience (e.g. transportation issues etc.) will not be considered a SAE.

9.4 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck and Clovis

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of pembrolizumab meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event will be considered an SAE and reported as outlined above There is currently no specific dosage of rucaparib that is considered an overdose. An overdose of rucaparib is NOT considered an SAE unless it is associated with a serious adverse event. If so, it will be reported as an SAE as outlined above.

9.5 Reporting of Pregnancy and Lactation to Merck and Clovis

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur from the time of study drug through 180 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator to the Coordinating Center. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events will be reported within the same timelines as an SAE.

9.6 Routine Reporting

All other adverse events are to be reported per current IRB guidelines.

9.7 Reporting of Unanticipated Problems

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

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

1. Unexpected (in terms of nature, severity, or frequency);

2. Related or possibly related to participation in the research; and

3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

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

10.0 CORRELATIVE STUDIES

10.1 PD-L1 expression

A specific cut-off for tumoral PD-L1 expression is not a pre-requisite for enrollment onto this protocol. Tumoral PD-L1 expression will be determined by immunohistochemistry (IHC) methods per institutional standards as testing is currently considered standard of care in all patients with metastatic NSCLC. PD-L1 expression will be divided as low (PD-L1<1%), intermediate (1-49%), and high (≥50%).

10.2 Tissue Requirements for Next Generation Sequencing.

Tumor mutational burden, homologous repair deficiency, and loss of heterozygosity will be determined through NGS (next generation sequencing). FFPE (formalin-fixed paraffin embedded) tissue samples will be sent to Foundation Medicine as outlined in the Laboratory Manual. Tissue requirements for this assay are 1) tissue block + 1 H&E (haematoxylin and eosin) slide, OR 2) 10 unstained slides (4-5µm in thickness) + 1 H&E slide. In order for the

tissue sample to be used, there must be histological evidence of at least 30% viable tumor content.

10.3 Tumor Mutational Burden

The methods for determining TMB have been previously described in detail.[22] TMB will be reported as mutations/megabase (mb) and will be divided into three groups: low (1-5 mutations/mb), intermediate (6-19/mb), and high (≥20 mutations/mb). TMB has been shown to be an independent predictor of favorable response to checkpoint inhibitors across different cancer types.[22]

10.4 Homologous Repair Deficiency (HRD)

The method for calculating HRD has already been previously described.[16] The sequence data will be processed using a customized analysis pipeline to detect protein truncating mutations, splice site mutations, homozygous base substitutions, short insertions/deletions, large protein truncating rearrangements, and deleterious missense mutations in *BRCA 1/2* and other homologous recombination genes. All genes and their corresponding mutations will be reported. Tumors with protein-truncating mutations (with the exception of amino acids 3' of codon K3226 in *BRCA2*) and splice-site mutations (±2 bp of exon starts/ends) in known or putative tumor suppressor genes will be classified as potentially deleterious. Homozygous deletions (deletions in both gene alleles of ≥1 exon in size) and large protein truncating rearrangements will be considered deleterious. Based on the Breast Cancer Information Core database[23], *BRCA 1/2* missense mutations known to be deleterious will also be classified.

10.5 Loss of Heterozygosity (LOH)

To compute the percent genomic LOH for each tumor, LOH segments will be inferred across the 22 autosomal chromosomes using the genome-wide aneuploidy/copy number profile and minor allele frequencies of the more than 3,500 polymorphic small nucleotide polymorphisms (SNPs) sequenced through Foundation Medicine's NGS assay. This method and calculation has also been described elsewhere.[16]

10.6 Circulating tumor DNA (ct-DNA)

The details of this assay have been described elsewhere.[24] In brief, blood samples will be collected at the start of the induction phase, start of the maintenance phase, and every 4 cycles (i.e. 12 weeks) while on the maintenance phase to evaluate for ct-DNA to determine if there is a correlation between levels of ct-DNA and radiographic progression of disease. See the Laboratory Manual for collection, handling and shipping of correlative samples.

10.7 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.

11.0 STATISTICAL ANALYSIS PLAN

11.1 Statistical Design

Small phase I run-in for safety: we will first treat a cohort of 6 patients at the approved dose of rucaparib of 600mg BID in combination with pembrolizumab, if < 2 dose limiting toxicity (DLT) are observed during cycle 1, we will consider the dose safe and continue to the Phase II portion using this dose, otherwise we de-escalate to dose-1 of rucaparib at 500mg BID and treat another 6 patients. If ≥2 DLT are seen with dose-1 of rucaparib, then a meeting will be held with the investigators, Merck, and Clovis to discuss whether the trial needs to be stopped or if the rucaparib dose can be further de-escalated. The pembrolizumab dose will remain fixed at 200mg IV every 21 days.

