MSK PROTOCOL COVER SHEET

Phase II Study of Rucaparib and Nivolumab in Patients with Leiomyosarcoma

Principal Investigator/Department: Sujana Movva, MD

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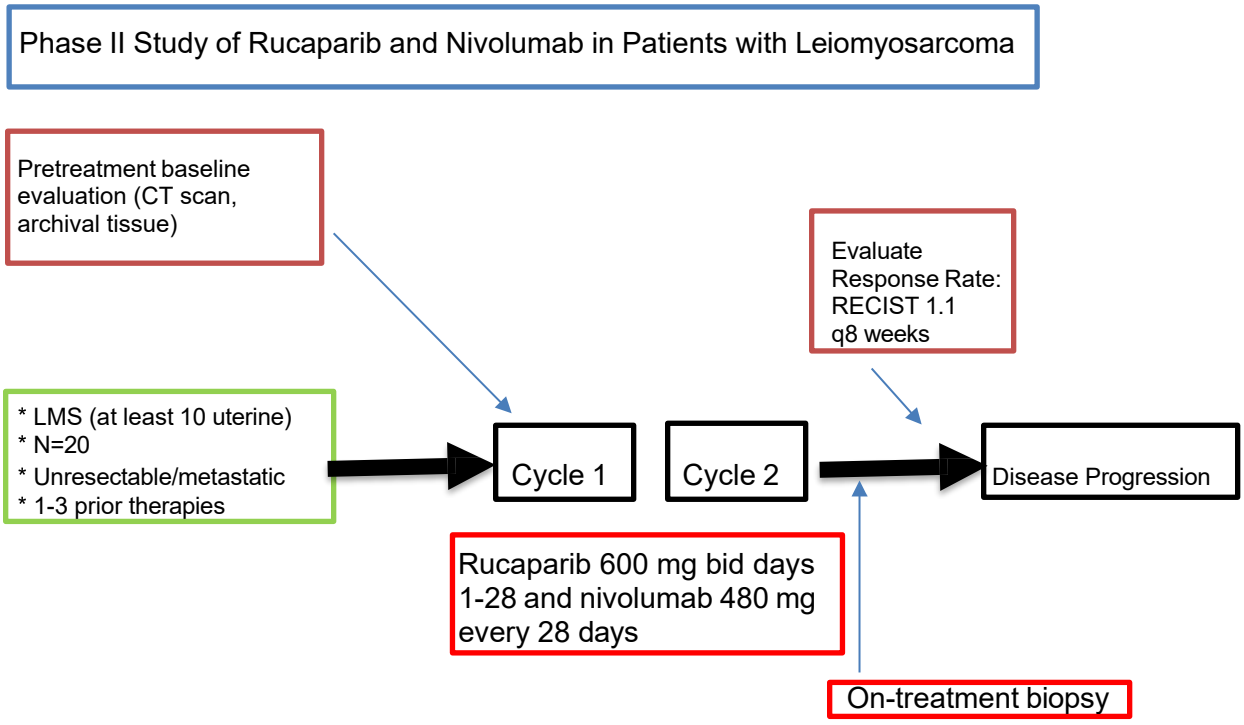
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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

PARP inhibition has been shown to have clinical activity and benefit in cancer types such as ovarian cancer, both in the presence and absence of BRCA 1 and 2 mutations.[1] It is hypothesized that dysfunction in other genes involved in the DNA damage response (DDR) may also confer sensitivity to PARP inhibition. Interrogation of our genomics portal generated by the MSK-IMPACT assay suggests that twenty percent of patients with leiomyosarcoma (LMS) have alterations in genes related to DDR. Studies of PARP inhibitors alone and in combination with chemotherapy are ongoing in LMS. Leiomyosarcomas are immunogenic neoplasms with a need for more therapeutic options. Despite sound pre-clinical rationale initial testing of checkpoint inhibitors in this disease have demonstrated stable disease without objective responses.[2,3] Recent investigation has revealed a wide immunological role for ADP-ribosylating enzymes such as PARP. PARP inhibition elicits its anti-cancer immunity by increasing intratumoral immune cell infiltration, and increasing the activities of the stimulator of interferon gene and interferon pathways.[4] Pre-clinical research demonstrated increased therapeutic efficacy in-vivo by combining a PARP inhibitor and anti-PD-L1 therapy compared to either agent alone.[5,6] Therefore, therapy with a PARP inhibitor, such as rucaparib in combination with a PD-1 inhibitor such as nivolumab could trigger antitumor immune responses in patients with LMS. This provides scientific rationale for clinical investigation of the combination of PD-1 blockade and PARP inhibition in patients with advanced LMS. The primary objective of this study is to evaluate the efficacy of a PARP inhibitor rucaparib given in combination with anti-PD-1 monoclonal antibody nivolumab in patients with advanced LMS. Secondary and exploratory objectives include demonstrating the safety and tolerability of this combination, determining the progression free survival (PFS) and overall survival (OS) in LMS patients treated with this combination and to identify biomarkers of response.

This is a Phase II open label study evaluating the combination of rucaparib and nivolumab in patients with refractory LMS. A total of 20 patients will be accrued, of which at least 10 patients will have a uterine LMS. Eligible patients should have had at least one prior therapy for unresectable or metastatic disease, but no more than 3 prior lines of therapy. Treatment naïve patients may be enrolled if they have refused standard systemic treatment. The purpose of this study is to determine the anti-tumor activity of this doublet therapy. Study drug administration will continue until disease progression, unacceptable toxicity or withdrawal of consent. All patients will need to have adequate archival tissue in order to be eligible as retrospective analysis will be performed on tissue samples to determine the association between DDR gene alterations and clinical response. Expected accrual is 1-2 patients per month.

Figure 1. Study Schema



The hypotheses for this study include:

Primary Hypothesis

Rucaparib given in combination with nivolumab, will ellicit an enhanced anti-tumoral response in patients with advanced LMS as assessed by RECIST 1.1

Secondary Hypotheses

1. Rucaparib given in combination with nivolumab will be safe and well tolerated in subjects with advanced LMS
2. Rucaparib given in combination with nivolumab will improve progression free survival and overall survival in patients with advanced LMS
3. Rucaparib given in combination with nivolumab will elicit an enhanced anti-tumoral response in patients with advanced LMS as measured by immune-related RECIST criteria (irRECIST)
4. In responding patients treated with rucaparib in combination with nivolumab an enhanced duration of response by RECIST and irRECIST will be demonstrated

Exploratory hypotheses

1. Rucaparib will activate antitumor immune responses in LMS, sensitizing these tumors to immune checkpoint inhibition with nivolumab regardless of BRCA status
2. Rucaparib given in combination with nivolumab will have activity in LMS irrerespective of site of primary tumor (e.g soft tissue LMS versus uterine)
3. Rucaparib given in combination with nivolumab therapy will interact with immune related characteristics of tumor tissue and peripheral blood in ways that may correlate with clinical outcome.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective:

1. To evaluate the efficacy of a PARP inhibitor rucaparib given in combination with anti-PD-1 monoclonal antibody nivolumab in patients with advanced LMS, as assessed by the best objective response rate (complete response + partial response) by RECIST 1.1

Secondary Objecitves:

1. To assess the safety and tolerability of rucaparib given in combination with nivolumab in patients with advanced LMS
2. To determine the progression free survival (PFS) rate at 24 weeks and overall survival (OS) for patients treated with rucaparib given in combination with nivolumab
3. To evaluate the efficacy of rucaparib given in combination with nivolumab in patients with advanced LMS as measured by immune-related RECIST criteria (irRECIST)
4. To evaluate the duration of response by RECIST and irRECIST among the responders treated with rucaparib given in combination with nivolumab

Exploratory Objectives:

1. To determine in an exploratory manner the relationship between DDR alterations (germline and somatic) and clinical outcome in patients with LMS treated with rucaparib and nivolumab
2. To compare in an exploratory manner the clinical activity of the combination of nivolumab and rucaparib, number of DDR alterations and immune-related biomarkers in LMS of soft tissue versus uterine origin
3. a) To evaluate the association between selected immune-related biomarkers measured in serial peripheral blood and with clinical efficacy, including immunophenotyping and Functional Analyses, evaluation of serum levels of chemokines, cytokines and other immune mediators, and characterization of T-cell receptor clonality in peripheral blood.

b) To assess the potential effect of rucaparib and nivolumab on selected biomarker expression measured in pre- and post-treatment tumor tissue and the association between these biomarkers and with clinical outcome, including characterization of PD-1/PD-L1 expression, tumor infiltrating lymphocytes (TILs) and tumor antigens, gene expression profiling and characterization of T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL).
c) To evaluate the association between baseline tumor mutational burden and neoantigen production on post-treatment samples with clinical efficacy of the study therapy.
d) To evaluate levels of genomic changes in circulating tumor DNA, collected at baseline and regular intervals during treatment and correlate with clinical outcome to rucaparib and nivolumab
e) To evaluate roles of Schlafen11 (SLFN11), PARP and gamma-H2AX as markers of response and reistance to rucaparib and nivoluamb

3.0 BACKGROUND AND RATIONALE

Leiomyosarcoma: Scope of Disease

Soft tissue sarcomas (STS) are uncommon tumors of the connective tissue with an incidence of approximately 12 000-14 000 new cases per year. Leiomyosarcoma (LMS) is one of the most common subtypes of STS and represents approximately 10% to 20% of these cases.[7] LMS is a tumor of smooth muscle origin, and common sites of presentation are the extremities, blood vessels, uterus or retroperitoneum. Despite optimal treatment, up to 50% of patients with LMS develop metastatic disease. In this setting, treatment with standard chemotherapy results in a response in 10-40% of patients and the average survival is 18 months. Importantly, patients with sarcomas are young, with a median age at diagnosis 10 years younger than in other cancers. Therefore, discovery of new and effective therapies without harsh toxicities impacting quality of life are of utmost importance in this disease.

PARP inhibition in cancer

Poly ADP-ribose polymerase (PARP) represents a family of at least 17 enzymes, two of which (PARP1 and PARP2) play important roles in DNA repair. PARP assists in the repair of single strand DNA breaks via the base excision repair pathway. PARP also interacts with the pathways involved in double strand DNA repair namely, the homologous recombination (HR) and non-homologous end-joining (NHEJ) pathways.[8] Isolated PARP inactivation does not lead to cell death, since overlapping mechanisms of DNA repair, may restore DNA



integrity.[9] Hence, concurrent events are required to induce genomic instability and cell death, in a concept named “synthetic lethality”. In BRCA1- and BRCA2- deficient cells, HR is defective and concurrent treatment with PARP inhibition in vitro was shown to results in cell cycle arrest and apoptosis.[10] Proof of concept phase II studies subsequently confirmed activity for PARP inhibition in breast and ovarian cancer patients with known BRCA1 and 2 mutations.[11,12] In 2014 the U.S. Food and Drug Administration (FDA), approved olaparib for the treatment of germline BRCA-mutant advanced ovarian cancer.[13] Niraparib, recently demonstrated significant improvement in PFS in ovarian cancer patients with recurrent platinum-sensitive ovarian cancer irrespective of BRCA mutational status.[1] It is hypothesized that dysfunction in other genes involved in DDR may also confer sensitivity to PARP inhibition.[14] Furthermore, it appears that PARP inhibition mediated modulation of the tumor immune microenvironment contributes to its therapeutic effects independently of *BRCA1/2* mutations. Rucaparib, has been FDA-approved as maintenance therapy for ovarian cancer regardless of BRCA mutational status, after demonstrating improvement in PFS in patients with mutations in non-BRCA genes such as CHEK2, RAD51C, RAD51D and RAD54L.[15]

DNA damage repair and response gene alterations and Leiomyosarcoma

Alterations in BRCA1/2 genes, including loss or mutation have reported frequencies of 20-80% in LMS.[16,17] More recently, whole exome sequencing has suggested that alterations in DDR genes are more common in LMS compared with other sarcomas.[18] Deleterious aberrations in multiple homologous recombination repair genes including PTEN(57%), BRCA2(53%), ATM(22%), CHEK1 (22%), XRCC3 (18%), CHEK2 (12%), BRCA1(10%), RAD51 (10%), and FANCA (27%) and FANCD2 (10%) have also been reported.[19] Trabectedin, a DNA damaging alkylating agent, with particular activity in LMS has been shown to be synergistic with PARP inhibitors in both cell lines and xenograft models. In a phase I dose finding study of olaparib and trabectedin in patients with a wide variety of sarcoma, five patients with LMS experienced a benefit of 6 months or longer.[20]

We retrospectively reviewed data on LMS patients treated at MSKCC who had targeted somatic DNA sequencing (MSK-IMPACT) performed on tumor tissue. A total of 33 DDR genes, including 16 HR genes, were analyzed for oncogenic alterations. A composite HR deficiency (HRD) score measured tumor genomic scarring for each patient. To determine if DDR pathway alteration was prognostic of outcome, we analyzed the recurrence-free survival (RFS) of patients who underwent complete resection, and the OS of the whole cohort. Of the 211 LMS patients who underwent MSK-IMPACT testing between March 2014 and October 2018, 20% of patients had an oncogenic DDR pathway alteration, 72% of which were in an HR pathway gene (Table 1). *BRCA2* (n=14 cases), *RAD51B* (n=8), and *ERCC5* (n=4) were most frequently altered. Uterine LMS (uLMS) patients had more DDR alterations than soft tissue sites, although not statistically significant (p = 0.084). HRD score significantly correlated with HRD alteration status (p = 0.004). DDR or HRD alteration

status and HRD score were associated with shorter RFS in patients with resectable disease, independent of age ($p < 0.05$). OS did not significantly differ based on DDR or HRD status ($p > 0.05$).

Though interrogation of MSK-IMPACT data suggested no difference in frequency of DDR alterations based on site, the TCGA investigators found that despite the overall similarity between uterine LMS and soft tissue LMS on integrated and individual platform analyses, uterine LMS had a higher DNA damage response score.[21] Therefore, whether dependence on the DDR pathway is different in uterine vs. soft tissue LMS is unclear.

