Document Coversheet

Study Title: Phase II Study of Combination Rucaparib With Nivolumab in Platinum-Sensitive Small Cell Lung Carcinoma Patients as Maintenance After Induction Therapy With Platinum Doublet

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	12/21/2022
NCT Number:	NCT03958045
IRB Number	49346
Coversheet created:	10/19/2023

MCC Protocol #: MCC-18-LUN-107-CLO-PMC
ClinicalTrials.gov Identifier: NCT03958045

TITLE: Phase II study of combination Rucaparib with Nivolumab in platinum sensitive small cell lung carcinoma patients as maintenance after induction therapy with platinum doublet.

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Agents: Rucaparib, Nivolumab
Funding Support: Clovis and BMS
IND: MCC with sponsors

Protocol Version / Version Date*:* Amendment 7 / 16.June.2021
Amendment 8 / 21.December.2022

Protocol Development History – Original Version to Current Version, w/ major Summary of Changes noted	
1/8/2019	PRMC approval
3/19/2019	IRB approval.
5/24/2019	CRSO Medicare analysis
9/3/2019	**OPEN TO ACCRUAL**
Amendment 1 12/10/2019	Protocol revised, new version date 10DEC2019.
Amendment 2 5/5/2020	Protocol revised, new version date 05MAY2020.
Amendment 3 8/3/2020	Protocol revised, new version date 03AUG2020. 8/12/2020 PRMC approval; 8/24/2020 IRB approval.
Amendment 4 9/16/2020	Protocol revised, new version date 16SEPT2020. For criterion 3.2.26, language clarified re: prior or concurrent malignancy to match NCI CTEP verbiage. 9/22/2020 PRMC approval; 9/24/2020 IRB approval
Amendment 5 3/10/2021	Protocol revised, new version date 10MARCH2020. Language to clarify dose modifications. PRMC approval, 3/25/2021; IRB approval, 3/31/2021.
Amendment 6 5/19/2021	Protocol revised, new version date 19MAY2021, to clarify that no formal interim analysis is planned. PRMC approval, 5/26/2021.
Amendment 7 6/16/2021	Protocol revised, new version date 16JUN2021, to clarify the timing of Off-treatment and 100-days safety visits (Section 8, Section 11).
Amendment 8 12/21/2022	Protocol revised to name Dr. Zhonglin Hao as study PI, and reassigned Dr. Aman Chauhan (former study PI) to now be a co-I upon his transition to a new institution.
Amendment 9 Date TBD	*Placeholder for future amendment.*

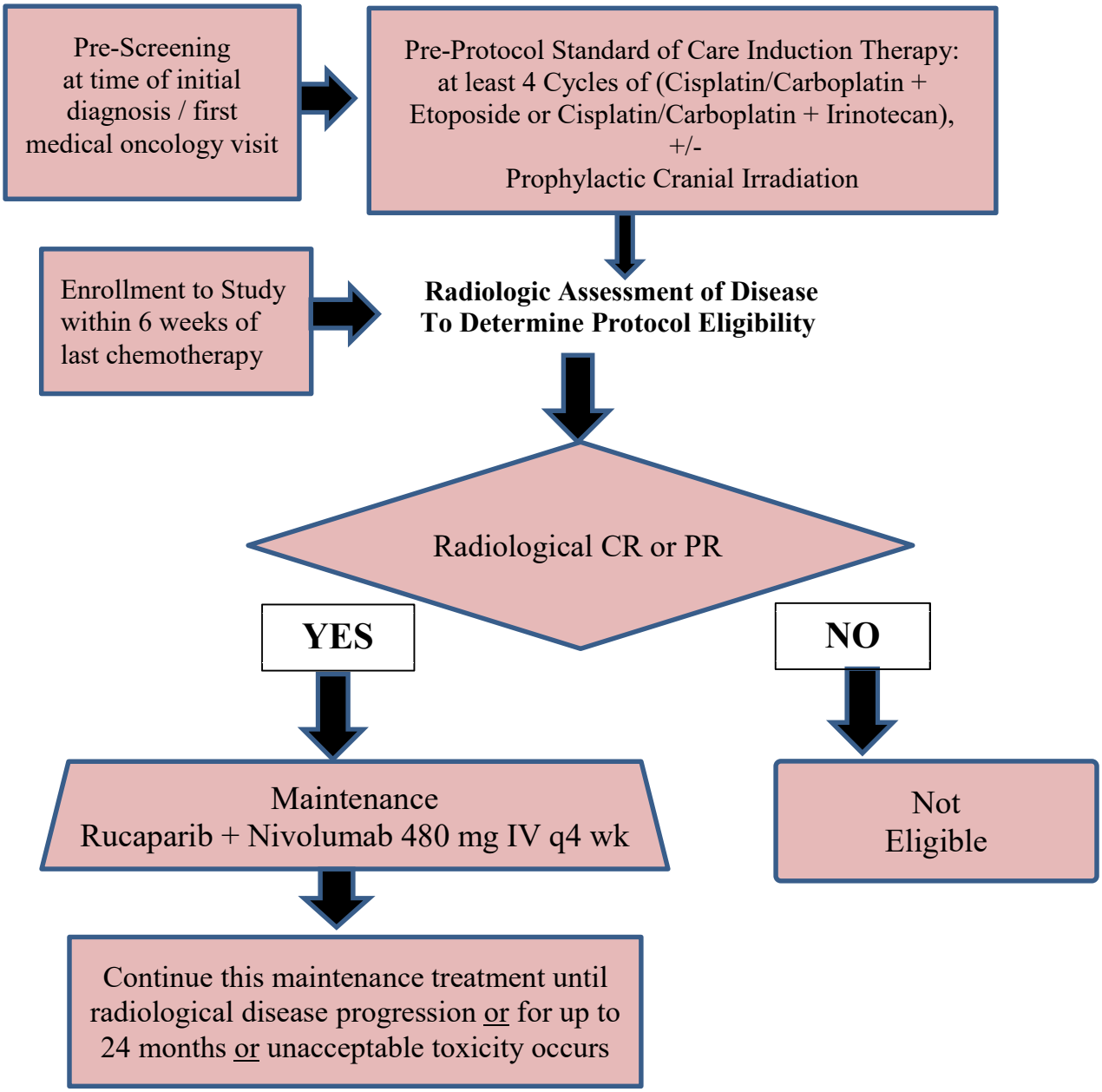
STUDY DESIGN

This is a single center, open label, Phase II study of combination rucaparib with nivolumab as maintenance in platinum sensitive small cell lung cancer post frontline platinum doublet.

Study Schema: Phase II Trial

Rucaparib + Nivolumab

Stage IV Small Cell Lung Cancer (Frontline Maintenance)



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1. OBJECTIVES

1.1 Primary Objective:

To evaluate progression free survival of the combination rucaparib and nivolumab as maintenance therapy in platinum sensitive (as defined by CR/PR via RECIST V1.1) extensive stage SCLC after response to initial platinum-based therapy.

1.2 Secondary Objectives:

1.2.1 To evaluate the disease control rate after 8 weeks, 16 weeks and 24 weeks of treatment. Disease control rate is defined as the percentage of subjects who had a partial response post initial chemotherapy and who have a confirmed reduction in tumor size compared to post induction chemotherapy baseline (complete response, CR; partial response, PR) or fulfilling the criteria for stable disease (SD) according to Response Evaluation Criteria in Solid Tumors (RECIST V1.1). Patients with CR will be considered to have disease control if they continue to remain in CR since they do not have measurable disease at baseline.

1.2.2 To evaluate 1-year and 2-year overall survival. Overall survival is defined as the time from first dose of trial medication to date of death due to any cause.

1.2.3 To evaluate potential biomarkers for durability of response, especially tumor mutation burden (refer to Biomarker Section).

1.2.4 To assess the toxicity profile of experimental drug combination.

1.2.5 To evaluate objective response rate at 8 weeks, 16 weeks and 24 weeks. Objective response rate is the proportion of patients with complete response or partial response according to RECIST V1.1. Patients with CR at baseline will be excluded from objective response rate (ORR) analysis.

1.2.6 To evaluate quality of life (QOL). Quality of life is assessed by the validated, standardized EORTC questionnaires (specifically the QLQ-C30 and the LC-13) on screening/pre-study (for pre-treatment baseline), once during treatment, and at the end of treatment. These EORTC QOL measures are located in Appendix D.

1.2.7 To explore in a preliminary manner the response of genomic subsets to treatment focusing on tumor mutation burden, cMEK and TP53 mutation analysis of tumor tissue and evaluation of response, using the Oncology Research Information Exchange Network (ORIEN) consortium whole exome sequencing platform to evaluate tumor mutation burden, somatic and germline mutations.

1.3 Exploratory Correlative Studies and Biomarkers

1.3.1 To evaluate, in a preliminary manner, immune-related response markers as follows:

1.3.1.1 Percentage of CD4 T cells and CD8 T cells expressing PD-1 and Ki-67.

1.3.1.2 Percentage of polyfunctional effector CD4 T cells and CD8 T cells (CD101+ and CD38+) producing IFNγ and TNFα.

1.3.1.3 Percentage of effector CD4 T cells and CD8 T cells expressing CD38, HLA-DR, CD28, ICOS, CD27, and low Bcl2 levels.

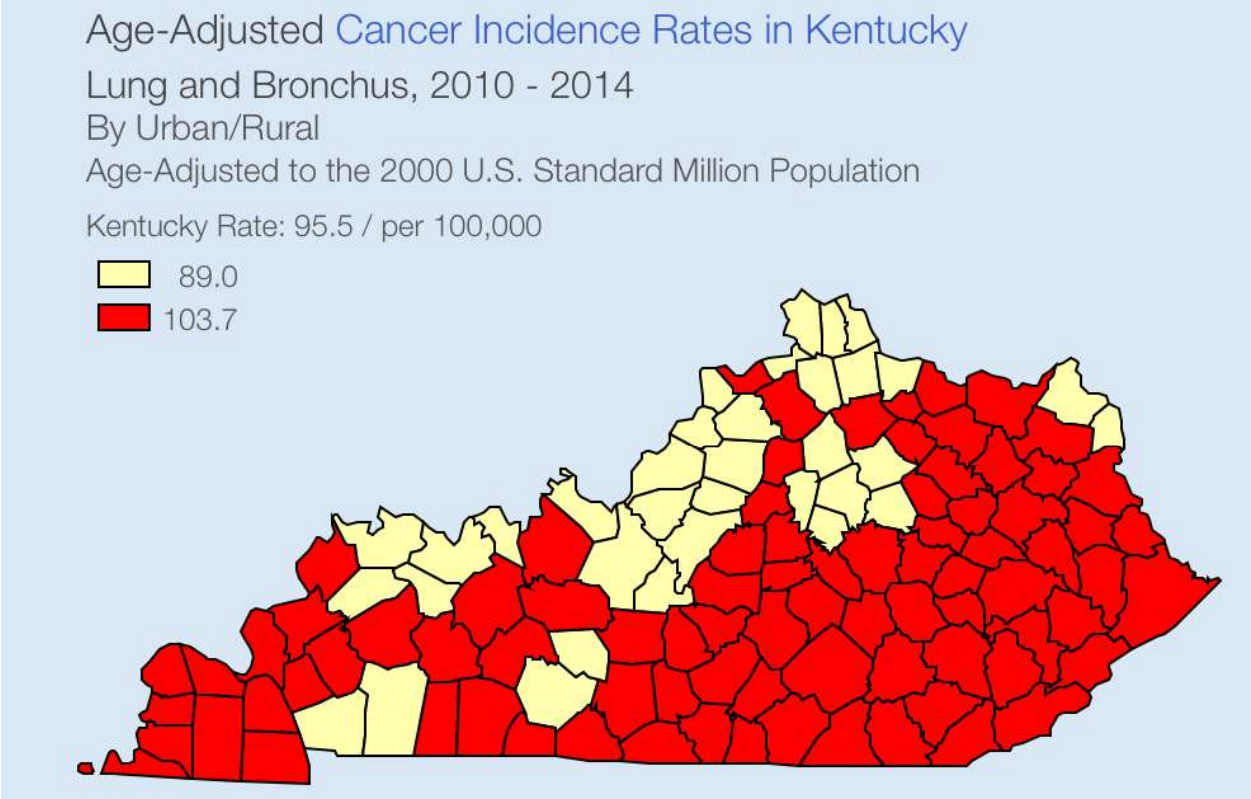
1.3.2 To correlate, when available, tumor mutation burden and specific gene mutations with treatment using results of sequencing of tissue collected and germline mutation testing from the Markey Cancer Center Total Cancer Care (ORIEN) protocol.

2. BACKGROUND AND RATIONALE

2.1 Background

Small cell lung cancer (SCLC) is one of the most aggressive malignancies with a 5-year survival rate less than 7%. SCLC is characterized by rapid doubling time, high growth fraction and early development of widespread metastases. SCLC accounts for roughly 93% of all high-grade neuroendocrine carcinomas [1]. The prognosis for SCLC is extremely poor with median survival less than a year for extensive-stage disease. Therapeutic options have not advanced significantly in over two decades, with frontline treatment consisting of platinum doublet therapy for 3-6 cycles. While most patients show an initial favorable response to Carboplatin/cisplatin + etoposide or Cisplatin/Carboplatin +Irinotecan, this response is usually short-lived. Most patients relapse with relatively resistant disease between 3 to 6 months after completion of initial chemotherapy. Topotecan, one of the FDA-approved second line agent for SCLC, is poorly tolerated and has dismal response rates.

SCLC is a critical area of unmet medical need. The Recalcitrant Cancer Research Act of 2012 (H.R. 733) requires the National Cancer Institute (NCI) to develop a scientific framework that assists in making progress against recalcitrant or deadly cancers, specifically cancers with 5-year relative survival rates below 50%. Small cell lung cancer clearly qualifies as a recalcitrant cancer via its less than 7% 5-year survival rate [2]. Kentucky unfortunately has highest lung cancer incidence and mortality in the U.S., with approximately 20% of lung cancer cases being SCLC [3].