Bayesian two-stage design: based on data from KEYNOTE-021 and KEYNOTE-189, the median PFS on CPP followed by pembrolizumab +/- pemetrexed maintenance is estimated to be 11 months. In this study, we want to demonstrate that maintenance therapy with rucaparib and pembrolizumab after induction therapy with CPP is better than pembrolizumab +/- pemetrexed maintenance. Thus, the null hypothesis is PFS median ≤ 11 months, while the alternative hypothesis is PFS median > 11 months. The hypothesized 11 months therefore corresponds to a 50% PFS rate at 11 months (PFS11) and we expect that the rucaparib and pembrolizumab will increase PFS11 to 64% (corresponding to a median of 17 monthsassuming an exponential model with a constant progression rate over time; i.e., log(0.5)/(log(0.64)/11)=17 months).

We will use a Bayesian decision-theoretic two-stage design.[25] In this design, costs (c2 and c3) are associated with making erroneous claims about the efficacy and the expenses of enrolling patients in the second stage. The risk is defined as the expected cost. The first stage will enroll **38**, and then we will pause patient recruitment until 75% of the 38 patients (≈ 29 patients) have progressed or have completed 17 months' follow-up. Based on the data collected at this time point, we will first decide whether to stop or continue the trial to the second stage by comparing the risks of stopping and continuation. If the risk of stopping is smaller, we will stop the trial and make a rejection or acceptance decision by comparing the risks of rejection and acceptance of the null hypothesis. We will choose the decision with the smaller risk. If the risk of continuation is smaller, we will enroll an additional **17** patients and follow the last patient for an additional 18 months to make the final decision. The final decision of rejecting and accepting the null hypothesis is again based on the risks of the two decisions. This design makes use of all patients' follow-up data and allows early stopping for both superiority and inferiority. The total number of patients enrolled will be approximately 55.

11.2 Sample Size Justification

Patients who are treated at the target dose in the safety run-in phase will be included in the phase II trial. The published survival data[6,26] has approximately an exponential distribution. We fix the design parameters c2=3.5 and c3=0.08 and assume that 3 patients will be enrolled per month. These values of c2 and c3 were determined by simulation to obtain approximately 80% power and 10% type I error in the overall study and probability of stopping at stage I >50%. Table 8 shows the trial operating characteristics based on 5000 Monte Carlo

simulations. If the PFS11 is truly 0.64 (an efficacious therapy), we will have approximately 53% probability of stopping at the first stage to declare that our proposed maintenance therapy is promising. The expected sample size is 44 and trial duration is 29 months on average. If the PFS11 is truly 0.50 (an inferior therapy), we will have approximately 68% probability of stopping at the first stage to show that the new maintenance therapy is inferior. The expected sample size is 42 and trial duration is 25 months on average. The trial has an overall type I error of 10% and power of 82% (see first column of **Table 8**) with a type I error at the end of the first stage of 8% (see third column of **Table 8**). The trial will pause patient enrollment for about 7-8.4 months before stage II. **Table 9** lists the PFS11 (posterior) estimates (mean and std) over 5000 simulated trial under different decisions. As shown in this table, stronger evidence is needed in order to show superiority and inferiority an earlier time point (stronger evidence means larger estimates of PFS11 for the superiority decision and smaller estimates of PFS11 for the inferiority decision). For example, the PFS11 estimate is 0.69 on average under the superiority decision, which is larger than PFS11 estimate of 0.64 at the end of the study; the PFS11 estimate is 0.47 on average under the inferiority decision, which is much smaller than PFS11 estimate of 0.53 at the end of the study. When the decision is to continue to stage II, PFS11 estimates are around 0.59 (± 0.02), which suggests no strong evidence in either decision.

Table 8: Trial operating characteristics based on simulation studies

True PFS11	Reject NULL	% Stop at Stage I for futility	% Stop at Stage I for efficacy	Expected Sample Size	Expected Trial Duration	Average Enrollment Pause Months at Stage I
0.50 (drug is inferior)	0.10	0.68	0.08	42	25.10	6.99
0.64 (drug is superior)	0.82	0.11	0.53	44	29.15	8.35

Table 9: PFS11 estimates across 5000 simulated trials under different decisions

PFS11	Continue at Stage I	At stage I stop for futility	At stage I stop for efficacy	At stage II show futility	At stage II show efficacy
Mean	0.59	0.47	0.69	0.53	0.64
Std	0.02	0.06	0.04	0.03	0.03

11.3 Population for Analysis

Intent-to-Treat Population: All patients consented and enrolled in the trial.