Table 1: Frequency of DDR alterations in LMS

		Total (n=211)	**stLMS (n=90)**	**uLMS (n=121)**
DDR Altered (%)	No	168 (80)	77 (86)	91 (75)
	Yes	43 (20)	13 (14)	30 (25)
HRD Altered (%)	No	180 (85)	81 (90)	99 (82)
	Yes	31 (15)	9 (10)	22 (18)
*HRD Score (%)	<=25	95 (51)	43 (57)	52 (48)

* Sum of scores from measures of genomic scarring: telomeric allelic imbalance; large-scale transitions and loss of heterozygosity

LMS: an immunogenic tumor

LMS is an inflammatory tumor exhibiting both PD-L1 expression and T-cell infiltration. LMS has been shown to have high levels of antigen presenting and T-cell-related gene expression, a pattern similar to that of undifferentiated pleomorphic sarcoma, a disease with responses to PD-1 inhibition.[22] Perplexingly, studies of single agent PD-1 inhibition alone in leiomyosarcoma have shown very little activity. Immune checkpoint pathways are important inhibitory pathways that prevent auto-immunity within the body. However, dysregulation of these pathways can result in the development of tumor immune resistance. Immune checkpoints are typically ligand-receptor interactions, which are amenable to blockade by antibodies. The SARC028 study studied the activity of pembrolizumab in 80 patients with 8 different sarcoma histological subtypes. In the cohort of 10 LMS patients, 60% had stable disease, but no objective responses were seen.[2] The Alliance (A091401) non-comparative, phase II study randomized patients with advanced sarcoma to receive either nivolumab alone or nivolumab in combination with ipilimumab. Of the 29 LMS patients, 3 had an objective response.[23] Finally, a phase II study of single agent nivolumab in uterine LMS did not complete second stage of accrual due to a lack of response in any of the first 12 patients enrolled.[3]

Therefore, combination therapy may be necessary in LMS as other mechanisms may be involved in immune evasion. Combination strategies that incorporate anti-PD-1 therapy with chemotherapy, radiation therapy, small molecule targeted therapies and immunotherapies that target different elements of the immune system are of considerable interest as a

means to improve clinical efficacy. The rationale for combination approaches rests on the knowledge that the sarcoma microenvironment can be manipulated and primed by anti-cancer therapy induced cell death that increases neo-antigen expression and stimulates the immune system the effects of which can be enhanced by the addition of immune checkpoint inhibition.

Synergy Between PARP Inhibition and Immune Checkpoint Blockade

Recent investigation has revealed a wide immunological role for ADP-ribosylating enzymes such as PARP. PARP-1 has been shown to be involved in the development of inflammatory responses and plays a role in adaptive immunity by modulating the ability of dendritic cells to stimulate T cells or by directly affecting the differentiation and functions of T and B cells.[24] It has been hypothesized that BRCA mutated tumors would be hypermutated and carry more tumor specific neoantigens. Indeed, in BRCA mutated ovarian cancers, there was a significantly higher predicted neoantigen load compared to tumors without alterations in homologous recombination genes. These tumors were also associated with increased CD3+ and CD8+ TILS as well as elevated PD-1 and PD-L1 expression.[25] In addition, PARP inhibition has been shown to increase the activity of the type I (alpha) and type II (gamma) interferon pathways.[5,6]

Preclinical studies using an immunocompetent, murine ovarian cancer model demonstrated synergism in therapeutic efficacy between PD-1 blockade and PARP inhibition regardless of BRCA status.[5,6] Interestingly, mice with tumors cured by PARPi monotherapy did not regrow tumors when re-exposed to the same tumor cell line, suggesting the establishment of immune memory.[5] In preclinical breast cancer cell lines, xenograft and syngeneic tumors, PARP inhibition resulted in upregulation of PD-L1 expression as a result of PARP inhibitor mediated inactivation of GSK3β. Engagement of the PD-1 receptor on T cells by PD-L1 results in immunosuppressive effects on T cell function whereas blockade of co-inhibitory ligation with monoclonal antibodies, such as PD-L1 or PD1 antibodies, restores T cell function and increases therapeutic efficacy.[26,27] Therefore, PARP inhibition enhances anti-cancer immunity via enhanced T cell infiltration in tumors and increased activities of the stimulator of interferon gene and interferon pathways. Other mechanisms, such as PARP inhibitor–mediated upregulation of PD-L1 expression, may also play a role in the synergy between PD-1 inhibitors and PARP inhibitors.

Recently, the TOPACIO study, of niraparib (a PARP inhibitor) and pembrolizumab in recurrent ovarian cancer, demonstrated an objective response rate of 25% and a duration of response of 9 months.[4] Interestingly, benefit was seen in patients without alterations in homologous repair genes in support of the preclinical models showing the same. Therefore, it is hypothesized that the antitumor immunity resulting from PARP inhibition in patients with LMS will be further enhanced through immune checkpoint blockade. Another phase I/II

study, the MEDIOLA trial studied the combination of olaparib and durvalumab in select solid tumors. This phase I study in patients with ovarian, triple-negative breast, cervical, or uterine cancer demonstrated tolerability of the combination, and early evidence of efficacy. In the phase II study among 32 patients with germline *BRCA1/2* mutant platinum-sensitive ovarian cancer, disease control rate at 12 weeks and objective response rate were 81% and 63%, respectively.[28] In castration resistant prostate cancer, durvalumab a PD-L1 inhibitor and olaparib a PARP inhibitor resulted in responses in patients with and without DDR alterations, with a durable PFS of 16.1 months for the entire cohort. Grade 3 or 4 toxicities were expected and included anemia, lymphopenia, infection and nausea. [29]

Biomarker Identification

One major challenge to harnessing combination therapeutic approaches in sarcomas is identifying patients who have the highest chance of benefit. To do this, lessons can be learned from other tumor types and applied to sarcomas. We believe the heterogeneity inherent in sarcomas can make them an ideal tumor type to validate a prospective biomarker for response to the combination of an immune activating agent (anti-PD-1 therapy) and a PARP inhibitor.

It is unclear how best to predict which patients will benefit from immune checkpoint inhibitors. While the initial phase I trial of nivolumab suggested tumors expressing PD-L1 by immunohistochemistry (IHC) may benefit more frequently from PD-1 blockade, more recent data from the combination ipilimumab plus nivolumab trial has cast doubt on the theory that PD-L1 expression is necessary for therapeutic benefit. Prior studies have suggested that PD-L1 is overexpressed in a variety of sarcomas.[16,30] In the SARC028 study PD-L1 was positive in only three (4%) of the 70 samples. All three were from patients with undifferentiated pleomorphic sarcomas, and two of three had a response; one had a complete respone and the other had a partial response.[2]

It is known that PD-L1 expression remains a dynamic marker that can change over time and under different conditions in the microenvironment. Tumor heterogeneity can also contribute varied PD-L1 expression. These data suggest either PD-L1 expression may change as a result of therapy with immune checkpoint inhibitors or that other mechanisms underlie the response to immune checkpoint blockade. There remains the need to define a better biomarker predictive of response to immune checkpoint blockade.

Similarly, previous clinical trials have demonstrated efficacy for PARP inhibitor monotherapy in the setting of BRCA mutant tumors. However, most recently, PARP inhibition with niraparib, demonstrated significant improvement in progression free survival in ovarian cancer patients with recurrent platinum-sensitive ovarian cancer irrespective of BRCA mutational status.[1] Hence, the role of genetic alterations, in genes involved in homologous



recombination repair pathway and other DNA damage response pathways, as predictive biomarkers of response to PARP inhibition remains to be determined.