2.2 Rationale for the Combination of PARP and Checkpoint Inhibition

2.2.1 PARP Inhibitors

Platinum-based compounds, the backbone of SCLC treatment, cause harmful DNA cross-links, which interfere with DNA repair mechanisms and induce DNA damage. Similar to other solid tumors, SCLC is characterized by genomic instability, and dysfunctional DNA repair mechanisms can contribute to this feature. Targeting DNA repair itself can also represent a novel therapeutic strategy for SCLC to increase cytotoxicity of anticancer agents, reverse chemotherapy resistance and improve therapeutic efficacy [4]. Poly (ADP-ribose) polymerase (PARP1) is a key enzyme of the base excision repair (BER) system, specifically involved in DNA single-strand break (SSB) repair, and an E2F1 co-activator. PARP1 was found to be expressed at the highest relative levels among the DNA repair proteins in SCLC [5]. Because PARP1 plays an independent role as an E2F1 co-activator [6, 7], it is hypothesized that its inhibition may have a dual role, with direct effects on DNA repair and on other E2F1-regulated DNA repair proteins. Antitumor activity of PARP1 inhibition was confirmed in SCLC cell lines [5].

2.2.2 Summary of Non-clinical Experience with rucaparib

The results from nonclinical studies are consistent with the anticipated mechanism of action and pharmacological effects of PARP inhibition. Pharmacological assessment demonstrated that rucaparib is a potent and selective inhibitor of PARP-1, PARP-2, and PARP-3 and has robust and durable in vitro and in vivo activity in multiple BRCA1/2-mutant cell lines and xenograft models.

Rucaparib was also active in a BRCA wild-type model, consistent with in vitro data suggesting that rucaparib is active in cells with other defects in homologous recombination repair (HRR) through synthetic lethality. In vitro screens suggested that rucaparib has a limited potential for off-target effects. Safety pharmacology studies suggest that when given orally, rucaparib poses a minimal risk for causing neurobehavioral and cardiac effects in patients.

In pharmacokinetic (PK) studies, rucaparib demonstrated species-dependent oral bioavailability, moderate plasma protein binding, and large volumes of distribution in nonclinical species. As a P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) substrate, rucaparib demonstrated minimal penetration of rucaparib-derived radioactivity through the blood-brain barrier in rats. In vitro data suggested slow metabolism by cytochrome P450 (CYP) enzymes, with CYP2D6 and to a lesser extent CYP1A2 and CYP3A4 contributing to the metabolism of rucaparib. Rucaparib was mainly excreted in feces in rats and dogs after oral dosing.

In vitro, rucaparib reversibly inhibited CYP1A2, CYP2C9, CYP2C19, and CYP3A, and to a lesser extent CYP2C8, CYP2D6, and uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 (UGT1A1). Rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4 in human hepatocytes at clinically relevant exposures. Rucaparib is a potent inhibitor of multidrug and toxin extrusion 1 (MATE1) and MATE2-K, a moderate inhibitor of organic cationic transporter 1 (OCT1), and may inhibit P-gp and BCRP in the gut.

Oral dosing of rucaparib in single- and repeat-dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an in vitro chromosomal aberration assay suggesting potential genotoxicity in humans.

Reproductive and development toxicity studies in rat showed that rucaparib caused maternal toxicity and was embryotoxic. Although no rucaparib-related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility [8-11].

2.2.3 Summary of Clinical Experience with rucaparib

Rucaparib is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer who have evidence of homologous recombination deficiency (HRD). There are 4 clinical studies in patients with relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer: a Phase 2 study in patients whose cancer is associated with a germline BRCA (gBRCA) mutation (Study CO-338-010 [Study 10]); a Phase 2 biomarker study (Study CO-338-017 [ARIEL2]) designed to refine the molecular signature based on HRD associated with a response to rucaparib; a randomized, placebo-controlled Phase 3 study (Study CO-338-014 [ARIEL3]) evaluating rucaparib as switch maintenance treatment; and Phase 3 Study CO-338-043 (ARIEL4), which is evaluating rucaparib versus chemotherapy in BRCA1/2-mutant ovarian cancer patients with relapsed disease.

Phase 2 Study CO-338-052 (TRITON2) and Phase 3 Study CO-338-063 (TRITON3) are evaluating rucaparib as treatment for patients with metastatic castration-resistant prostate cancer

(mCRPC) associated with HRD. An additional Phase 2 study in mCRPC patients is evaluating rucaparib in combination with nivolumab. Additional studies of rucaparib as monotherapy and in combination with other anti-cancer therapies in ovarian and prostate cancer, as well as other tumor types, are planned. The rucaparib clinical studies and results are described in more detail in the rucaparib investigator brochure (IB).

PARP1 inhibition has shown clinical activity in SCLC as single agent and in combination with cytotoxic chemotherapy [12, 13]. Because of the abovementioned preclinical and clinical data, PARP1 inhibitors are considered among the target of choice for high-grade neuroendocrine carcinoma.

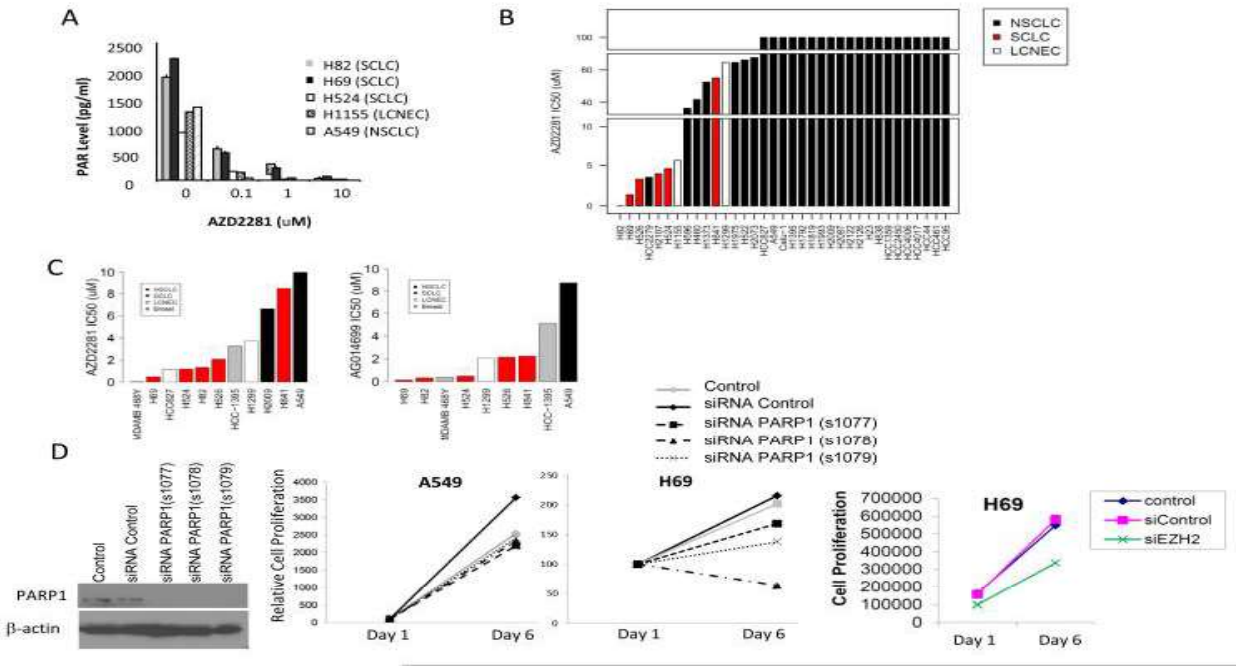


Fig 1: SCLC and LCNEC are sensitive to PARP1 inhibition in vitro. (Byers et al. Cancer Discovery)

2.2.4 **Immune Checkpoint Inhibitors**

Immunotherapy has revolutionized the field of oncology due to relatively low toxicity of these agents and potential for durable response. High tumor mutation burden and expression of PD-1 and PD-L1 are often predictive of response to immune-checkpoint inhibitors. This may also hold true for SCLC [14]. Up to 18% of SCLC patients have PD-L1 expression in tumor infiltrating macrophages and 48% SCLC cases showed PD-1 positive lymphocytes [15]. Another study reported PD-L1 expression in 10.4% of LCNEC and 5.8% of SCLC tumors [16]. Based on strong preclinical rationale, immune checkpoint inhibitors are being evaluated as single agent or in combination with chemotherapy for SCLC.

Immune checkpoint inhibitors have also made it to NCCN guidelines for the management of progressive metastatic SCLC as well as front line treatment in combination with chemotherapy. IM

Power 133 Phase III clinical trial reported efficacy of atezolizumab in SCLC. 201 patients were randomly assigned to the atezolizumab group, and 202 patients to the placebo group. At a median follow-up of 13.9 months, the median overall survival was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio for death, 0.70; 95% confidence interval [CI], 0.54 to 0.91; P=0.007). The median progression-free survival was 5.2 months and 4.3 months, respectively (hazard ratio for disease progression or death, 0.77; 95% CI, 0.62 to 0.96; P=0.02) (50). Because of the above-mentioned positive study, Atezolizumab is now a one of the category 1 recommended option for frontline treatment of metastatic extensive stage SCLC in combination with platinum-based chemotherapy.

The investigators of current protocol believe that optimal time to start immune checkpoint inhibitor is during maintenance phase, since the benefit during first 3-4 month is mostly from platinum-based chemotherapy. A detailed look at IM Power 133 Kaplan Meier curves will highlight that benefit of adding atezolizumab was not evident until 2-4 months into the maintenance phase (Fig 2). Moreover, since the cycle 1 of chemotherapy is commonly given in the hospital immediately post-diagnosis, atezolizumab will likely not be given until cycle 2 as outpatient due to financial reasons. Lastly, the OS benefit in IM Power 133 was a modest 2 months. Considering SCLC is an aggressive cancer with dismal outcomes, we ought to strive for better responses and therapies. We believe that by selecting a platinum sensitive SCLC patient population and by adding a potent anti-tumor agent (PARP inhibitor) to immune checkpoint inhibitor, we will hopefully see a sharp improvement in outcomes.

Since Atezolizumab is now considered standard of care (SOC) frontline treatment option for SCLC, we will offer newly diagnosed SCLC patient Atezolizumab + Platinum doublet chemotherapy per SOC. However, we will also make patients aware of our clinical trial and if they are interested then we will prescreen them for the trial. If patient meets any of the exclusion criteria, they will be offered SOC therapy instead.

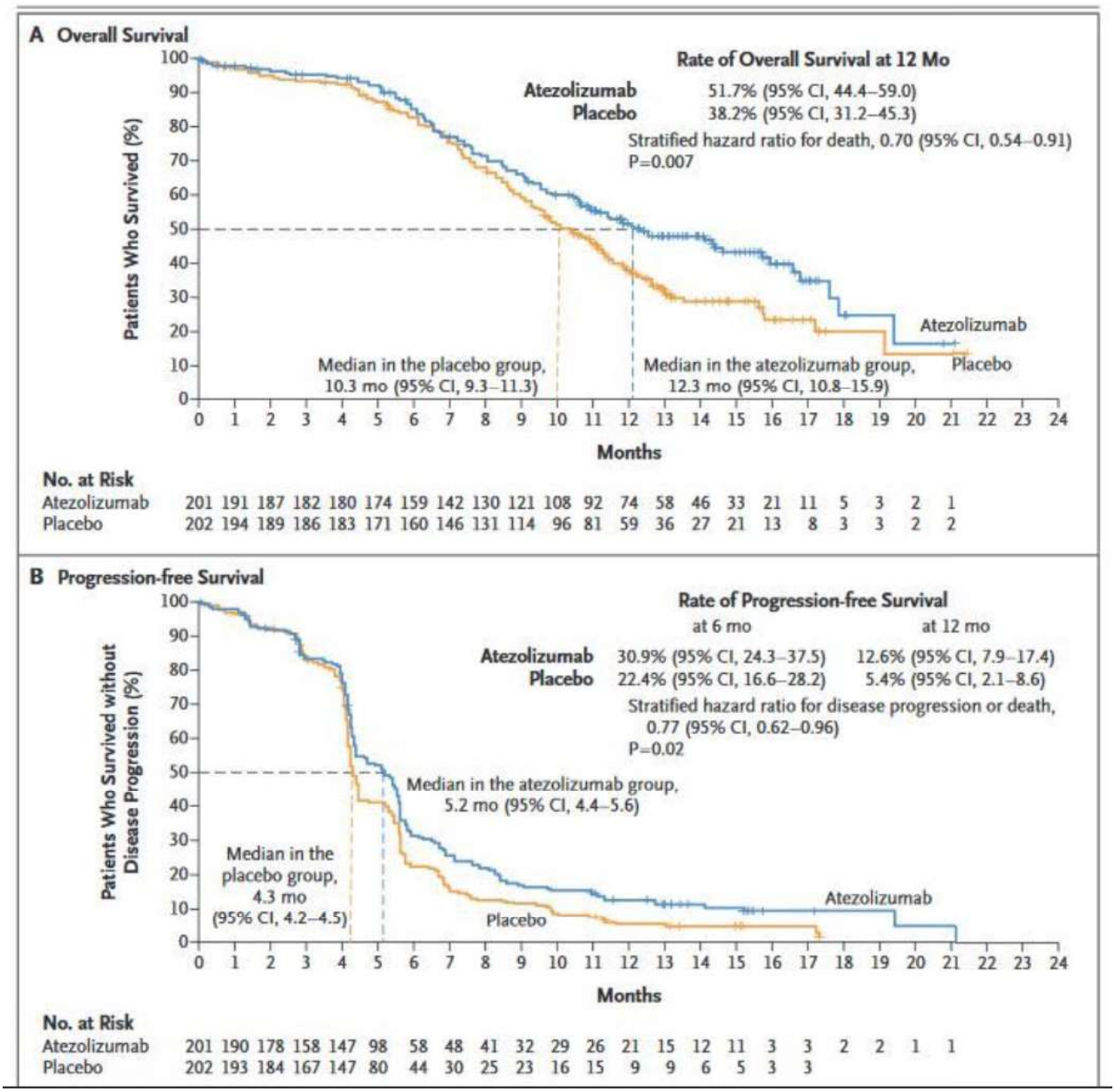


Fig 2: OS and PFS KM Curves of IM Power 133.