Evaluable Population: Only those patients who have received at least one cycle of maintenance therapy with rucaparib and pembrolizumab at the safe dose will be considered evaluable; this will include the patients in the safety run-in phase that received the safe dose.

Safety Evaluable Population: Patients who receive any treatment on protocol will be considered evaluable for safety.

11.4 Analysis of Primary Objective:

The proposed Bayesian decision theoretic approach will be used to make decisions at both stages. Since the real data may not follow an exponential distribution, we will also consider a Weibull distribution in the Bayesian decision theoretic approach.[25] At the end of the study, the Product-limit (Kaplan-Meier) method will be used to estimate PFS11 and median PFS, along with 95% confidence intervals.

11.5 Analysis of Secondary Objectives

1. *To evaluate the safety and tolerability profile of pembrolizumab and rucaparib.* The toxicity profile will be described, both overall and by grade. Toxicity rates will be tabulated by type and category.

2. *To evaluate the OS in patients treated with pembrolizumab and rucaparib following induction therapy with CPP.* Kaplan-Meier method will be used to estimate OS. Median survival will be calculated, along with 95% confidence intervals.

3. *To evaluate response based in immune response RECIST (irRECIST)*. The response rate will be calculated with a 95% confidence interval.

11.6 Analysis of Exploratory Objectives

Log-rank tests or Cox proportional hazard regression models will be used to associate the genomic features, including PD-L1 expression, TMB, HRD, LOH and presence of somatic HR mutations to PFS.

12. 0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

12.1 Investigational Drugs

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

Pembrolizumab is available as below. It will be administered intravenously every 21 days. It will be supplied by Merck and Co.

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

Rucaparib camsylate (formerly known as PF-01367338 and AG-014447) is an oral formulation with a molecular weight of 555.67 Daltons. Rucaparib tablets for oral administration will be supplied by Clovis Oncology.

Drug Name:	Rucaparib
INN:	Rucaparib
Formulation:	Tablet; film coated; 200 mg, 250 mg, 300 mg
How Supplied:	200, 250, and/or 300 mg strength (based on free base) in high-density polyethylene bottles or equivalent with child-resistant caps. Patients may receive 1 or more strengths. Each bottle contains 60 tablets
Storage Conditions:	15–30 °C (59 and 86° F)

12.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Rucaparib tablets are provided in high-density polyethylene (HDPE) bottles with child-resistant caps and should be stored in the provided containers between 15° and 30° C (59 and 86° F). Patients will be dispensed one or more strengths depending on their current dose of rucaparib. The number of bottles of each strength dispensed will be sufficient to supply 21 days treatment per cycle, including a small overage.

Study drug containers containing rucaparib tablets will be labeled according to national regulations for investigational products.

12.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

12.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

12.5 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck and Clovis, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

13. 0 ADMINISTRATIVE AND REGULATORY DETAILS

13.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

13.2 Quality Management System

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

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

13.3 Multi-Site 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 EDC
        - Subject Status
        - Demographics
- During study participation
    - All data should be entered online within 10 business days of data acquisition. Information on Serious Adverse Events must be entered within the reporting timeframe specified in Section 9.3 of the protocol.

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

13.4 Data and Safety Monitoring Procedures

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 monthly (during phase I) and quarterly (during phase II). Depending on the protocol activity, the meeting cadence may be more frequent. This data review meeting may be achieved via a teleconference or another similar mechanism to discuss matters related to:

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

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

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

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

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

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

13.5 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 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 a 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/her 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 Rogel Cancer 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/course]. The study site will send the de-identified source documents to the Coordinating Center for monitoring. 'Centralized' monitoring may be requested by the Coordinating Center if an amendment requires changes to the protocol procedures. The site will send in pertinent de-identified source documents, as defined by the Coordinating Center for monitoring.

The first annual 'On-site' monitoring visit should occur after the first five study participants are enrolled or twelve months after a study opens, whichever occurs first. The annual visit may be conducted as a 'Centralized' visit if less than three subjects have enrolled at the study site. The type of visit is at the discretion of the Coordinating Center. At a minimum, a routine

monitoring visit will be done at least once a year, or once during the course of the study if the study duration is less than 12 months. The purpose of these visits is to verify:

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

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

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

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

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15.0 APPENDICES

I. ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

II. Common Terminology Criteria for Adverse Events V4.03 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for adverse event reporting. (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)