Schlafen11 (SLFN11) is an emerging biomarker of response. Low levels of SLFN11 have been associated with resistance to PARP inhibitors. The mechanism of SLFN11 has not been fully elucidated but it may decrease synthesis of PARP. Gamma-H2AX is a universal pharmacodynamic marker of DDR inhibition

Rucaparib

Overview

Poly (ADP-ribose) polymerase (PARP) proteins are involved in deoxyribonucleic acid (DNA) replication, transcriptional regulation, and DNA damage repair. Inhibition of PARP converts common single-strand DNA breaks into double-strand breaks during DNA replication. DNA-bound PARP1/2 catalyzes the synthesis of poly (adenosine diphosphate [ADP]-ribose) (PAR) onto a range of DNA-associated proteins that mediate DNA repair. PARP1 also undergoes auto-PARylation, a molecular change that ultimately leads to its release from DNA.

Small-molecule inhibitors of PARP1/2 represent a class of anti-cancer agents that exert their cytotoxic effect by modulating the PARylation activity of PARP1/2 and trap PARP proteins on damaged DNA.

Recent data supports the evaluation of PARP inhibitors in solid tumors carrying mutations in *BRCA1* and *BRCA2*. Recent sequencing data indicates that tumors may have other homologous recombination (HR) defects due to germline and /or somatic loss of function in key HR genes including *BRCA2*, *ATM*, *CHEK2*, *NSBP1*, and *FANCJ*, that could potentially confer a '*BRCA*ness' phenotype and susceptibility to PARP inhibition via synthetic lethality.

In the clinic, PARP inhibitors (olaparib, rucaparib, niraparib, and talazoparib) have demonstrated sustained anti-tumor responses as a single agent in patients with *BRCA1*- or *BRCA2*-mutant tumors, with an acceptable safety profile.

SUMMARY OF INVESTIGATIONAL PRODUCT

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 LOH. Rucaparib was approved by the US FDA in December 2016 for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with 2 or more chemotherapies. 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 the biomarkers responsible for PARP inhibitor sensitivity.

Clinical Experience

Rucaparib is being evaluated in Phase 1, 2, and 3 clinical studies in patients with advanced cancer who have evidence of 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 IB.

Nivolumab

Overview

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Nivolumab is approved for the treatment of several types of cancer in multiple

regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies. Single-dose nivolumab monotherapy was also investigated in a Phase 1b study and a Phase I/II study of patients with sepsis who were also managed according to established best practice care for sepsis.

Clinical Experience

Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 20,200 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care. Based on data from a completed Phase 1b study and a Phase I/II study, single doses of either 480 mg or 960 mg nivolumab did not result in unexpected safety findings for participants with sepsis or septic shock.

The nivolumab clinical studies and results are described in more detail in the nivolumab IB.

Summary Statement

MSKCC is a leading sarcoma research center with the expertise, resources, and high clinical volume to conduct scientifically sound clinical studies. Prior immunotherapeutic agents have shown promise in select sarcoma patients. Both uterine and soft tissue LMS appear to harbor genomic alterations in genes involved in DDR. Using a combination of a PARP inhibitor, rucaparib, and the anti-PD1 monoclonal antibody, nivolumab, to treat patients with advanced LMS and our planned scientific correlates, we believe we can assess the safety and efficacy of combination PARP and checkpoint inhibition and better understand the effects of this combination therapy in antitumoral immune response.

Rucaparib and nivolumab do not have overlapping safety issues and therefore these agents have been selected for use in this study The safety of combining a PARP inhibitor with a PD-1 inhibitor at full individual doses has been evaluated in various studies. The **ATHENA**

trial is a placebo-controlled phase III evaluating rucaparib and nivolumab in combination or as monotherapy in the maintenance setting following response to front-line treatment in newly diagnosed ovarian cancer patients. The combination arm will receive rucaparib 600mg BID and nivolumab 480mg intravenously every 4 weeks. Prior to starting the ATHENA study, data from a small group of patients (at least 6 patients) treated in the phase II CHECKMATE-9KD study were to be reviewed to assess the safety of the combination. The outcomes from this review are not publicly available; however, evaluation has been completed and the study has progressed to the randomized treatment phase. Arm A of the phase II **CHECKMATE-9KD** study is also evaluating nivolumab 480 mg intravenously combined with rucaparib 600 mg twice daily in patients with metastatic castrate resistant prostate cancer who have received 1-2 prior taxane-based regimens in the mCRPC setting. Other studies of PARP inhibitors in combination with PD-1 inhibitors have not identified any new safety signals of the combination either.[31]

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is an open-label, single-center, single arm, phase II study that will test the hypothesis that rucaparib in combination with nivolumab will ellicit an enhanced anti-tumoral response in patients with LMS as assessed by RECIST 1.1.

A total of 20 patients with unresectable/metastatic LMS will be enrolled onto the study. At least 10 patients will be required to have LMS of uterine origin. Patients will be required to have had at least one prior line of therapy but no more than three prior lines. Treatment naïve patients may be enrolled if they have refused standard systemic treatment. Patients will be required to have archival tissue for entry onto the study.

The primary objective of the study is to evaluate the efficacy of a PARP inhibitor rucaparib, given in combination with anti-PD-1 monoclonal antibody nivolumab in patients with locally advanced/metastatic LMS as assessed by the best objective response rate (complete response + partial response) by RECIST 1.1.

4.2 Intervention

One treatment cycle will consist of 28 days. Patients will receive rucaparib at 600 mg, orally, twice daily, continuously for 28 days. They will receive 480mg of nivolumab intravenously on day 1 of every four-week cycle. This is the recommended phase II dose of the combination therapy. Re-staging scans will be performed every 8 weeks. Treatment will be repeated until the patient develops progressive disease or unacceptable toxicity or for a maximum duration of 26 cycles as long as patients are receiving benefit from treatment, have not had disease progression, met any criteria for study withdrawal and are tolerating therapy.

Any patient who discontinues study therapy after 2 years of treatment and demonstrated objective clinical benefit at the end of a 2-year treatment duration may resume study therapy in the setting of subsequent progression of disease off all therapy following discussion with the principal investigator. Any patient in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue any component of study treatment after agreement between the PI and treating investigator (see section 11.7 for additional details). A delay in the start of subsequent cycles due to holidays, weather, or other circumstances will be permitted up to 7 days.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS & NON-THERAPEUTIC ASSESSMENTS

5.1 Mechanism of Action

Rucaparib is a potent, selective inhibitor of PARP1, PARP2 and PARP3.

Nivolumab is a humanized IgG4-variant monoclonal antibody drug against PD-1.

5.2 Formulation, storage, packaging

Rucaparib Formulation

Rucaparib tablets contain rucaparib camsylate as the active ingredient. Rucaparib is available in 200, 250, and 300 mg (as free base) strength tablets for oral administration.

Nivolumab Formulation

Nivolumab is formulated for iv injection in a single use vial containing 100 mg antibody in 10 ml of isotonic solution.

Storage

The storage conditions for the study drugs will be described in the package information leaflet or package label and in the IB.

Rucaparib Storage

Rucaparib tablets must be stored at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF) [*see USP Controlled Room Temperature*].

Nivolumab Storage

Nivolumab vials 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. The study medication will be dispensed by an authorized person at the investigator's site.

Rucaparib Packaging

The tablet supplies of rucaparib will be provided in high-density polyethylene bottles with child-resistant induction seal closures. They will be open-label.

Nivolumab Packaging

Nivolumab has been filled in Type I flint glass vials closed with a fluoropolymer film-laminated rubber stopper and sealed with an aluminum seal. Nivolumab injection is a 100mg/Vial (10 mg/mL) solution.