2.2.5 **Combination of Rucaparib (PARP inhibitor) with Nivolumab (Immune checkpoint inhibitor)**

There is preclinical evidence suggesting that DNA damage promotes neo- antigen expression, and DNA-damaging agents result in systemic antitumor responses [17]. Increased DNA damage by a PARP inhibitor (PARPi) could potentially yield a greater mutational burden and expand neo-antigens [18]. Therefore, addition of PARPi to immune checkpoint blockade could complement the clinical benefit of immune checkpoint inhibition. Recently Jiao et al. demonstrated that PARPi upregulated PD-L1 expression in breast cancer cell lines and animal models. This is thought to be regulated by

inactivation of GSK3β by PARPi, which in turn enhanced PARPi-mediated PD-L1 upregulation. PARPi attenuated anticancer immunity via upregulation of PD-L1, and blockade of PD-L1 resensitized PARPi-treated cancer cells to T-cell killing [19]. PARPi blocks DNA repair, resulting in DNA breaks [20]. Fragments of these DNA breaks can enter the cytoplasm and bind to cyclic GMP-AMP synthase (cGAS) leading to an upregulation of the cGAS-STING pathway within the tumor microenvironment, a potent activator of a type I interferons and other immunomodulatory molecules [21]. This may explain why olaparib and talazoparib up-regulate PD-L1 expression in preclinical models [19]. This could potentiate an anti-tumor immune response.

Cancers with defects in DNA repair generate excessive tumor neo-antigens, making them sensitive to both PARP inhibition and immune activation with immune checkpoint inhibitors. Therefore, we anticipate the combination of rucaparib and nivolumab to be synergistic. The lack of therapeutic options in high grade neuroendocrine carcinomas like SCLC, dismal survival statistics, non-overlapping toxicity profile of PARP inhibitors and immune checkpoint inhibitors, and robust preclinical data supporting potential activity of PARP inhibitors and immune checkpoint inhibitors in high grade neuroendocrine carcinoma make this combination suitable for maintenance post induction chemotherapy. Phase I/II clinical trials of PARP inhibitors in combination with immune checkpoint inhibitors are currently being explored in a variety of solid tumors. (niraparib in combination with pembrolizumab and olaparib in combination with durvalumab) [22].

Based on preclinical data supporting the role of immune checkpoint inhibitors and PARP inhibitors in small cell lung cancer, we feel that combining these two agents has the potential to prolong progression free survival and overall survival. These two classes of drugs have non-overlapping toxicities. This novel combination has not been tried in a front-line maintenance setting for SCLC.

A single arm Phase II trial will be performed using FDA approved single agent dosage for both nivolumab and rucaparib. Median progression-free survival (PFS) will be compared to historical PFS for stage IV SCLC. Based on a phase III randomized clinical trial conducted by Eastern Oncology Cooperative Group (ECOG), the historical median PFS for Stage IV SCLC post platinum doublet in platinum sensitive patients is 2.3 months in the observation arm vs 3.6 month on maintenance topotecan arm, a 56 % improvement [23]. We expect our experimental combination will outperform topotecan. Assuming a median PFS of 3.6 months from the topotecan arm as historical data, we will hypothesize a 75% improvement with the combination of rucaparib and nivolumab (median PFS = 6.3 months). This is justified by the recently presented data on single agent nivolumab (unpublished) which exhibited exceptional durable responses in second and third line SCLC. Of 59 treated patients with nivolumab 3 mg/kg investigator-assessed objective response rates were 12% (95% CI, 5% to 23%). Responses were observed regardless of tumor-programmed death-ligand 1 status. With a median follow-up of 28 months, 12-month progression-free survival rates were 8%, 12-month OS rates were 39% respectively [49]

Thus, it is reasonable to hypothesize that the proposed combination of nivolumab and rucaparib as maintenance after front line chemotherapy will show even better responses.

2.3 **Study Agents: Rucaparib**

Rucaparib is a small molecule inhibitor of PARP-1, PARP-2, and PARP-3 that has demonstrated preclinical and clinical activity in cancers associated with a deleterious mutation in BRCA1/2 or other HRR gene and/or high level of genomic loss of heterozygosity (LOH). Rucaparib was approved by the US FDA in December 2016 for the treatment of patients with deleterious BRCA mutations (germline and/or somatic) associated advanced ovarian cancer who had been treated with 2 or more chemotherapies [24] More recently, rucaparib demonstrated improved PFS in the maintenance treatment of patients with recurrent platinum-sensitive ovarian cancer. Although HRD was predictive of response to rucaparib, activity was also observed in HRD-negative patients, suggesting an incomplete understanding of biomarkers responsible for PARP inhibitor sensitivity [25].

2.3.1 Prior Experience with rucaparib

OVERVIEW OF CLINICAL PHARMACOLOGY

Assessment of rucaparib PK in cancer patients showed an approximate dose-proportional exposure after once daily (QD) or twice daily (BID) dosing, rapid absorption with maximum plasma concentration (C_{max}) achieved within 1.5 to 6 hours. The oral bioavailability was 36% and terminal half-life ($T_{1/2}$) was approximately 24 hours. Rucaparib was moderately bound to human plasma proteins in vitro (70%).

At a dose of 600 mg rucaparib BID, steady-state was achieved after approximately 1 week with approximately 4-fold accumulation. At the target clinical dose of 600 mg, a high-fat meal increased the C_{max} and area under the 0 to 24 hour plasma concentration-time curve (AUC_{0-24h}) of rucaparib by 20% and 38%, respectively, and delayed the median time to occurrence of C_{max} (T_{max}) by approximately 2.5 hours as compared with these parameters under fasted conditions. The effect of food on rucaparib PK is not considered to be clinically significant, thus rucaparib can be taken with or without food.

In cancer patients, M324, a carboxylic acid, was a major inactive metabolite of rucaparib. Drug interactions with rucaparib as a substrate were assessed in a population PK analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultra-rapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyperinducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play a limited role in rucaparib metabolism in vivo. Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. No rucaparib dose adjustment is needed when concomitantly administered with CYP inhibitors or inducers.

Concomitant treatment with proton pump inhibitors (PPIs) showed no clinically significant effect on rucaparib PK. No dose modification of rucaparib is required for patients who are receiving concomitant treatment with a PPI. Results from Study CO-338-044 evaluating potential drug-drug interactions (DDI) with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant

effect on the PK of oral digoxin (a P-gp substrate). Caution should be exercised in the concomitant use of drugs that are sensitive clinical substrates of the above CYP enzymes.

2.3.2 OVERVIEW OF EFFICACY

Ovarian Cancer Treatment Indication

On 19 December 2016, the FDA granted accelerated approval for the marketing of rucaparib (Rubraca®) for monotherapy treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with ≥ 2 chemotherapies [26]. The recommended dose of rucaparib is 600 mg BID. The basis for the approval of rucaparib as monotherapy for the treatment of ovarian cancer are the data sets and analyses of patients with advanced ovarian cancer covering the primary efficacy analysis population. The primary efficacy analysis population included 106 patients pooled from the open-label, single-arm Phase 2 studies, Study CO-338-010 Part 2A and Study CO-338-017 Parts 1 and 2, with BRCA-mutant ovarian cancer, who received ≥ 2 prior chemotherapy regimens, at least 2 of which were platinum-based, and who had at least 1 dose of 600 mg rucaparib. The primary endpoint on which approval was based is investigator-assessed ORR by RECIST Version 1.1 (v1.1), with ORR determined by central independent radiological review (IRR) conducted as a supportive analysis. ORR by investigators was 53.8%, while ORR by IRR was 41.5%, which confirms the investigator' assessment for this endpoint [27]. Responses were durable, indicated by a duration of response (DOR) by investigator assessment of approximately 9.2 months [24].

2.3.3 Ovarian Cancer Maintenance Indication

The efficacy of rucaparib monotherapy for patients with advanced ovarian cancer in the maintenance setting was demonstrated from Study CO-338-014 showing significant benefit of rucaparib compared to placebo across primary, secondary, and exploratory endpoints [25]. In this study, investigator-assessed PFS was the primary efficacy endpoint, with PFS by blinded central IRR conducted as a key, stand-alone, secondary endpoint. Rucaparib maintenance treatment significantly improved PFS compared with placebo in all primary analysis groups of patients with recurrent ovarian cancer after a complete or partial response to platinum-based therapy (**Table 1**). Overall, rucaparib as maintenance treatment reduced the risk of progression by 63.5% (hazard ratio 0.365 [95% CI, 0.295 0.451]; $p < 0.0001$) in the ITT population, demonstrating a strong treatment effect over placebo. Analysis of non-nested, non-overlapping patient subpopulations indicated that the significant improvement in PFS observed in the ITT population was not driven only by the HRD or tBRCA (deleterious tumor alteration in BRCA) subpopulations (**Table 1**). Nearly half (44.6%) of the patients in the rucaparib group showed benefit at 1 year compared to 8.8% in the placebo group [25]. At 18 and 24 months, 32.0% and 26.0%, respectively, of patients who received rucaparib were still progression-free compared to 5.8% and 2.6% in the placebo group [25]. These investigator-assessed results were confirmed by results of central IRR assessment [25].

Table 1. Summary of Primary Efficacy Analyses and Selected Exploratory Endpoints for ARIEL3 [25]

ARIEL3 **Analysis Population**	**PFS by Investigator Review** ***(Primary Endpoint)***		**PFS by Blinded Independent Central Review** ***(Key Secondary Endpoint)***	
	Hazard Ratio	**Median PFS** **Rucaparib vs. Placebo** **(months)**	**Hazard Ratio**	**Median PFS** **Rucaparib vs. Placebo** **(months)**
tBRCA mut (n=196)	0.23; p<0.0001	16.6 vs. 5.4	0.20; p<0.0001	26.8 vs. 5.4
HRD-positive (n=354)	0.32; p<0.0001	13.6 vs. 5.4	0.34; p<0.0001	22.9 vs. 5.5
Intent-to-Treat (n=564)	0.36; p<0.0001	10.8 vs. 5.4	0.35; p<0.0001	13.7 vs. 5.4
$BRCA^{wt}$/HRD-positive (n=158)	0.44; p<0.0001	9.7 vs. 5.4	0.55; p=0.0135	11.1 vs. 5.6
$BRCA^{wt}$/HRD-negative (n=161)	0.58; p=0.0049	6.7 vs. 5.4	0.47; p=0.0003	8.2 vs. 5.3

2.3.4 OVERVIEW OF SAFETY - RUCAPARIB

The US prescribing information (USPI) for rucaparib in the treatment setting is based on 377 patients with advanced ovarian cancer. The most common treatment-emergent adverse events (TEAEs) were nausea, asthenia/fatigue, vomiting, anemia/hemoglobin decrease, increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST), constipation, decreased appetite, and dysgeusia [26]. Commonly experienced Grade 3 or higher TEAEs included anemia/hemoglobin decreased, asthenia/fatigue, and increased ALT/AST. Results of a more recent integrated safety analysis in over 900 patients with ovarian cancer who received 600 mg rucaparib BID in the treatment or maintenance setting showed that the most common TEAEs reported were primarily mild to moderate (Grade 1-2) in severity and included gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, anemia/decreased hemoglobin, increased ALT/AST, decreased appetite, and dysgeusia. The most common TEAEs ≥ Grade 3 included anemia/decreased hemoglobin, increased ALT/AST, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue.

Laboratory abnormalities were consistent with the TEAEs; the most commonly occurring were decreased hemoglobin (and associated increases in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine. Decreased platelets, neutrophils, leukocytes, lymphocytes, and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib, in either the treatment or maintenance settings were not associated with abnormal increases in bilirubin or other criteria for drug-induced hepatotoxicity, and generally resolved over time. Furthermore, no cases met Hy's law criteria for drug-induced liver injury (DILI) and few patients discontinued rucaparib due to ALT/AST elevations [24, 25]. Similarly, elevations in creatinine were self-limiting and stabilized over time. Elevated serum creatinine levels resolved upon interruption or discontinuation of rucaparib, were not accompanied by changes in blood urea nitrogen (BUN) and did not lead to discontinuation of rucaparib treatment [24, 25]. Increased creatinine with rucaparib treatment is likely due to the potent inhibition by rucaparib of MATE1 and MATE2-K renal transporters.

Effects on cardiac channel activity in vitro and a comprehensive assessment of the effects of rucaparib on electrocardiogram (ECG) parameters in cancer patients demonstrated a low risk of cardiac effects by rucaparib.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs), as these events have been observed in patients exposed to cytotoxic chemotherapy (e.g., platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as deleterious BRCA mutations [28, 29]. Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib. Clovis has added these potential risks to all Informed Consent Forms (ICFs) / Patient Information Sheets (PISs). AESI's (both serious and non-serious) will be reported to Clovis within 48 hours of detection and will continue to be reported to Clovis under serious adverse event (SAE) reporting requirements.

More information on AESIs for rucaparib is provided in the rucaparib IB. This information is also found in Appendix B.

2.4 Nivolumab

For details regarding study agent please refer to IB provided by the sponsors and attached with this protocol. CA209032 is an ongoing Phase 1/2, open-label study of nivolumab monotherapy or nivolumab combined with ipilimumab at different dose levels in subjects with several types of advanced or metastatic solid tumors, including SCLC.