5.3 Nivolumab Preparation

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding (polyether sulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is fixed (e.g., 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Specific instructions for nivolumab preparation and administration are provided in the IB.

5.4 Administration

The treatments to be administered during the study are:

- Nivolumab will be administered as an IV infusion, every 28 days at a dose of 480 mg. Nivolumab will be administered over a thirty minute infusion.
- Rucaparib will be administered orally (PO) BID, once in the morning and once in the evening 12 hours apart at a starting dose of 600 mg twice daily.

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

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

On the first day where both study drugs are administered, nivolumab will be given IV infusion after the morning dose of rucaparib. Subsequently in the evening, rucaparib administration is repeated. On subsequent days of the first cycle, twice daily dosing of rucaparib will continue in the morning and evening (at approximately the same time), for a 27-day period of continuous drug administration. During subsequent cycles, the treatment will repeat every 28 days for 25 cycles (2 years) from Day 1 to Day 28.

Any patient in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue any component of study treatment based on discretion of study PI.

6.0 CRITERIA FOR PARTICIPANT ELIGIBILITY

6.1 Participant Inclusion Criteria

- Male or female age ≥ 18 years at the time of informed consent
- Be willing and able to provide written informed consent/assent for the trial
- Be willing to comply with treatment protocol
- Subjects must have a histologically confirmed unresectable/metastatic LMS
- Availability of archival tissue for correlative studies. Either a paraffin block or at least 20 unstained slides are acceptable
- Adequate performance status: ECOG 0 - 2

- Subjects must have had at least 1 but not more than 3 prior lines of systemic therapy (e.g. chemotherapy, immunotherapy, targeted or biological therapy) for their LMS. Patients who decline the standard of care first-line systemic therapy will be eligible for this trial. Prior adjuvant therapy will not count provided it was completed more than 6 months previously.
- Presence of measurable disease per RECIST v1.1. Target lesions must not be chosen from a previously irradiated field unless there has been radiographically and/or pathologically documented tumor progression in that lesion prior to enrollment.
- Adequate organ function determined within 14 days of treatment initiation, defined as per Table 2:

Table 2: Definition of Adequate Organ Function

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1.5 K/mcL
Platelets	≥100 K/ mcL
Hemoglobin	≥9 g/dL
Renal	
Serum creatinine **OR** Measured or calculated creatinine clearance	Estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2. For calculated CrCL, the Cockcroft Gault formula or institutional standard formula can be used.
Hepatic	
Serum total bilirubin	<1.5 X ULN **OR** <2 X ULN if hyperbilirubinemia is due to Gilbert's syndrome
AST (SGOT) and ALT (SGPT)	Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 × upper limit of normal (ULN); if liver metastases, then ≤ 5 × ULN
Coagulation	
International Normalized Ratio	≤1.5 X ULN (≤ 2.5 × ULN if on anticoagulants)

- Women of childbearing potential must have a negative serum pregnancy test at screening and ≤ 72 hours prior to the first dose of study treatment.
- Female subjects of childbearing potential must be willing to use an adequate method of contraception as outlined in Section 15.1.6 and not breastfeed, for the duration of the study and for at least 6 months after the last after the last dose of study medication. Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
- Non-sterile male subjects and their female partners must be willing to use a highly effective method of contraception during the study treatment period and for at least 7 months after the last dose of study treatment (see section 15.1.6). Nonsterile males must avoid sperm donation for the duration of the study and for at least 7 months after last study drug.
- Patients who were treated with chemotherapy or any investigational therapies or other anti-cancer agent, if eligible, must have been completed at least 3 weeks or at least 5 half-lives (whichever is longer, but no less than 3 weeks) before the study drug administration. All AEs must be ≤ NCI CTCAE v5 Grade 1, except alopecia and stable neuropathy, which must have resolved to Grade ≤ 2 or baseline. Patients who were treated with estrogen modulating therapies (aromatase inhibitors, tamoxifen, GnRH agonists etc.) must have been treated at least 2 weeks prior to study drug administration.
- Patients who were treated with radiotherapy must have completed radiation therapy at least 2 weeks before the study drug administration.
- Must be willing to agree to an on-treatment biopsy if deemed safe and feasible by the treating physician

6.2 Participant Exclusion Criteria

- Uncontrolled intercurrent illness including current active or chronic infection requiring systemic therapy or the following cardiac criteria:
    - Symptomatic congestive heart failure (NYHA classification III or IV) within 6 months
    - Acute myocardial infarction ≤6 months prior to Day 1
    - Grade ≥2 ventricular arrhythmia ≤6 months prior to Day 1
    - History of cerebrovascular accident within 6 months before first dose of study drugs
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Patients with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using

steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

- Evidence of clinically significant immunosuppression such as the following:
    - Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease
    - Concurrent opportunistic infection
    - Receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrollment. However, in the setting of non-immune mediated indications for steroid use, chronic/active low dose steroid use may be permitted at the discretion of the principal investigator. The dose of steroid allowed in this setting is also at the discretion of the principal investigator. (Use of inhaled or topical steroids is permitted.)
- History or evidence of symptomatic autoimmune disease (e.g., pneumonitis, glomerulonephritis, vasculitis, or other), or history of active autoimmune disease that has required systemic treatment (i.e., use of corticosteroids, immunosuppressive drugs or biological agents used for treatment of autoimmune diseases) in past 2 years prior to enrollment. Replacement therapy (e.g., thyroxine for hypothyroidism, insulin for diabetes or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment for autoimmune disease.
- Known history of a positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
- History of non-viral hepatitis or cirrhosis
- A history of alcohol abuse
- Use of any live vaccines (e.g., against infectious diseases such as varicella) within 4 weeks (28 days) of initiation of study therapy
- Has a known history of active TB (Bacillus Tuberculosis)
- Prior therapy with a PARP inhibitor and/or PD-1/PD-L1 monoclonal antibody is not permitted.
    - Patients who have not recovered from clinically significant adverse events of prior therapy to ≤ NCI CTCAE v5 Grade 1, except alopecia and stable neuropathy, which must have resolved to Grade ≤ 2 or baseline. Except for AEs not considered a likely safety risk (e.g., alopecia, neuropathy)
    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy events due to a previously administered agent.
- Presence of a gastrointestinal condition that may affect drug absorption



- Known allergy or reaction to any component of either study drug formulation
- Has evidence of active, non-infectious pneumonitis.
- Women who are pregnant or breast feeding
- Subjects expecting to have a child within the projected duration of the trial, starting with the pre-screening or screening visit through 6 months after the last dose of study treatment(s) for women or 7 months for men.
- Presence of any other concurrent malignancy requiring active therapy or thought to potentially interfere with the safe conduct or assessment of outcomes on this trial
- Prior allogeneic stem cell transplantation or organ transplantation.

7.0 RECRUITMENT PLAN

Both men and women and members of all races and ethnic groups are eligible for this trial. The clinical trial will be listed on the clinicaltrials.gov website and on the websites of participating institutions. Patients will be identified through internal referrals and external referrals by Medical and Surgical Oncologists, nationally and internationally. Patients will be recruited through the Sarcoma Disease Management Team of the Memorial Sloan Kettering Cancer Center. The Sarcoma Service and the Sarcoma Disease Management Team each hold weekly interdepartmental meetings to identify study participants for open clinical trials. We will also discuss the trial and patient recruitment with several Sarcoma patient support groups. The principal investigator will be available to all patients for further questions and information through a contact number, which will be provided on the consent form.

7.1 Research Participant Registration

Eligibility will be confirmed as defined in the section entitled Inclusion/Exclusion Criteria. Informed consent will be obtained by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

8.0 INFORMED CONSENT PROCEDURES

The consent form/research authorization meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature, objectives, potential risks, and benefits of the intended study.
2. The length of study, what it entails, and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.
6. How the participants' data will be protected, who will have access to their PHI, and what data will be disclosed for research purposes

Prior to inclusion in the study and before protocol-specified procedures are carried out, the consenting professionals will explain the details of the protocol as outlined in the consent and research authorization to the participants/LARs. The participant/LAR will also be informed that they are free to withdraw from the study at any time. The consent discussion may occur in person or remotely via teleconference, telephone, or videoconference.

All participants/LARs must sign an IRB/PB-approved consent form/research authorization indicating their consent to participate. Each participant/LAR and consenting professional will sign and date the consent form. The participant/LAR must receive a copy of the signed informed consent form.

9.0 PRE-TREATMENT/INTERVENTION

Screening

All aspects of the screening evaluation should be completed prior to entering the study, unless otherwise noted. Pre-treatment evaluations include:

Within 28 days of enrollment:

- Confirmation of disease: Pathologic confirmation of LMS at MSKCC
- Confirmation of availability of archival tissue (receipt of tissue is not required for study enrollment or initiation)
- Informed Consent
- Informed consent to protocol 12-245 part A & C (somatic and germline DNA testing) next generation sequencing of archival/pre-treatment tissue and blood using MSK-IMPACT assay.
- Full medical history, physical exam, assessment of performance status by ECOG
- Review of prior and concomitant medications, any surgical/medical procedures

- Complete vital signs (pulse, blood pressure, temperature, respiratory rate, oxygen saturation) as well as weight and height. Height may be documented at any time prior to registration.
- Standard baseline imaging of chest, abdomen, pelvis (CT or MRI), with CT scan or MRI of brain or other site if applicable. The same methods used to detect lesions at baseline are to be used to follow lesions throughout the clinical study. If a patient has known brain metastases, this disease should be evaluated at each required assessment time
- 12-lead electrocardiogram (ECG)
- Echocardiogram (ECHO)

Within 14 days of enrollment:

- Serum pregnancy test for women with child-bearing potential (within 72 hours).
- Complete blood count with differential.
- PT (or INR)
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ASL, AST), phosphorus, magnesium
- TSH, T4 free, T3
- Amylase and lipase
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), HCV antibody, HIV 1/2 antibodies, and HBV DNA and/or HCV RNA if needed.
- Collection of a blood sample for exploratory biomarker analysis
- Review of inclusion and exclusion criteria

Please refer to Study Calendar in Section 11 for additional information.

10.0 TREATMENT/INTERVENTION PLAN

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in section 11.2.1. Modifications and dose delays due to toxicity are described further in section 11.2.

Patients will start rucaparib 600 mg twice daily on day one of the first cycle, continuously for 28 days. They will receive nivolumab 480 mg intravenously on day 1 of every four-week

cycle (±3 days) starting on day 1 of cycle 1. A delay in the start of subsequent cycles due to holidays, weather, or other circumstances will be permitted up to 7 days. Treatment will be repeated until the patient develops progressive disease or unacceptable toxicity or for a maximum duration of 26 cycles (approximately 2 years) as long as subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal and are tolerating therapy. Any patient who discontinues study therapy after 2 years of treatment and demonstrated objective clinical benefit at the end of a 2-year treatment duration may resume study therapy in the setting of subsequent progression of disease off all therapy following discussion with the principal investigator. Any patient in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue any component of study treatment after approval by principal investigator.

No additional investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy

10.1 Duration of Therapy

Study treatment may continue until one of the following criteria applies:

- Until a total of 26 cycles (approximately 2 years) of treatment has been administered as long as subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal outlined below. Any subject in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue any component of study treatment after agreement between the principal investigator and treating investigator.
  Note: Any patient who discontinues study therapy after 2 years of treatment and demonstrated objective clinical benefit at the end of a 2-year treatment duration may resume study therapy in the setting of subsequent progression of disease off all therapy.
- Clinical or radiographic disease progression as defined by RECIST 1.1. Patient may be allowed to continue treatment after progression if they are deriving clinical benefit (section 9.4).
- Intercurrent illness that prevents further administration of treatment
- Intolerance of study treatment (as defined in sections 11.2 and 11.3)
- Patient decides to withdraw from the study



- Physician decides to withdraw a patient from the study for a reason not listed here
- Pregnancy in patient
- The patient is lost to follow-up
- Inability of the patient to comply with the requirement of the protocol for treatment or evaluation.

10.2 Treatment Beyond Initial RECIST 1.1 Defined Progression of Disease

Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of the combination therapy of rucaparib and nivolumab. The patient may be allowed to continue study treatment after initial RECIST 1.1 defined progression if they are assessed by the treating physician to be deriving clinical benefit and tolerating study treatment. The treating physician may consult with the overall study PI for help with assessing the patient suitability for continued treatment in the setting of progression. Such patients should discontinue study therapy upon further evidence of progression at the discretion of the treating physician. A short interval scan performed 3-4 weeks after continuation of study therapy beyond the initial documented progression of disease may be considered.

10.3 General Concomitant Medication and Supportive Care Guidelines

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

Supportive Care: Best supportive care and treatment will be given as appropriate to each subject as per Clinical Center and ASCO guidelines (antiemetics, antibiotics, packed red blood cell and platelet transfusions, nutritional support, and radiation palliative treatment for pain).

Steroids: Doses up to 10mg of prednisone daily (or equivalent) will be allowed concurrently with continuous treatment incorporating nivolumab.

If the subject requires corticosteroid dosing of >10 mg prednisone daily (or equivalent) and/or other immunosuppressive medication for related toxicities, nivolumab dosing must be held until the corticosteroid dose has decreased to ≤10 mg prednisone daily (or equivalent) and the administration of the other immunosuppressive medication has discontinued. Higher doses of prednisone (. i.e., >10mg) may potentially be allowed in combination with the study therapy if they are prescribed for non-immune mediated indications at the discretion of the

principal investigator. The use of steroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.

Vaccines: Use of any live vaccines (e.g., against infectious diseases such as varicella) within 4 weeks (28 days) of initiation of study therapy and 60 days after the last administration of the study medication.

Radiation: Palliative radiation to existing sites of metastatic disease to alleviate the tumor obstruction and/or pain will be allowed provided nivolumab dosing does not occur within 1-week pre- or post-radiation. Rucaparib should be held 3 days before and resume 3 days after completion of radiation.

Surgery: Subjects must not schedule any elective surgeries during the treatment period and for at least 30 days after the last administration of study drugs. If a subject undergoes any unexpected surgery or local intervention during the course of the study, all study treatments must be withheld, and the investigator or designee should notify the PI as soon as possible. A subject may be allowed to resume study drugs if both the investigator and the PI agree to restart study therapy.

10.4 Drug Interactions

Rucaparib

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.

Drug-drug Interactions (Reference Appendix B)

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 in patients on rucaparib taking concomitant medicines that are substrates of CYP1A2, CYP2C9, and/or CYP3A (see IB and Appendix B). 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. Selection of an alternative concomitant medication is recommended.