Subjects with SCLC were included if they had advanced or metastatic SCLC with progressive disease after ≥ 1 prior platinum-containing regimens. Key efficacy data for nivolumab monotherapy (3 mg/kg Q2W IV) and nivolumab + ipilimumab combination therapy (nivo 1 mg/kg+ ipi 3 mg/kg Q3W IV) in subjects with SCLC based on a 30-Mar06-Nov-2017 database lock date are provided in Table 2.3.3. Responses were observed regardless of platinum sensitivity, line of therapy, or PD-L1 status.

2.4.1 ***Recommended Storage and Use Conditions***
Vials of nivolumab injection must be stored at 2□C to 8□C (36□F to 46□F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25□C, 77□F) and room light for up to 48 hours. Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container

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

2.4.2 Adverse Event List(s) for nivolumab (For a complete list please refer to IB; also noted in Appendix C)

- Fatigue/lack of energy
- Musculoskeletal pain (back pain, neck pain, pain in extremities)
- Diarrhea
- Nausea
- Hypertension
- Autoimmune side effects
- Infusion-related reactions (chills, fever, back pain, hypersensitivity reactions and low blood pressure)
- Rash and skin redness
- Decreased appetite
- Swelling of the extremities
- Joint pain
- Constipation
- Abdominal pain
- Vomiting
- Itching
- Weight loss
- Cough
- Shortness of breath
- Dizziness
- Headache

Table 2.4: Nivolumab Monotherapy or in Combination with Ipilimumab in Subjects with SCLC-CA209032

Summary of Efficacy Results with Nivolumab Monotherapy and Nivolumab in Combination with Ipilimumab in Subjects with SCLC - CA209032

	≥ Third-Line		≥ Second-Line	
	Nivo 3 (N = 109)	Nivo 1 + Ipi 3 (N = 58)	Nivo 3 (N = 245)	Nivo 1 + Ipi 3 (N = 157)
Objective Response Rate (per BICR) [a]				
n (%)	13 (11.9)	16 (27.6)	29 (11.8)	35 (22.3)
95% CI	6.5, 19.5	16.7, 40.9	8.1, 16.6	16.0, 29.6
Median Duration of Response (95% CI), months [b]	17.94 (7.92, 42.05)	10.61 (4.01, NA)	17.94 (7.92, 42.05)	10.41 (6.93, 26.48)
Min, Max [c]	3.0, 42.1	1.8, 31.8+	1.4+, 42.1	1.5, 34.6+
n (%) responders with DoR ≥ 6 mo. [d]	10 (76.9)	10 (62.5)	21 (72.4)	25 (71.4)
n (%) responders with DoR ≥ 12 mo [d]	8 (61.5)	6 (37.5)	13 (44.8)	14 (40.0)
Progression-Free Survival (per BICR)				
Median (95% CI), months [b]	1.38 (1.31, 1.64)	1.87 (1.41, 2.89)	1.35 (1.31, 1.38)	1.58 (1.38, 2.33)
6-month PFS rate (95% CI) [b]	17.2 (10.7, 25.1)	28.1 (17.2, 40.1)	15.3 (11.0, 20.2)	24.2 (17.8, 31.2)
Overall Survival				
Median (95% CI), months [b]	5.62 (3.09, 6.83)	8.38 (5.39, 14.46)	5.09 (3.75, 6.74)	6.67 (3.91, 8.41)
1-year OS rate (95% CI) [b]	28.3 (20.0, 37.2)	41.4 (28.7, 53.6)	29.2 (23.5, 35.1)	34.4 (27.0, 41.9)

Source: CA209032 Final SCLC CSR;[81] database lock 06-Nov-2017; minimum follow-up: ~ 12 months

Nivo 3 = nivolumab 3 mg/kg Q2W

Nivo 3 + Ipi 1 = nivolumab 3 mg/kg plus ipilimumab 1 mg/kg Q3W

[a] Based on RECIST v1.1, confirmation of response required. CR+PR, confidence interval based on the Clopper and Pearson method

[b] Computed using Kaplan-Meier method

[c] + symbol indicates a censored value

[d] The proportion is the number of subjects observed to be in response at that timepoint divided by the total number of responders.

Abbreviations: BICR = blinded independent central review, CI = confidence interval, CR = complete response, CSR = clinical study report, DoR = duration of response, PR = partial response, QxW = every x weeks, RECIST = Response Evaluation Criteria in Solid Tumors, SCLC = small-cell lung cancer

2.5 Rationale for suggested Biomarkers:

Tumor mutation burden (TMB): Immune checkpoint inhibitor responders tend to have high tumor mutation burden (e.g., melanoma, NSCLC, bladder cancer, and microsatellite unstable colorectal cancers) [35-38]. Recent data presented at World Lung Meeting suggested a superior response to nivolumab in SCLC patients with high TMB [39].

Smoking status: Smoking has been associated with higher tumor mutational burden and might portend a favorable response to immune checkpoint inhibition [40]. We will evaluate whether smoking is associated with distinctive mutations, which might predict a favorable response to therapy among SCLC patients.

Micro Satellite Instability (MSI) Status: MSI occurs in a small portion of cancers and represents a potential subgroup of patients who might benefit from checkpoint inhibitor therapy. [35, 37]

Germline BRCA1/2 Mutation: PARP inhibitors work by synthetic lethality in patients with mutated BRCA1 or BRCA 2. PARPi selectively targets BRCA-mutant cells by increasing DNA single-stranded breaks that result in irreparable DNA double-strand breaks during replication, culminating in cell death. We will check for presence of germline BRCA1/2 mutations and evaluate as a correlation to response.

2.6 Rationale for Immune Biomarkers

The Society for Immunotherapy of Cancer (SITC) has provided the roadmap and regular updates on immune biomarker development. [41-43].Immunological changes in peripheral blood and the tumor could potentially reflect tumor response in patients and serve as immune biomarkers.

For all study participants: we will be collecting peripheral blood (two 8ml CPT Vacutainer tubes with sodium citrate) for flow cytometry at two timepoints, pre-study baseline and during treatment (Cycle 3 Day 1) by Dr. Cohen's lab. A total of 16 mL of blood will be collected at each timepoint, for cumulative total of 32 mL.

For all study participants, we will be collecting an additional 10 ml of whole blood (Streck tube) at pre-study baseline, and approximately every 2 months (e.g., at 2-months, at 4-months) and at the time of progression (for up to a total of 4 blood sample collections) based on SITC recommendations to evaluate TP53 levels (Dr. Kolesar's lab). It is possible that a total of 40 mL of blood will be collected (one 10mL tube drawn at 4 different timepoints).

For any study participant co-enrolled in Total Cancer Care, peripheral blood is collected at baseline per the ORIEN protocol for germline mutation testing. Additionally, for these co-enrolled participants, tumor tissue (if available) for whole exome sequencing is also collected at baseline per the ORIEN protocol. These blood/tissue collections are not part of this study protocol, however the results re: tumor mutations will be used in ancillary analyses of correlatives studies in this protocol.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients with histologically or cytologically confirmed stage IV, extensive stage, small cell lung cancer who achieved either PR or CR per RECIST 1.1 post frontline chemotherapy with platinum doublet (Cisplatin/Carboplatin-etoposide or Carboplatin/Cisplatin-Irinotecan).
- No later than 6W after the last dose of platinum-based chemotherapy in cycle 4 (or later cycles) .
- Subjects may have measurable (PR status) or non-measurable (CR) disease

3.1.2 ECOG performance status ≤ 2 (Appendix A)

3.1.3 Male or female subjects aged ≥ 18 years

3.1.4 Adequate Bone Marrow Function is required as defined by the following:
- Absolute neutrophil count (ANC) ≥ 1.5×10^9/L
- Platelets ≥ 100×10^9/L
- Hemoglobin ≥ 9g/dL

3.1.5 Adequate Hepatic Function is required as defined by the following:
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, then ≤ 5 × ULN
- Bilirubin ≤ 1.5 × ULN; < 2 × ULN if hyperbilirubinemia is due to Gilbert's syndrome

3.1.6 Adequate Renal Function is required as defined by:
- Measured or calculated creatinine clearance (CrCL) ≥ 30 mL/min.
- For calculated CrCL, the Cockcroft Gault formula or institutional standard formula can be used.

3.1.7 Written informed consent: Signed and dated informed consent of the subject must be available before start of any specific trial procedures. The subject must be able to understand the nature, importance and individual consequences of the clinical trial.

3.2 Exclusion Criteria

3.2.1 Prior therapy with any antibody/drug targeting T-cell co-regulatory proteins (immune checkpoints).

3.2.2 Also excluded is major surgery within 4 weeks of initiation of study medication.

3.2.3 Current use of immunosuppressants is prohibited **EXCEPT** for the following:

- intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection);
- Systemic corticosteroids at physiologic doses ≤ 10 mg/day of prednisone or equivalent;
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

3.2.4 Prior organ transplantation, including allogeneic stem cell transplantation.

3.2.5 Active infection requiring systemic therapy.

3.2.6 HIV/AIDS: known history of testing positive for human immunodeficiency virus or known acquired immunodeficiency syndrome.

3.2.7 Autoimmune disease: Active autoimmune disease including autoimmune paraneoplastic syndromes that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.

3.2.8 Persisting toxicity related to prior therapy (NCI Common Terminology Criteria for Adverse Events (CTCAE) v. 5 Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable

3.2.9 Pregnancy and contraception: Pregnancy is an exclusionary criterion.

3.2.10 Male patients are considered as having reproductive potential unless permanently sterile by bilateral orchiectomy or vasectomy.

3.2.11 Pregnancy and contraception: Pregnancy is an exclusionary criterion.

3.2.12 Female patients or partners of male patients are considered to be of childbearing potential unless one of the following applies:

- Considered permanently sterile. Permanent sterilization includes hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy
- Postmenopausal, defined as no menses for at least 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level consistently in the postmenopausal range (30 mIU/mL or higher) may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy; however, in the absence of 12 months of

amenorrhea, a single FSH measurement is insufficient to confirm a postmenopausal state.

3.2.13 To be eligible for enrollment, female patients of childbearing potential must have a negative serum or urine pregnancy test result within two weeks prior to administration of study treatment. Once on-study, pregnancy status of female patients will be evaluated per standard of care.

3.2.14 Women of childbearing potential must not consider getting pregnant, and must avoid pregnancy during the study and for at least 6 months after the last dose of rucaparib or Nivolumab, or longer if requested by local authorities.

3.2.15 Male patients of reproductive potential with female partners of childbearing potential must not consider getting pregnant, and must avoid pregnancy during the study and for at least 6 months after the last dose of rucaparib or Nivolumab, or longer if requested by local authorities.

3.2.16 Male patients are required to use a condom during sex with a partner to avoid the possibility of exposing the partner to Rucaparib or Nivolumab, regardless of whether the partner is a woman of childbearing potential or not. Male patients must not make semen donations during treatment and for 6 months following the last dose of rucaparib or Nivolumab. Males who are sexually active with women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment and 6 months after last dose of nivolumab or rucaparib.

3.2.17 Female and male patients of reproductive potential must practice highly effective methods (failure rate < 1% per year) of contraception with their partners during treatment, and for 6 months following the last dose of rucaparib or Nivolumab, or longer if requested by local authorities. Highly effective contraception includes:

- Ongoing use of progesterone-only injectable or implantable contraceptives;
- Placement of an intrauterine device (IUD) or intrauterine system (IUS);
- Bilateral tubal occlusion;
- Sexual abstinence as defined as complete or true abstinence, acceptable only when it is the usual and preferred lifestyle of the patient; periodic abstinence (e.g., calendar, post-ovulation methods) is not acceptable;
- Male sterilization, with appropriate post-vasectomy documentation of absence of sperm in ejaculate.

3.2.18 Patients should be instructed to notify the investigator if pregnancy is discovered either during or within 6 months of completing treatment with rucaparib or Nivolumab.

3.2.19 Other severe acute or chronic medical conditions [including immune colitis, inflammatory bowel disease, immune pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behavior] or laboratory abnormalities that may increase the risk associated with study participation, study treatment administration and/or may interfere with the interpretation of study results and/or in the judgment of the investigator, would make the patient inappropriate for entry into this study.

3.2.20 Vaccination: Vaccination within 4 weeks of the first dose of nivolumab and while on trial is prohibited EXCEPT for administration of inactivated vaccines

3.2.21 Hypersensitivity to the study drugs: Known prior severe hypersensitivity to nivolumab or rucaparib or any components in their formulations, including known severe hypersensitivity reactions to monoclonal antibodies and PARP inhibitors (NCI CTCAE v5 Grade ≥ 3).

3.2.22 Cardiovascular disease: Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to enrollment), myocardial infarction (< 6 months prior to enrollment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.

3.2.23 Participation in other clinical trials involving an investigational drug during the present clinical trial or within the last 30 days, or five terminal phase half-lives of the drug whichever is longer, prior to baseline assessment (this also includes investigational formulation of market products).whichever is longer, prior to baseline assessment (this also includes investigational formulation of market products).

3.2.24 Subjects who received platinum in the adjuvant or neoadjuvant setting are eligible; however, subjects may not have relapsed within 6 months of the last dose of prior platinum therapy

3.2.25 Untreated CNS metastases or leptomeningeal carcinomatosis

3.2.26 Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of this trial's investigational regimen should be excluded.

3.2.27 Patients with active pneumonitis will be excluded from the study.

3.2.28 Current use of Warfarin, Coumadin, Tizanidine and/or Aripiprazole is excluded. Use of other agents/medications that affect CYP will be reviewed for eligibility at the discretion of the treating physician.

3.2.29 Subjects with active autoimmune disease and subjects requiring systemic corticosteroids (>10 mg daily prednisone equivalent) within 24 hours of study registration. Subjects taking systemic corticosteroids for PCI treatment are eligible.