Anticoagulants

Rucaparib is a weak inhibitor of CYP2C9 in vivo. Caution should be exercised in patients receiving rucaparib and concomitant warfarin (Coumadin). Patients taking warfarin should have INR monitored regularly per standard clinical practice.

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 decrease renal elimination and 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).

<u>Nivolumab</u>

Restricted Medications/Treatment

Steroids see section 10.3.

Prohibited Medications

Any investigational medication other than the study drugs.

Use of any anticancer medications other than the study medications.

11.0 EVALUATION DURING TREATMENT/INTERVENTION

11.1 Standard evaluations

Evaluations at clinic visits will occur on days 1 and 15 (± 3 days) of cycle 1 and day 1 (± 3

days) of every cycle thereafter.

The clinical evaluations are delineated further in the study calendar (Table 3) and include:

- Full medical history, physical exam, assessment of performance status by KPS or ECOG status
- Review of concomitant medications
- Review of adverse events
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate, and oxygen saturation) as well as weight and height. Height may be documented at any time prior to registration
- Echocardiogram and EKG

All patients will undergo a baseline staging CT scan of the chest (with or without contrast), abdomen and pelvis (with or without contrast), and CT/MRI of the affected area if deemed necessary by the treating physician. Response evaluations will occur at week 8 and every 8 weeks subsequently (± 1-week window) until 56 weeks, and then every 12 weeks thereafter or as per the discretion of the treating investigator.

Routine/standard blood samples and urinalysis will be obtained at screening, day 1 of cycle 1 and then prior to every scheduled treatment visit (± 3 days) thereafter. All routine blood samples should be obtained prior to the dose of rucaparib and nivolumab on day 1 of every cycle. Labs will also be repeated on day 15 of cycle 1. These samples will be used for routine tests and are part of standard of care. The following analyses will be assessed at various time points during the study:

- Hematology: Complete blood count with differential
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ALT, AST), phosphorus, magnesium
- Serum pregnancy test for women with child-bearing potential
- TSH, T4 free, T3
- Amylase and lipase at screening only
- Additional tests if clinically indicated
- PT (or INR)
- Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), HCV antibody, HIV 1/2 antibodies, and HBV DNA and/or HCV RNA if needed. Hepatitis E antibody or HEV RNA should be performed at baseline if testing is available



Research blood samples and tumor biopsies will be obtained as per the study calendar.

Table 3. Study Calendar

	Screening	Cycle 1				Cycle 2				Cycle 3 and every D1 of every cycle				EOT (within 1 week post-tx)	28-day follow up visit[N]	LTFU – every 12 weeks up to 1 year[O]
	Wk	1	2	3	4	5	6	7	8	9	10	11	12			
Rucaparib[A]		X	X	X	X	X	X	X	X	X	X	X	X			
Nivolumab[B]		X				X				X						
Informed consent	X															
Archival Tissue[C]	X															
Informed consent to #12-245 part A &C[D]	X															
Review of concomitant medications	X	X		X		X				X				X	X	
Review of adverse events		X		X		X				X				X	X	X
Vital signs[E]	X	X		X		X				X				X	X	
Height	X															
Weight	X	X		X						X				X	X	
Physical exam	X	X		X		X				X				X	X	
ECOG/KPSperformance status	X	X		X		X				X				X	X	
Routine laboratory tests[F]	X	X		X		X				X				X	X	
Hepatitis B, C, and HIV[G]	X															
Pregnancy Test[H]	X	X				X				X				X		
Urinalysis	X	X		X		X				X				X	X	
ECG[I]	X									X				X		

ECHO	X														
CT and/or MRI[J]	X								X						
Blood collection for IMPACT under 12-245[K]	X														
Research blood sample collection[L]		X				X				X				X	
Research blood sample for cfDNA[L]		X				X				X				X	
Biopsy[M]									X					X	
Optional Biopsy at Progression														X	
Survival Status															X

A. Rucaparib will be administered twice daily, orally, continuously from day 1-28 (inclusive) of each treatment cycle, each treatment cycle consists of 28 days
B. Nivolumab will be administered once at a dose of 480mg, intravenously, on day 1 of cycle 1 and every 28 days (±3 days) thereafter
C. Sufficient archival tissue for correlative assessments should be obtained
D. Informed consent to #12-245 part A &C (if not completed already) and MSK-IMPACT testing utilizing pre- and post-treatment tumor tissue (if previously performed prior to study enrolment these results may be used).
E. Vital signs will include blood pressure, pulse, respiratory rate, oxygen saturation and body temperature and will be taken after the patient has been resting for at least 5 minutes
F. Routine laboratory tests at screening, day 1 and 15 of cycle 1 and then prior to every scheduled treatment visit (± 3 days) thereafter. All routine blood samples should be obtained prior to the daily dose rucaparib and nivolumab. Routine laboratory tests include: CBC with differential, PT/INR and a PTT, comprehensive metabolic panel, magnesium and phosphorus, fT4, TSH, T3 and total cholesterol. Fasting is not required before blood sampling Lipase and amylase will only be performed at screening and then again as clinically indicated. Coagulation parameters should be evaluated in the event of a Grade 2 or higher aminotransferase increases occur and as clinically necessary.
G. Hepatitis B surface antigen (HBsAg), Hepatitis B core antibody (HBcAb), HCV antibody, HIV 1/2 antibodies, and HBV DNA and/or HCV RNA if needed. Hepatitis E antibody or HEV RNA should be performed at baseline if testing is available.
H. Serum pregnancy test (Female subject of childbearing potential should have a negative serum pregnancy at screening and within 72 hours prior to receiving the first dose of both study drugs, D1 of every cycle (± 1 week) and at the off-study visit.)
I. An ECG will be performed at baseline, week 9, every 8 weeks subsequently (± 1-week window) and at the End of Treatment (± 1-week window)
J. Standard Imaging studies will be performed at baseline, week 8 and every 8 weeks subsequently (± 1 week window) until 56 weeks, and then every 12 weeks thereafter or as per the discretion of the treating investigator and will include CT of chest/abdomen/pelvis and/or MRI of the affected area if deemed necessary by the study investigator.
K. Blood sample for IMPACT will be collected during screening (if not already done previously)
L. Research blood samples for cfDNA (2x10mL streck tubes) and biomarkers (4x8mL sodium heparin tubes) will be collected at week 1,5, 9, 17, 25 and at the date of the End of Treatment (± 3 days).



M. Mandatory tumor tissue biopsies where feasible, will be required at week 8 (± 7 days). An optional biopsy at time of progression of disease will also be offered.
N. The 28-Day Follow Upvisit will take place 28 days (+/- 7 days) after the last dose of study therapy. First
O. LTFU visit will be completed every 12 weeks (+/- 28 days) up to 1 year after the 28-day Follow Up visit. This can be completedby phone call or clinic vist. AE assessment is only required at the 1st LTFU.

11.2 Dose adjustments, delays, rules for withholding and restarting treatment and permanent discontinuation.

In the absence of unacceptable toxicity, subjects may continue with administrations of the combination of rucaparib and nivolumab at the same dose unless a dose interruption or modification is required based on the guidance described below, or at the discretion of the investigator after consultation with the PI. The subjects with disease progression that the investigator considered to be consistent with “pseudo-progression” will be allowed to continue the study drug treatment of rucaparib alone or nivolumab alone or the combination of rucaparib and nivolumab if the subject is benefiting from the treatment in the judgment of the investigator after consultation and agreement with the principal investigator.