3.3 Inclusion of Women and Minorities

Women and members of minority groups and their subpopulations will be included.

4. REGISTRATION PROCEDURES

4.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's (MCC) Protocol Review and Monitoring Committee (PRMC) and the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky (UK) Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the MCC Clinical Research Office (CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, study sponsor and the UK IRB.

4.2 Enrollment Guidelines

Eligible patients will be identified by the principal investigator (PI) and co-investigators of this study. Potentially eligible patients will be screened in the UK MCC clinics by the investigators, study personnel, and the PI. Upon obtaining informed consent, patients will be enrolled into the study.

4.3 **Informed Consent**

The goal of the informed consent *process* is to provide sufficient information so that potential participants can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent *document* provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent *document* is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent shall be provided as a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered part of the protocol and must be submitted by the investigator with the protocol at the time of IRB review.

4.4 **Compliance with Laws and Regulations**

The study will be conducted in accordance with U.S. Food and Drug Administration and International Conference on Harmonization Guidelines for Good Clinical Practice, the Declaration of Helsinki, any applicable local health authority, and IRB requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the investigator's annual report to the IRB and copies of the IRB continuance of approval must be maintained by the MCC CRO. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee (DSMC) of the MCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per standard operating procedure (SOP)'s of those entities. MCC DSMC will review all adverse events of this investigator-initiated trial (IIT) as per its SOP.

5. TREATMENT PLAN

5.1 Enrollment and Screening Process

Prior to any study-required tests, patients must first provide written informed consent to participate in this study.

All radiographic studies should be completed within 6 weeks prior to starting investigational agents.

Pre-study screening shall include:
- complete medical history and evaluation of ECOG Performance Status;
- EKG;
- pathological (biopsy) or cytologically proven SCLC;
- CT with contrast of chest and upper abdomen to include the liver and adrenals;

All lab tests should be completed within 2 weeks prior to study registration:
- CBC with differential;
- Serum chemistries to include: alkaline phosphatase, glucose, creatinine, electrolytes, TSH, AST (SGOT), ALT (SGPT), and total bilirubin (see Study Calendar for complete list).
- Serum or urine pregnancy test for women of childbearing potential.

5.2 Nivolumab and Rucaparib Administration

The recommended starting dose of rucaparib as a continuously administered oral monotherapy is 600 mg BID. Patients may take rucaparib with or without food. Each dose should be taken with approximately 8 oz. (240 mL) of room temperature water. Tablets should be swallowed whole without crushing or chewing. Patients should take rucaparib doses as close as possible to 12 hours apart, preferably at the same time 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 by taking the next scheduled rucaparib dose. Missed or vomited doses should not be made up.

Modification of rucaparib dose may be a necessary component of AE management, and study-specific protocol guidelines for dose modifications should be followed. See Section 6.

Nivolumab will be administered as intravenous infusion once every 4 weeks at fixed dose of 480 mg. The FDA has approved a supplemental biologics license application adding a 4-week dosing schedule for nivolumab (Opdivo) across several of the PD-1 inhibitor's indications (non-small cell lung cancer, renal cell carcinoma, metastatic urothelial carcinoma, Hodgkin lymphoma, metastatic squamous cell carcinoma and hepatocellular carcinoma). Adding a q 4 weekly regimen will be convenient for patients and will be more cost effective as it will reduce number of visits to infusion center. We have had no problem with using q4 week dosing in SCLC at our center. No dose modification will be allowed (other than hold or discontinue). Please refer to Section 6 for guidance regarding Nivolumab schedule in response to toxicity**.**

5.3 Drug-drug Interactions

5.3.1 Cytochrome P450 Isoenzyme Inhibitors, Inducers, and Substrates

Based on the results from the in vivo CYP interaction study (CO-338-044), rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Caution should be used with concomitant medications that are sensitive clinical substrates of CYP1A2, CYP2C9, CYP2C19, and/or CYP3A (see IB for rucaparib). Although in vitro rucaparib metabolism mediated by CYP3A4 was slow, a significant contribution of CYP3A4 in vivo cannot be excluded. Caution should be used for concomitant use of strong CYP3A4 inhibitors or inducers such as **voriconazole, clarithromycin** etc. (see the FDA website for a list of examples of sensitive clinical substrates and strong perpetrators of the above--mentioned enzymes). Selection of an alternative concomitant medication is recommended, and concomitant medication use among study participants will be monitored by study staff and the study PI.

Effects of Rucaparib on Other Medicinal Products or Concomitant Drugs
At the steady-state following treatment with 600 mg rucaparib BID, rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A. Rucaparib also marginally inhibits P-gp in the gut, but this is unlikely to be clinically significant.

CYP1A2 Substrates When co-administering medicinal products metabolized by CYP1A2, particularly medicines that have a narrow therapeutic index (e.g., tizanidine, theophylline), dose adjustments may be considered based on appropriate clinical monitoring.

CYP2C19 Substrates No dose adjustment is considered necessary for co-administered medicinal products that are CYP2C19 substrates. CYP3A Substrates Caution is advised when co-administering

medicinal products that are CYP3A substrates with a narrow therapeutic index (e.g., alfentanil, astemizole, cisapride, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine). Dose adjustments may be considered, if clinically indicated based on observed AEs.

P-gp Substrates No dose adjustment is recommended for co-administered medicinal products that are P-gp substrates.

Other Enzymes and Transporters Interaction of rucaparib with other enzymes and transporters was evaluated in vitro. Rucaparib is a weak inhibitor of CYP2C8, CYP2D6, and UGT1A1. Rucaparib down regulated CYP2B6 in human hepatocytes at clinically relevant exposures.

In vitro, rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib.

In addition, rucaparib is an inhibitor of the BCRP with an IC_{50} value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrates (e.g., rosuvastatin).

Effect of Food on Rucaparib Exposures: A high-fat meal increased C_{max} by 20% and increased AUC_{0-24} by 38%. The effect is not considered clinically significant. In clinical studies, rucaparib was administered with or without food.

There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

5.3.2 Anticoagulants

Rucaparib is a weak inhibitor of CYP2C9 in vivo. Warfarin, Coumadin, Tizanidine and Aripiprazole are exclusion criteria for study eligibility. Use of similar medications inhibiting CYP2C9 will be reviewed by the treating investigator to determine eligibility and additional monitoring for AEs if patient is enrolled on-study.

5.3.3 Other Concomitant Medications

Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications should be avoided, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems.

- **Herbal and complementary therapies** should be discouraged because of potential for unknown side effects and adverse drug interactions, but any that are taken by the patient should be documented appropriately on the eCRF.

- Rucaparib marginally increased **digoxin** area under the plasma concentration-time curve (AUC) by 20%. Caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. Patients taking digoxin should have their digoxin levels monitored after starting rucaparib and then regularly per standard clinical practice.

- In vitro, rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of **metformin,** caution is advised when metformin is co-administered with rucaparib.

- In addition, rucaparib is an inhibitor of the BCRP with 50% inhibitory concentration (IC50) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (e.g., **rosuvastatin**).

5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for *24 months* or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

- The date and the reason for removal from study treatment must be documented in the Case Report Form.

5.5 Duration of Follow-Up

Patients will be followed until death or 3 years after registration for survival, whichever occurs first. Patients removed from study therapy due to unacceptable adverse event(s) will be followed per protocol, until resolution or stabilization of the adverse event.

5.6 Criteria for Removal from Study

Patients will be removed from study therapy when any of the criteria listed in Section 5.4 applies and followed per section 5.5. The reason for study therapy removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Doses of oral study drug (rucaparib), and/or IV study drug (nivolumab), may be interrupted or delayed for toxicity and other protocol-specified criteria. **Dose reductions are permitted for Rucaparib, but not for Nivolumab.** The assessment for delay or discontinuation should be made separately for the oral study drug (rucaparib) and the IV study drug (nivolumab) where class-specific safety profiles do not overlap; however, if toxicity is considered related to all study drugs or if the investigator is unable to determine which study drug is the cause of the AE, then all study drugs in the combination should be delayed and/or discontinued. For management of AEs which can be clearly attributed to rucaparib OR nivolumab, independent dose modification for either agent is allowed. If the relationship to an AE that is common to both drugs can be clearly distinguished, then a recommendation from the ET CCART for continuation of the non-offending drug can be requested by the investigator. Treatment may be prematurely discontinued due to withdrawal of consent, unacceptable toxicity, disease progression, completion of treatment cycles, or termination of the study, whichever occurs first.

Dose modification and re-treatment of oral and/or IV study drug are to be based on criteria presented in Table 4.

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment
Non-hematological Non-skin AEs					
Adverse event, except fatigue	2	None	N/A	Hold	Grade ≤ 1 or baseline[3]
Any adverse event (related events lasting > 7 days for nivolumab, exceptions below)	3 or 4	Hold	≤ Grade 2[4]	Discontinue	
Exceptions with rucaparib					
Nausea, Vomiting, Diarrhea adequately controlled with systemic antiemetics/antidiarrheal medications lasting <7 days.	3	None			
ALT/AST provided no signs of liver dysfunction (see laboratory section below)	3	None			
Exceptions with nivolumab					
Uveitis, pneumonitis, bronchospasm, neurological toxicity, hypersensitivity reason or infusion reaction of any duration	3			Discontinue	
Endocrinopathies, adequately controlled with only physiologic hormone replacement	3			Hold	Grade ≤ 1 or baseline[3]
Drug-related adrenal insufficiency or hypophysitis	2			Hold	Grade ≤ 1 or baseline[3]
Adrenal insufficiency regardless of control with hormone replacement	3			Discontinue	
Laboratory abnormalities except as specified below	3			Hold	Grade ≤ 1 or baseline[3]
Drug-related ALT, AST, or bilirubin	3			Discontinue[5]	
Adverse event or laboratory abnormality except for those below that do not require delay	4			Discontinue	
Isolated electrolyte imbalances/abnormalities not associated with clinical sequelae/corrected w/supplementation /appropriate management w/in 72 hours of onset	3			Hold	Grade ≤ 1 or baseline[3]

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment
Endocrinopathy AEs[6]	3			Hold	Grade ≤ 1 or baseline[3]
Non-hematological Toxicity (Skin)					
Adverse event	3	Hold	Grade 2[4]	Hold	
Hematological Toxicity					
Hematological toxicity (related events lasting >7 days for nivolumab, exceptions below)	3-4	Hold[7]	Grade 2[4]	Discontinue	
Confirmed MDS or AML (all new secondary malignancies are Grade 4 per CTCAE 5.0)	4	Discontinue		Discontinue	
Exceptions with nivolumab					
Laboratory abnormalities except as specified below	3			Hold	Grade ≤ 1 or baseline[3]
Thrombocytopenia > 7 days or associated with bleeding	3			Discontinue	
Laboratory abnormality except for those below that do not require delay	4			Discontinue	
Neutropenia ≤ 7 days	4			Hold	Grade ≤ 1 or baseline[3]
Lymphopenia or leukopenia	4			Hold	Grade ≤ 1 or baseline[3]
Laboratory Abnormalities					
Laboratory abnormality	3	Hold	Grade 2[4]	Hold	
ALT, AST, and/or bilirubin abnormalities	2	None	N/A	Hold[8]	Grade ≤ 1 or baseline[3]
ALT/AST elevations	3	None, provided no signs of liver dysfunction[9]	N/A	Discontinue[7]	
ALT/AST elevations	4	Hold	≤Grade 2 Reduce dose[10]	Discontinue	

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment
ALT or AST > 3 × ULN AND bilirubin > 2 × ULN (suspected DILI)		Hold[9]		Discontinue	
Creatinine elevations	2 (≥ 1.5 x baseline[11])	None	N/A	Hold	Grade ≤ 1 or baseline[3]
Creatinine elevations	3	Hold	Grade 2[4]	Hold	Grade ≤ 1 or baseline[3]
Exception with nivolumab					
Grade 3 lymphopenia or asymptomatic amylase or lipase	3			None	
Dosing-related					
Any event that leads to delay in dosing lasting > 8 weeks from the previous dose requires discontinuation, with the exception of dosing delays to allow for prolonged steroid tapers to manage AEs. • Dosing delays lasting > 8 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the study medical monitor/designee				Discontinue	
Toxicity despite dose reduction steps to 200 mg BID or interruption of oral drug for > 14 consecutive days except if allowed if approved by the study medical monitor/designee. • Prior to re-initiating treatment in a patient with a dosing delay > 14 days, the study medical monitor/designee must be consulted.		Discontinue			

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AML = acute myeloid leukemia; AST = aspartate aminotransferase; BID -= twice daily; CTCAE = Common Terminology Criteria for Adverse Events; DILI = drug-induced liver injury; IV = intravenous; MDS = myelodysplastic syndrome; N/A = not applicable; ULN = upper limit of normal

Table 4. Dose Modification and Re-treatment Criteria for Oral and IV Study Drugs

Adverse Event	Severity (CTCAE Grade)	Oral Study Drug (rucaparib)		IV Study Drug (nivolumab)	
		Dose Modification[1]	Re-treatment	Dose Modification[2]	Re-treatment

[1]Oral drug may be discontinued for any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued oral study treatment dosing. In addition, and at the discretion of the investigator, the dose of oral study drug may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

[2]In addition to the criteria below, nivolumab should be held if there is any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, warrants delaying the dose of study medication or discontinued if there is any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial risk to the patient with continued IV study drug dosing. Patients who require dose hold should be re-evaluated weekly or more frequently if clinically indicated and resume dosing during the next scheduled dosing window (Cycle X, Day 1 ±3 days) after re-treatment criteria are met.

[3]Patients may resume treatment with IV study drug when the drug-related AE(s) improve to Grade ≤ 1 or resolve to baseline value, with the following exceptions which are allowed: Grade 2 fatigue, Grade 2 skin toxicity (if no Grade 3 drug related skin AE). For patients with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete. Drug-related pulmonary toxicity, diarrhea or colitis must have resolved to baseline before treatment is resumed. Patients with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the study medical monitor. Patients with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the study medical monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

[4]The patient may continue at same or reduced dose at the discretion of the investigator. If treatment is resumed at the same dose, and the patient experiences the same toxicity, treatment should be interrupted, then resumed at a reduced dose following improvement of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted; however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID.

[5]In most cases of Grade 3 ALT or AST elevation, IV study drug will be permanently discontinued. For patients with Grade 3 ALT or AST elevations after the start of IV dosing, but on a background of previous elevations on the first cycle of oral study drug, IV study drug hold is required, but discontinuation is not required, if ALT/AST elevations begin to resolve before the next scheduled infusion, and toxicity is considered to be mainly related to oral study treatment, after the investigator discusses the case with the study medical monitor. Levels will be monitored every 3 days; if they continue to rise more than 20%, the Hepatic Adverse Event Management Algorithm for a Grade 3 event will be followed . Treatment with IV drug may be resumed if levels return to Grade 2. If total bilirubin elevations > 2 × ULN accompany any of the ALT/AST elevations, IV drug should be discontinued.

[6]Such as, hyper- or hypothyroidism, or glucose intolerance, that resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the study medical monitor/designee. Grade 4 drug-related adrenal insufficiency or hypophysitis requires discontinuation regardless of control with hormone replacement.

[7]If any blood parameters remain clinically abnormal > 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice.

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[8]For patients with Grade 2 ALT or AST elevations with onset after dosing of oral study drug, IV study treatment hold is not required if ALT/AST elevations begin to resolve before the next scheduled infusion and toxicity is considered to be mainly related to oral study treatment. If a subsequent ALT/AST increase of more than 20% is observed following infusion of IV study drug, the next IV study drug administration will be held and, if further increase is observed, the Hepatic Adverse Event Management Algorithm will be followed In this case, IV study drug should be discontinued if Grade 2 elevations return post re-challenge. If total bilirubin elevations > 2 × ULN accompany any of the ALT/AST elevations, IV drug should be discontinued.

[9]Bilirubin must be within normal limits and alkaline phosphatase must be < 3 x ULN. Monitor liver function tests weekly. If the patient has Grade 3 ALT/AST and continues on oral study drug, and levels do not decline within 2 weeks or they continue to rise, treatment interruption and improvement to ≤ Grade 2 will be required before oral study drug can be resumed, either at the current dose or at a reduced dose.

[10]Monitor liver function tests weekly for 3 weeks after oral study drug has been restarted.

[11]Grade 2 for nivolumab is described as ≥ 1.5 x baseline and baseline is the day the combination treatment starts (ie, Cycle 2 Day 1 in Cohort A1 and A2, and Cycle 1 Day 1 in Cohort B)

RECOMMENDED DOSE ADJUSTMENTS FOR RUCAPARIB		
	Dose	***Total mg per day***
Starting Dose	600 mg twice daily (each dose is two 300-mg tablets)	1200 mg per day
First Dose Reduction	500 mg twice daily (each dose is one 300-mg tablet **and** one 200-mg tablet)	1000 mg per day
Second Dose Reduction	400 mg twice daily (each dose is two 200-mg tablets)	800 mg per day
Third Dose Reduction	300 mg twice daily (each dose is one 300-mg tablet)	600 mg per day

7. ADVERSE EVENTS

The following list of adverse events (Section 7.1, Appendices B and C) and the characteristics of the observed AEs (Section 7.2) will determine whether the event requires expedited reporting via the MedWatch Forms **in addition** to routine reporting.

7.1 Expected Toxicities and Supportive Care guidelines

Adverse Event List for rucaparib; nausea, fatigue (including asthenia), vomiting, anemia, dysgeusia, AST/ALT elevation, constipation, decreased appetite, diarrhea, thrombocytopenia, neutropenia, stomatitis, nasopharyngitis/URI, rash, abdominal pain/distention, and dyspnea. Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML) and Embryo-Fetal Toxicity. See also Appendix B.

Adverse Event List for nivolumab: Fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, abdominal pain, and vomiting. Immune-mediated pneumonitis, Immune-mediated colitis, Immune-mediated hepatitis, Immune-mediated endocrinopathies, Immune-mediated nephritis and renal dysfunction, Immune-mediated skin adverse reactions, Immune-mediated encephalitis, Infusion reactions. See also Appendix C.

7.1.1 Supportive care guideline for rucaparib and nivolumab toxicity

Opportunistic Infections: It is rare for a patient receiving immunosuppression for nivolumab-related AEs to develop an opportunistic infection. Subjects with inflammatory events of any organ category expected to require more than 4 weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered for antimicrobial/antifungal prophylaxis, per institutional guidelines, to prevent opportunistic infections such as P. jiroveci (formerly P carinii) and fungal infections.

Immune-Mediated Pneumonitis: Nivolumab can cause immune-mediated pneumonitis, defined as requiring use of corticosteroids and no clear alternate etiology. Fatal cases have been reported.
Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for moderate (Grade 2) or more severe (Grade 3-4) pneumonitis, followed by corticosteroid taper. Please refer to section 6 for dose modification guidance.

Immune-Mediated Colitis: Nivolumab can cause immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology. Monitor patients for signs and symptoms of colitis. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid

taper for severe (Grade 3) or life- threatening (Grade 4) colitis. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) colitis of more than 5 days duration; if worsening or no improvement occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day prednisone equivalents. Refer to section 6 for dose modification guidance.

Immune-Mediated Hepatitis: Nivolumab can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) transaminase elevations, with or without concomitant elevation in total bilirubin. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) transaminase elevations. Refer to section 6 for dose modification guidance.

Immune-Mediated Endocrinopathies: Nivolumab can cause immune-mediated hypophysitis. Monitor patients for signs and symptoms of hypophysitis. Administer hormone replacement as clinically indicated and corticosteroids at a dose of 1 mg/kg/day prednisone equivalents followed by corticosteroid taper for moderate (Grade 2) or greater hypophysitis. Refer to section 6 for dose modification guidance.

Adrenal Insufficiency: Nivolumab can cause immune-mediated adrenal insufficiency. Monitor patients for signs and symptoms of adrenal insufficiency. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by a corticosteroid taper for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Please refer to section 6 for dose modification guidance.

Immune-Mediated Nephritis and Renal Dysfunction: Nivolumab can cause immune-mediated nephritis, defined as renal dysfunction or Grade 2 increased creatinine, requirement for corticosteroids, and no clear alternate etiology. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents followed by corticosteroid taper for life-threatening (Grade 4) increased serum creatinine. Administer corticosteroids at a dose of 0.5 to 1 mg/kg/day prednisone equivalents for moderate (Grade 2) or severe (Grade 3) increased serum creatinine, if worsening or no improvement occurs, increase dose of corticosteroids to 1 to 2 mg/kg/day prednisone equivalents. Please refer to section 6.

Immune-Mediated Encephalitis: Nivolumab can cause immune-mediated encephalitis with no clear alternate etiology. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture.

Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infectious or other causes of moderate to severe neurologic deterioration. If other etiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day prednisone equivalents for patients with immune-mediated encephalitis, followed by corticosteroid taper. Permanently discontinue OPDIVO for immune-mediated encephalitis

Infusion Reactions: Nivolumab can cause severe infusion reactions, which have been reported in less than 1.0% of patients in clinical trials. Discontinue OPDIVO in patients with severe or life-threatening infusion reactions. Interrupt or slow the rate of infusion in patients with mild or moderate infusion reactions

7.1.2 Rucaparib

Rucaparib 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.
Anticoagulants: Rucaparib is a weak inhibitor of CYP2C9 in vivo. Use of Warfarin, Coumadin,

Tizanidine, and Aripiprazole is now an exclusion criterion for study eligibility.

Other Concomitant Medications
Therapies considered necessary for the patient's well-being may be given at the discretion of the investigator and should be documented on the eCRF. Other concomitant medications, except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems, should be avoided. Herbal and complementary therapies should not be encouraged because of unknown side effects and potential drug interactions, but any taken by the patient should be documented appropriately on the eCRF. Rucaparib marginally increased **digoxin** area under the plasma concentration-time curve (AUC) by 20%. Caution should be exercised for patients receiving rucaparib and requiring concomitant medication with digoxin. **Patients taking digoxin should have their digoxin levels monitored after starting rucaparib** and then regularly per standard clinical practice. In vitro, rucaparib is a potent inhibitor of MATE1 and MATE2-K, a moderate inhibitor of OCT1, and a weak inhibitor of OCT2. As inhibition of these transporters could increase metformin renal elimination and decrease liver uptake of metformin, **caution is advised when metformin is co-administered with rucaparib**. In addition, rucaparib is an inhibitor of the BCRP with 50% inhibitory concentration (IC50) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (e.g., rosuvastatin).

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf
- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above (and in the Investigational Brochures for both nivolumab and rucaparib in the appendices) should be reported only if the adverse event varies from expected toxicities (differs in nature, and/or exceeds anticipated intensity or frequency as noted in the provided expected toxicity information).
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 7.3.3 (Expedited Adverse Event Reporting under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions).
- **Attribution of the AE:**
  - Related – The AE is clearly related to the study treatment.
  - Unrelated – The AE is clearly NOT related to the study treatment.

7.3 Expedited Adverse Event Reporting

BMS-specific SAE reporting guidelines:

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

An appropriate SAE form (e.g., USA = Medwatch form) should be used to report SAEs to BMS. If you prefer to use your own Institutional form, it must be reviewed by BMS prior to study initiation. Note: Please include the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

  - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
  - The MedWatch form is available at: MedWatch 3500 Form

- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.
- The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.
- BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.
  - Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
  - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on either CIOMS, MedWatch, or approved site SAE form.

Pregnancies must be reported and submitted to BMS on any of the following form(s):

1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

7.3.1 Markey Cancer Center (MCC) IITs Reporting Guidelines

MCC IIT investigators **must** report to the PI any SAE that occurs after the initial dose of study treatment, during treatment, or within 100 days of the last dose of treatment (Nivolumab or Rucaparib) on the local institutional SAE form.

SAEs for rucaparib must be reported to PI regardless of causality even after reporting period.

This applies to the following categories:

- **Grade 3 (severe) *Medical* Events** – Events that are related or unrelated with the Intervention.
- **ALL Grade 4 (life-threatening or disabling) *Medical* Events** –
- **ALL Grade 5 (fatal) Events**

Note: If subject is in long-term follow-up, death is reported at continuing review.

7.3.2 The following table outlines the required forms and reporting structure for clinical trials.

Study type	Expedited reporting to MCC	Expedited reporting to External Agency	Non-expedited AE	Form	IRB
Industry-sponsored studies	Yes, if it meets the sponsor-required SAE reporting	Yes, if it meets the sponsor-required SAE reporting	Sponsor required process	MedWatch 3500 or 3500a per industry sponsor OnCore for all SAEs	Yes

MCC Expedited Reporting Guidelines for MCC IITs

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and UK IRB reporting policy. IRB reporting is as outlined in IRB SOP: http://www.research.uky.edu/ori/SOPs_Policies/C2-0350 Unanticipated_Problems_Adverse_Events_SOP.pdf

Attribution	MCC Reportable SAEs				
	Grade 2 AE Expected	**Grade 2 AE Unexpected**	**ALL Grade 3 and Grade 4 AEs**	**ALL Grade 4 AE**	**ALL Grade 5 AE**
Unrelated Unlikely	Not required	Not required	Within 5 calendar days	Within 5 calendar days	Within 24 hours*
Possible Probable Definite	Not required	Within 5 calendar days	Within 5 calendar days	Within 5 calendar days	Within 24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* The SAE should be reporting **within 24 business hours** of learning of the event for participants enrolled and actively participating in the study ***or*** for SAEs occurring within 100 days of the last intervention of Nivolumab and also Rucaparib.					

7.3.3 Exclusions to Protocol-Specific Expedited Adverse Event Reporting

The adverse events listed below do not require expedited reporting however, they still must be reported through the routine reporting mechanism (i.e., case report form)..

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments
	Nausea or vomiting occurring for less than 3 days	1 & 2		All	
	Alopecia	All		All	

7.4 Expedited Reporting to External Agencies

Overall PI will comply with the policies of all external funding agencies and the University of Kentucky IRB regarding expedited reporting, as per the IRB's SOP on safety reporting: http://www.research.uky.edu/ori/SOPs_Policies/C4-0150-Mandated_Reporting_to_External_Agencies_SOP.pdf.

Grade 5 SAEs will be also reported to BMS and Clovis Oncology within 24 hours of the learning of the event, up to the point of 100-days after the last dose of Nivolumab and Rucaparib.

7.4.1 Expedited Reporting to the FDA

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.4.2 Expedited Reporting to Hospital Risk Management

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to the institutional policy.

7.5 Routine Adverse Event Reporting

All AEs **must** be reported in routine study data submissions to the Overall PI on the OnCore case report forms per timeline guidance mentioned in section 7.3.3 **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. STUDY CALENDAR

Baseline (pre-study) evaluations will be conducted within 2 weeks prior to start of protocol therapy. Scans and x-rays must be done ≤ 46 weeks prior to the start of therapy. If the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	**Treatment Period** (continues until radiologic progression or unacceptable toxicities or 24 months, whichever comes first)	**Cycle 1 Day 15**	**Off Treatment Visit (within 30 days)**	**100-days Safety Visit** (+/- 14-days)	**Follow-Up** Every 6 mos up to max of 3 years from on-study
Informed Consent	R					
Demographics	R					
HCG [1]	S					
Concomitant Medications	← ---------- R ----------→			R	R	
Adverse Event evaluation [11]		Q 4 weeks *,***		R	R [12]	
Rucaparib, 600 mg PO BID		Daily *,***				
Nivolumab, 480 mg IV q4 wks		Q4 weeks *,***				
Pill Diary (Ruca)		R		R		
Medical History	S					
Physical Exam	S	*Per S*			S	
Vital Signs	S	*Per S*			S	
Height	S					
Weight	S	*Per S*				
ECOG Performance Status	S	Q 4 weeks *,***		R	S	
CBC w/diff [2]	S	Q 4 weeks *,**		S	S	
Serum chemistry [3, **]	S	Q 4 weeks *,**	R [3,4]	S	S	
EKG [5]	R	As clinically indicated				
Smoking Status	R					
Imaging						
CT Chest w. contrast	S/R	Q 8 weeks *,***		S, as clinically indicated		
CT Abdomen w. contrast	S/R	Q 8 weeks *,***				
Bone scan		As clinically indicated				
Patient-Reported Outcomes (Quality of Life) [6]	R	R [6]				
PBMCs collection for Flow Cytometry studies (BPTP SRF, Cohen lab) [7]	R	At Cycle 3, Day 1				
TP53 assay - blood collection: One 10mL streck tube (Kolesar lab) [8]	R	Also collected at 2-months, at 4-months; and, if applicable, at the time of disease progression.				

Check status of enrollment to ORIEN Protocol for Tumor Whole Exome Sequencing and Germline Mutation Testing [9]	R [9]					
Survival Status [10]						R [10]

S = standard of care / R = research-related activity / QOL = quality of life
*: A scheduling window of ± 7 days exists to accommodate adverse weather, holidays, or other issues.
** These tests are not required on the Cycle 1 Day 1 visit IF evaluated during the participant's pre-study visit.

*** : dose delays could move the visit windows out of the 7-day allowance – this will be noted in the eCRF and dates adjusted as needed.

1 : to ascertain eligibility of sexually active female patients who are pre-menopausal/of child-bearing potential (serum or urine pregnancy test).

2: CBC with diff as per Standard of Care. Only recording results for the following labs in the eCRF: ANC, Absolute lymphocytes, WBC, Platelets, and Hemoglobin.

3: CMP Panel includes SGOT [AST], SGPT [ALT], total bilirubin, creatinine, Albumin, alkaline phosphatase, bicarbonate, BUN, calcium, chloride, TSH, glucose, potassium, total protein, sodium.

4 : Cycle 1 Day 15, CMP in order to assess liver function. Only AST/ALT will be recorded in the eCRF.

5 : EKG at baseline, and as clinically indicated during active treatment.

6: Patient-Reported Outcomes assessing quality of life comprise two complementary, validated, standardized questionnaires, the EORTC QLQ-C30 and LC13. These two questionnaires will be administered at baseline (pre-treatment), at 4-months (with a +3 week window to allow this to be collected in the course of a regularly scheduled clinic visit), and at the time of disease progression (if greater than 4-months).

7: PBMCs for Flow Cytometry; collected for Biospecimen SRF. Each sample consists of two 8 mL BD Vacutainer CPTs with Sodium Citrate, so 16 mL is collected at pre-study, and again at Cycle 3, Day 1 (+/- 7-day study visit windows per *).

8: One 10 mL whole blood draw in streck tube up to a total of at 4 timepoints (i.e., 4 total samples collected). The timepoints for collection comprise: Pre-study; twice during active treatment (approximately every 2 months, e.g., Cycle 3 Day 1, and Cycle 5 Day1), and at time of disease progression.
Samples will be processed by Dr. Kolesar's lab.

9: Checking status of enrollment on ORIEN protocol, 17-MTB-01 (Yes/No status for each patient on-study).

10: **Survival Status** – patients are in follow-up up to 3 years post-registration. Survival will be checked every 6-months (once patient is off-treatment) up to a total of 3 years post-registration. Survival Status can be ascertained via clinic visit or phone calls.

11: Additionally, S/AEs will be reported per protocol, 100-days after the last dose of study drug.

12: **Nivolumab and Rucaparib 100-days Safety Visit reporting window**: Adverse Events for Nivolumab and Rucaparib will be monitored and reported for a 100-day period after Off-Treatment (i.e., the last dose of Nivolumab and Rucaparib per protocol). The 100-day safety visit allows a study visit window of +/- two-weeks to capture late sequelae of Nivolumab and Rucaparib, as well as any other ongoing treatment-related S/AEs).

9. MEASUREMENT OF EFFECT

9.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every *8* weeks per standard of care.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised RECIST (version 1.1) [45]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST V1.1 criteria.

9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of first dose of study medication.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, and have received at least 75% of the intended doses of cycle 1 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.)

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

9.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm (≥1 cm) with CT scan or MRI. 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 (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. In addition, bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable disease.

Note: Simple cysts, defined as cystic lesions that meet the criteria for radiographically defined simple cysts, should not be considered malignant lesions (neither measurable nor non-measurable).

Conversely, 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. *However, if* non-cystic lesions are present in the same patient, the preferred category is as target lesions.

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 will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, AND additionally should be lesions that lend themselves to reproducibly repeated measurements. For instance, if the largest lesion does not lend itself to reproducible measurement, then the next largest lesion which can be measured reproducibly should be selected as a target lesion.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Additional measurement of these non-target lesions is not required, but the presence, absence, or in rare cases unequivocal progression of each non-target lesion should be noted throughout follow-up.

9.1.3 Methods for Evaluation of Measurable Disease

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

9.1.4 Response Criteria

9.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes

(whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

9.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or PI).

9.1.4.3 Evaluation of Best Overall Response

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

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	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	

*See RECIST V1.1 manuscript for further details on what is evidence of a new lesion.
**Only for non-randomized trials with response as primary endpoint.
***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.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

*'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

10. DATA REPORTING / REGULATORY REQUIREMENTS

10.1 Data Reporting

10.1.1 Method

This study will require data submission and reporting via the OnCore Database, which is the official database of the MCC CRO. Instructions for submitting data is listed in Study-Specific Data Management Plans (DMP) created by the CRO staff.

10.1.2 Responsibility for Data Submission

Study staff are responsible for submitting study data and/or data forms to OnCore as per the MCC CRO's SOPs. This trial will be monitored by the MCC DSMC on a schedule determined by PRMC at its initial review. The CRO staff are responsible for compiling and submitting data for all participants and for providing the data to the PI for review.

11. STATISTICAL CONSIDERATIONS AND DATA MANAGEMENT

11.1 Study Design and Sample Size

A single arm Phase II trial will be performed using FDA approved single agent dosage for both nivolumab and rucaparib. We will estimate the proportion of patients who exhibit PFS at 6 months. Based on a phase III randomized clinical trial conducted by ECOG, the historical median PFS for Stage IV SCLC, post platinum doublet in platinum sensitive patients, is 2.3 months in the observation arm vs 3.6 month on maintenance topotecan arm [23]. Assuming that the proportion who exhibit PFS at 6 months is 50%, a sample of 36 patients produces a one-sided 90% confidence interval with a lower limit equal to 38%, providing some evidence of efficacy.

11.2 Data Analysis

Analysis of Primary and Secondary Endpoints

Progression-free survival will be estimated using the Kaplan-Meier curve and the proportion who do not exhibit PFS at 6 months and at other specific timepoints will be calculated along with confidence intervals. The median PFS and confidence interval will also be calculated. Other time to event endpoints including OS will be estimated using the same methods. The disease control rate, objective response rate and best overall response rate will be estimated, along with exact 95% binomial confidence intervals.

Immune markers including percentage of CD4 T cells and CD8 T cells expressing PD-1 and Ki-67, expression of CD101 and CD38 will be summarized descriptively at baseline and at each time point of evaluation. The change from baseline will also be calculated and compared using paired test statistics. QOL measures will also be summarized using descriptive statistics.

Analysis of baseline whole exome sequencing data (where available) will be performed in the Biostatistics and Bioinformatics Shared Resource at MCC. Customized data processing and data

analysis pipelines will be applied and exploratory comparisons of mutation data with response and clinical outcomes will be performed using Fisher's exact test with control for false discovery rate (FDR).

11.3 Data Management

The study statistician and staff from the MCC Biostatistics and Bioinformatics Shared Resource Facility will work closely with the study team, the Clinical Research Office, and the Cancer Research Informatics Shared Resource Facility to implement several aspects of data management for this trial. This will include development of eCRFs in the Oncore system, trial-specific processes for data entry, generation of reports, data management and statistical analysis. Specifically, the statistician will attend several meetings including the eCRF development meeting, the data management process meeting and the protocol initiation meeting. Appropriate and accurate collection of primary and secondary study endpoints and inclusion of valid values and range checks for data fields will be designed for the eCRFs. The OnCore clinical trial management system, managed by MCC CRO and Cancer Research Informatics Shared Resource Facility, will be the primary database repository of clinical data from all patients enrolled into this trial. Data will be accessed by the study statistician on a regularly scheduled basis to perform statistical programming for conduct of data quality control, data management, generation of interim reports and statistical analysis. In collaboration with the study team, procedures will be developed for data quality control timelines, resolution of data queries, interim reporting and final data analysis.

A protocol-specific DMP will be authored by a senior data manager in collaboration with the biostatistician and the CRO, each team will be expected to review and sign off on the DMP prior to finalization. In order to maintain best clinical practices in data management, the DMP may include, but is not limited to, CRF/eCRF design, database build and design, database training, edit check/validation specifications, study database testing/release, data and paper workflow, report, metrics, query/discrepancy management, management of external (including lab) data, medical coding, SAE handling/reconciliation, data transfers and database lock. The protocol specific DMP will additionally define the schedule at which data will be accessed by study statisticians to perform statistical programming for conduct of data quality, data control, data management, generation of interim reports and statistical analysis. Cross-team members will collaborate to establish procedures and timelines for quality control, audits, query resolution, interim and final data analysis.

12. CORRELATIVE STUDIES

12.1 Immune studies:

Two 8.0 ml BD Vacutainer® CPT™ Mononuclear Cell Preparation Tubes - Sodium Citrate will be drawn prior to treatment (on the day of treatment) and 2 weeks after treatment (per study calendar). This should yield up to 16 million PBMCs for each blood draw that will be analyzed by flow cytometry. We will evaluate three different sets of immune cell markers to identify clinical benefit.

12.1.1 Percentage of CD4 T cells and CD8 T cells expressing PD-1 and Ki-67.

- Increased circulating blood levels of Ki-67, PD-1 expressing T cells is a predictor of clinical benefit while on anti-PD-1 therapy. A positive signal will be an increased in cells expressing Ki-67, PD-1 on CD4 and CD8 T cells while on treatment compared to the pre-treatment sample

[47].

12.1.2 Percentage of polyfunctional effector CD4 T cells and CD8 T cells (CD101+ and CD38+) producing IFNγ and TNFα.

- Polyfunctional T cells expressing multiple cytokines have been shown to have enhanced anti-tumor activity and CTLA-4 blockade increased the number of polyfunctional T cells in patients with metastatic melanoma. [48]

12.1.3 Percentage of effector CD4 T cells and CD8 T cells expressing CD38, HLA-DR, CD28, ICOS, CD27, and low Bcl2 levels.

- Patients responding to anti-PD-1 therapy have an increase in proliferating effector T cells defined by expression of CD38, HLA-DR, CD28, CD27, ICOS, and low Bcl2 levels.

The part of the study is based on peripheral blood to assess immune activation. The following steps for processing and cryopreservation of blood samples listed below are to be performed in Flow Cytometry and Cell Sorting Shared Resource Facility (FCCS SRF). FCCS provides flow cytometric analysis and cell sorting as well as human immune monitoring services. These services include blood processing and cryopreservation of PBMC. All samples cryopreserved by the FCCS are then banked and managed by the Biospecimen Procurement and Translational Pathology Shared Resource Facility (BPTP SRF) until all samples for a subject have been collected. Once all samples are collected, all stored samples for a subject will be thawed and analyzed simultaneously by the FCCS to obtain correlative endpoints as described above. Data analysis will be performed by Dr. Cohen with members of his laboratory along with review and discussion of data with Drs. Jerry Woodward (Co-director FCCS) and Aman Chauhan.

Isolation of Mononuclear Cells from Peripheral Blood

- 15 ml of blood will be collected from patients at the indicated times (Whole Blood tube w/ Anticoagulant, BD Vacutainer™ CPT™ Tube with Sodium Citrate). Blood collection will be performed in clinic and handed to FCCS staff.
- The FCIM group will perform the following steps to process the samples for cryopreservation.
  - Centrifuge at 400 x g for 30 minutes at room temperature
  - Aspirate buffy coat at interface, resuspend cells in sterile saline and wash by centrifugation. Repeat wash procedure twice.
  - Resuspend pellet containing PBMCs in ice cold 100% fetal calf serum (FCS)
  - Determine cell concentration and viability
  - Perform flow cytometry analysis on one fresh aliquot and store remainder on ice for cryopreservation by FCCS.

NOTE: PBMCs from all blood collections from each patient will be cryopreserved by the FCCS and banked by the BPTP SRF until all blood collections are completed. Flow cytometric analysis by the FCCS SRF will be performed on fresh samples as they are collected and in bulk on all cryopreserved samples per patient.

- Following determination of cell number and viability, PBMCs in FCS will be adjusted to a

concentration of 2 x 10^6 viable cells/ml.

- 2 x 10^6 viable cells will be added to cryopreservation vials containing DMSO to obtain a final concentration of 10% DMSO.
- Vials will be transferred to cryopreservation containers for slow freezing in a -80°C freezer.
- Following overnight freezing, vials will be transferred to liquid nitrogen freezers maintained by the BPTP SRF for banking until all patient blood samples are collected.

Activation of Peripheral Blood Mononuclear Cell (PBMC) for Intracellular IFNγ and TNFα detection (performed by FCCS SRF).

- Culture 2 x 10^6 freshly thawed PBMC will be incubated for 5 hours in 37^{o}C incubator in complete RPMI medium containing PMA (50ng/ml) and Ionomycin (1ug/mL), plus Brefeldin A to activate cells
- Cells will then be washed by centrifugation and then stained as follows for flow cytometry analysis:
- Suspend cells in FACS buffer (PBS, 1% BSA, sodium azide [0.01%]) at a concentration of 10^7 cells per ml
- Add Fc Block to all tubes and incubate for 10 minutes on ice
- Add all of the indicated fluorochome-labelled antibodies for surface membrane staining as indicated in antibody panels below (**Table**)
  - Anti- human CD3, CD4, CD8 (T cell subset markers)
  - Anti-human CD38, CD101 (effector T cell markers)
  - Anti-human CD27, CD28, Bcl2, HLA-DR, ICOS (activation markers)
  - Anti-human CD279 (PD-1)
- Incubate on ice in the dark for 30 minutes
- Wash cells twice with PBS+Azide to remove excess antibody
- Fix and permeabilize cells (paraformaldehyde/saponin)
- Stain cells for intracellular IFNγ and TNFα with fluorochrome-labeled anti-human IFNγ and TNFα antibodies or Ki-67
- Wash cells by centrifugation and resuspend in FACS buffer for flow cytometry analysis

Flow cytometric analysis (performed by FCCS SRF).

- Set the flow cytometer on the following gates
  - Live cell gate
  - Lymphocyte gate
- Set the following fluorescent gates on the live lymphocyte population
  - $CD3^+$, $CD4^+$ to identify helper T-cells
  - $CD3^+$, $CD8^+$ to identify cytotoxic T-cells
- Analyze both the helper T-cell and cytotoxic T-cell subpopulations for expression of the following
  - Surface expression levels of CD27, CD28, Bcl2, HLA-DR, ICOS, CD38, CD101, and PD-1
  - Intracellular expression levels of IFNγ and TNFα

Flow Cytometry Antibody Panels for PD-1/PARP	
Panel #1 (Fresh blood)	Panel #2 (Cryopreserved blood)
CD3	CD3
CD4	CD4
CD8	CD8
PD-1	CD38
Ki-67	CD101
CD27	PD-1
CD28	IFN gamma
CD38	TNF alpha
Bcl-2	Viability dye
HLA-DR	
ICOS	
Viability dye	

Analysis and storage of flow cytometric data (performed by FCCS SRF).

- Flow cytometric data will be analyzed using FlowJo analytical software to determine the percentage of T cell subsets ($CD4^+$ and $CD8^+$) which express surface and intracellular biomarkers as indicated above.

- Calculated results for each patient and blood collection will be recorded in an Excel spreadsheet. Note: patients will be identified only with the unique code assigned for each patient.

Spreadsheet containing all results will be stored in a private folder on Dr. Cohen's UK server site, which UK backs up daily.

- Raw flow cytometry data and spreadsheet containing calculated results will also be submitted to the OnCore Database, the official database of the MCC CRO, as required.

Only the following individuals will have access to the results in the private folder of Dr. Cohen: Dr. Chauhan, Dr. Weiss, and the biostatistician assigned to the study.

Analytical procedures

Patient PBMCs will be analyzed by the FCCS SRF for the percentage of cells expressing each marker and for the mean fluorescence intensity for each marker. PBMC samples will be analyzed on a Beckman-Coulter CytoFLEX LX cell analyzer with 19 color detection capacity. Flow cytometric data sets will be interpreted by the MCC Biostatistics and Bioinformatics Shared Resource Facility by computational flow cytometry using SPADE algorithm to automatically identify populations.

12.1.4 Assessment of baseline tumor mutational burden and correlation with radiological response.

All patients enrolled in the study will be assessed as to whether they have also enrolled on the Markey Cancer Center Total Cancer Care (ORIEN protocol; Yes/No status will be documented in the eCRF).

- Patients enrolled on ORIEN protocol undergo whole exome sequencing of tumor tissue (at baseline, and progression, when available) and germline mutation testing via peripheral blood or buccal swab. Genomic profiling will be done under Markey Cancer Center Total Cancer Care (ORIEN) protocol, wherein all consenting patients treated at MCC are sequenced. Genomic testing is funded by the ORIEN protocol.

For our on-study patients who are also co-enrolled in ORIEN (participant status is "Yes"), we will study patterns of tumor mutation burden and correlate genomic data to durability of treatment response and treatment resistance patterns using bioinformatics pipelines developed by the Biostatistics and Bioinformatics Shared Resource Facility at Markey.

12.1.5 The ORIEN Total Cancer Care is a very large clinical research protocol and data are stored within the Moffitt Data Warehouse (DW). For further details, please visit www.oriencancer.org.

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APPENDIX A. ECOG PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Descriptions
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 out any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B. ADVERSE EVENTS LIST FOR RUCAPARIB

Rucaparib Side Effects

The following is a list of reported side effects as well as other notable side effects considered to be possibly due to rucaparib, as reported by physicians about their patients who are taking rucaparib alone:

Very common (Occurring in 10% or more of patients)

• Nausea

• Feeling tired

• Low Blood Counts (red blood cells, white blood cells, and platelets). Sometimes fever occurs with the low blood counts. These low blood count effects may be more likely to occur after multiple cycles of treatment.

- A low red blood cell count may make you feel tired or dizzy. If you feel dizzy while taking rucaparib, you should avoid potentially hazardous tasks such as driving or operating machinery.
- A low white blood cell count puts you at higher risk for bacterial or viral infection. Having a high temperature or fever while your white blood cell count is low is a medical emergency and you must proceed to the nearest emergency room as soon as possible
- A low platelet count affects the ability of your blood to clot and could lead to bleeding events. Symptoms include but are not limited to easy bruising, prolonged bleeding from cuts, blood in stools or urine, or nose bleeding. It is possible that rucaparib may make your skin and eyes more sensitive to sunlight. You should take all of the usual sun protection precautions when going outside. It is advised that you avoid excessive sun exposure, wear protective clothing (including wearing a hat and sunglasses), and use sunscreen regularly (sun protection factor 50 or greater).

• A low phosphate level in your blood. Usually there are no symptoms but if the levels are critically low, you may notice trouble breathing, confusion, muscle weakness, or irritability.

• Increase in cholesterol. If your cholesterol increases significantly, your doctor may prescribe a medicine to lower your cholesterol level.

• Changes in kidney and liver function blood tests. These changes will be evaluated by your study doctor along with any other side effects that you are experiencing as well as other test results.

• Changes in your sense of taste.

• Stomach-related effects such as constipation, vomiting, diarrhea, decreased appetite, stomach pain (epigastric pain), and indigestion.

• Difficulty breathing

• Dizziness

• Photosensitivity reaction

• Fever sometimes can occur independent of a low blood count. If you experience elevation of your temperature, please refer to your study doctor for fever management.

• Difficulty sleeping

Common Side Effects of Rucaparib (Occurring in 1% to less than 10% of patients)

• Rash, which will appear as changes in your skin color (e.g. redness) and texture (e.g. bumps, blisters, peeling). Some rashes may be itchy, painful, or cause no symptoms at all. This can vary in severity from mild to severe.

• Upper airway infection (like the common cold). You may experience infections involving the nose, pharynx, larynx, and sinuses. Symptoms include a blocked (congested nose, a runny nose, and sneezing. You may also have clear discharge (mucus) from the nose. You may feel generally unwell and may also be associated with fever. Treatment is usually supportive but if symptoms persist please inform you doctor.

• Hand-Foot Syndrome (Palmar-plantar erythrodysaesthesia syndrome) When a small amount of drug leaks out of the blood vessels, it damages the surrounding tissues. Symptoms would include tingling, burning, redness, flaking, swelling, blistering, and sores of the hands and feet due to the increased friction and heat your extremities are exposed to. If you experience these symptoms, apply ice packs and elevate hands and feet, then contact your study doctor immediately for treatment.

Uncommon Side Effects of Rucaparib (Occurring in 0.1% to less than 1% of patients)

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML)[a] have been reported in a very small number of patients treated with rucaparib during the safety period (while on treatment with rucaparib and 28 days after last dose). MDS is a pre-cancerous condition where the bone marrow is not as good at producing blood cells (red and/or white blood cells and/or platelets). People with MDS may need transfusions (red blood cells and/or platelets) and/or other treatments. In some cases, MDS can progress to AML, which is a cancer of the bone marrow where more abnormal and immature white blood cells (also called blasts) are made than normal white blood cells. People with AML need treatment with chemotherapy and/or a bone marrow transplant. Patients may develop AML without first being diagnosed with MDS.

Events of MDS and AML have also been reported with PARP inhibitors similar to rucaparib. At this time, it is not known whether rucaparib or other PARP inhibitors cause MDS or AML, or if these developed as a result of previous chemotherapy these patients received. Your study doctor will closely monitor your blood cell levels during treatment. If he/she has any concerns about your blood counts you may be asked to have a biopsy of your bone marrow.

a These risks have not yet been determined by Clovis as related to rucaparib. Some of these risks have been reported in a high frequency of patients in clinical trials involving rucaparib (e.g. itchy skin, rash), others have been reported in a small number of patients but pose significant risk (e.g. MDS/AML) or are generally known to be caused by other anti-cancer treatments (e.g., palmar-plantar erythrodysaesthesia).

APPENDIX C. ADVERSE EVENTS LIST FOR NIVOLUMAB

Nivolumab Side Effects

Very common: (Occurring in 10% or more of patients)

- Diarrhea
- Fatigue
- Itching
- Rash

Common: (Occurring in 1% to fewer than 10% of patients)

- Abdominal pain
- Alkaline phosphatase increased: lab test result associated with liver or bone abnormalities
- Allergic reaction/hypersensitivity
- ALT Increased: lab teste result associated with abnormal liver function
- Amylase increase: lab test associated with pancreas inflammation_
- AST Increased: lab teste result associated with abnormal liver function
- Bilirubin (liver function blood test) increased
- Chills
- Constipation
- Cough
- Creatinine increased: lab test associated with abnormal kidney function _
- Decreased appetite
- Dizziness or vertigo (feeling off balance, which can lead to dizziness)
- Dry skin
- Fever
- Headache
- High Blood Pressure
- Increased Blood Sugar
- Inflammation of the colon
- Inflammation of the mouth
- Infusion related reactions
- Joint pain or stiffness
- Lipase increased: lab test result associated with pancreatic inflammation
- Loss of color (pigment) from areas of skin
- Lung inflammation (pneumonitis—see details below)
- Musculoskeletal pain
- Nausea

• Redness (of the skin)
• Shortness of breath
• Sodium levels in the blood low
• Swelling including face, arms, legs
• Thyroid gland function decreased/thyroid stimulating hormone increased (lab test associated with abnormal thyroid function)
• Thyroid gland function increased
• Tingling, numbness, burning or weakness
• Upper respiratory tract infections
• Vomiting

Uncommon Side Effects of Nivolumab: (Occurring in 0.1% to less than 1% of patients)

• Adrenal gland function decreased
• Bronchitis
• Cranial nerve disorder
• Diabetes
• Dry eyes and/or blurred vision
• Hair loss
• Heart rate increased
• Hear rhythm abnormal
• High blood pressure
• Hives
• Inflammation of the eyes
• Inflammation of the kidney
• Inflammation of the pancreas
• Inflammation of the pituitary gland
• Inflammation of the stomach, intestines, colon
• Inflammation of the thyroid gland
• Liver inflammation
• Low Blood pressure
• Lung infiltrate associated with infection or inflammation
• Pituitary gland function decreased
• Psoriasis, a skin condition characterized by scaly patches of skin.
• Kidney failure or kidney injury
• Respiratory failure

Rare: [Occurring in 0.01% to less than 0.1% of patients]

• Anaphylactic reaction (severe allergic reaction)

- Damage to the protective covering of the brain, nerves and spinal cord.
- Diabetes complication resulting in increased blood acid and diabetic coma
- Guillain-Barre syndrome, an autoimmune disorder associated with progressive muscle weakness or paralysis
- Inflammation of blood vessel
- Inflammation of the brain, potential life threatening or fatal
- Inflammation of the heart
- Muscle inflammation
- Myasthenic syndrome (neurologic syndrome characterized by muscle weakness) including myasthenia gravis, a nerve disease that may cause weakness of eye, face, breathing, and swallowing muscles.
- Pemphigoid: blistering of the skin or mouth caused by the immune system attacking healthy tissue.
- Rhabdomyolysis: muscle fiber released into the blood stream, which could damage your kidneys
- Rosacea: acne-like skin condition resulting in redness of face
- Sarcoidosis, a disease involving abnormal collections of inflammatory cells (granulomas) in organs such as lungs, skin, and lymph nodes
- Stevens Johnson syndrome: inflammatory disorder of skin and mucous membranes, resulting in blistering and shedding of skin
- Toxic epidermal necrolysis: a potentially fatal disease characterized by blistering and peeling of the top layer of skin resembling a severe burn
- Histiocytic necrotizing lymphadenitis or Kikuchi lymphadenitis: disorder of the lymph nodes, which causes the lymph nodes to become enlarged, inflamed and painful, commonly affecting lymph nodes of the neck and possibly associated with fever or muscle and joint pains.
- Vogt Koyanagi Harada syndrome; a disease that affects the pigmented tissue; this may affect the eye, leading to swelling, pain and/or blurred vision; the ear, leading to hearing loss, ringing in the ears; and /or the skin, leading to loss of skin color

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported in those treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue. Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation.

APPENDIX D. PATIENT-REPORTED OUTCOMES: QUALITY OF LIFE MEASURES

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_|_|_|_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_|_|_|_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week : Not at	**All**	**A Little**	**Quite a Bit**	**Very Much**
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4
If yes, where _____				

43. Did you take any medicine for pain?

1 No **2 Yes**

If yes, how much did it help?	1	2	3	4