In general dose delays for reasons other than management of AEs are discouraged. A dose delay of ≤14 consecutive days for rucaparib or a dose delay of ≤ 42 consecutive days for nivolumab is allowed under the following guidance and at the discretion of the investigator after consultation with the PI.

In case a patient is benefiting from the study treatment while meeting the discontinuation criteria, continuation of study treatment may occur upon discussion and agreement with the PI.

If the timing of a protocol-mandated study visit coincides with a holiday, weekend, or other event, the visit should be scheduled on the nearest feasible date, with subsequent dosing continued the 28-day intervals afterward.

If a dose is delayed for rucaparib, the subject can continue nivolumab dosing every 28 days and can resume rucaparib at any time. If a dose is delayed for nivolumab for ≤ 14 days for a planned dosing cycle (e.g. Cycle 3 Day 1), nivolumab should be administered and all assessments should be conducted according to the original cycle (i.e., Cycle 3); if the delay is more than 14 days, the subject should skip nivolumab dose, and nivolumab will be administered on Day 1 of the next planned cycle (i.e., Cycle 4 Day 1). Subjects who experience AE related to one investigational agent may continue treatment with the other investigational agent according to the protocol schedule after consultation with the PI.

If nivolumab cannot be resumed within 42 consecutive days of last dose due to nivolumab

treatment-related events, or if corticosteroid dose for an irAE is not able to be reduced to <10 mg prednisone or equivalent per day by the end of 42 days' dose interruption, the subject should be discontinued from nivolumab, and continue rucaparib monotherapy once the irAE is resolved. If rucaparib cannot be resumed within 14 consecutive days of the last dose due to rucaparib treatment-related events, rucaparib will be permanently discontinued and the subject may continue nivolumab monotherapy alone. Exemptions may be considered for those subjects who are determined by the investigator to have received clinical benefit and it is considered safe and to be in the best interest of the subject to resume the treatment after consultation with the PI.

11.2.1 Rucaparib

Rucaparib Dose Reduction Steps

Dose modifications (interruption, reduction, and re-escalation) must be recorded for each patient in the appropriate section of the eCRF.

Table 4. Rucaparib Dose Reduction Steps

Starting Dose	**600 mg BID**
Dose Level -1	500 mg BID
Dose Level -2	400 mg BID
Dose Level -3	300 mg BID

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

- Grade 3 or 4 hematologic toxicity. Anemia should be managed as described below
- Grade 3 or Grade 4 ALT/AST elevations should be managed as described below
- Grade 3 or 4 non-hematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines or grade ≤ 3 asymptomatic lab abnormalities if not considered a safety risk to the patient by treating MD).
- In addition, and at the discretion of the investigator, the dose of rucaparib may be held and/or reduced for Grade 2 toxicity not adequately controlled by concomitant medications and/or supportive care.

For patients who meet treatment interruption guidelines above, treatment with rucaparib should be held until the toxicity improves to ≤ CTCAE Grade 2 (unless otherwise specified) Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose, and the patient

experiences the same toxicity, treatment should be interrupted, then resumed at a reduced dose following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted to 300 mg twice daily. If a patient continues to experience toxicity despite dose reduction steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed and documented between the investigator and the PI.

Table 5. Management of Anemia including Evaluation for MDS/AML and Follow-up of Patients who Discontinue Treatment with Ongoing Anemia:

Anemia CTCAE Grade ≥ 3	• Rucaparib treatment should be held until the anemia improves to CTCAE Grade ≤ 2 whereupon daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion (transfusion is permitted per section 10.3) • If the duration of dosing is interrupted for > 14 consecutive days due to anemia CTCAE Grade ≥ 3, treatment should be permanently discontinued, unless otherwise agreed and documented between the investigator and the PI. • In addition, if anemia CTCAE Grade ≥ 3 persists for > 14 consecutive days, or a dependence upon blood transfusion occurs, then weekly complete blood counts should be performed until resolution of the event. • If, after 42 days of interruption of rucaparib, the anemia has not improved to CTCAE Grade ≤ 1 then the patient should be referred to a hematologist and analysis of the bone marrow with cytogenetic studies are recommended according to standard hematologic practice. • The bone marrow analysis should include a bone marrow aspirate (for cellular morphology, cytogenetic analysis, and flow cytometry) and a core biopsy (for bone marrow cellularity).

Table 6. Management of Rucaparib and Nivolumab Treatment-Emergent ALT/AST Elevations:

ALT/AST elevations have been observed with rucaparib, and are also a potential side effect of nivolumab. Rucaparib-mediated elevations in ALT/AST (without accompanying rise in bilirubin) can be observed to start within 15 days of starting drug, and may subsequently spontaneously improve even in the setting of continued rucaparib therapy. The following guidelines discuss ALT/AST elevations for both rucaparib and nivolumab.

Grade 4 ALT/AST elevation:	• If accompanied by elevation in bilirubin, discontinue from study and initiate management of potential immune-related hepatitis. Increase frequency of monitoring of liver enzymes to every 1-2 days. Initiate 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist. If returns to grade 2: Taper steroids over at least 1 month. If does not improve in >3-5 days, worsens or rebounds: Add mycophenolate mofetil 1 g BID; If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines. • If no accompanying elevation in bilirubin, hold study drugs and initiate management of potential immune-related hepatitis. Monitor liver enzymes every 2-3 days. Initiate 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent. Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist. If returns to grade 2: Taper steroids over at least 1 month. If does not improve in >3-5 days, worsens or rebounds: Add mycophenolate mofetil 1 g BID; If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines. If ALT/AST elevation appears to be related to rucaparib (i.e. within first 2 weeks of rucaparib initiation) and immune-related hepatitis is less likely, re-challenge with rucaparib at the next lower dose level may be considered after discussion with the PI and once transaminases resolve to grade 1 or better. Nivolumab may not be reinstituted until rucaparib has been received for at least 2 weeks and ALT/AST levels remain Grade 1 or better. In select patients whose ALT/AST levels remain stable or improved at Grade 2 after at least 4 weeks of rucaparib dosing, re-initiation of nivolumab may be considered after discussion with the PI. *Patients can be switched from IV to oral steroids at taper or earlier once clinical improvement is seen.
Grade 3 ALT/AST elevation:	• ALT/AST > 8x ULN: Manage per Grade 4 ALT/AST elevation. • ALT/AST ≤ 8x ULN with rise in bilirubin above ULN: Hold study treatment and monitor liver enzymes every 2 to 3 days. If ALT/AST elevation increases to >8x ULN, discontinue from study and initiate management of potential immunerelated hepatitis as above. If ALT/AST resolves to Grade 2, rucaparib dosing may be resumed at the ongoing dose or with a dose reduction in rucaparib, per investigator discretion, with liver enzymes being monitored every 3 days. Nivolumab dosing should not be resumed until ALT/AST resolve to Grade 1 or better. Consideration should be made to hold nivolumab dosing until rucaparib has been received for at least 2 weeks and ALT/AST levels remain Grade 1 or better. Select patients whose ALT/AST elevations resolve to Grade 2 and have improving but persistent Grade 2 ALT/AST levels for at least 2 weeks on rucaparib may be considered for resumption of nivolumab dosing after discussion with the PI. • ALT/AST ≤ 8x ULN without accompanying rise in bilirubin: Hold nivolumab and monitor liver enzymes every 2 to 3 days. Rucaparib dosing may be continued. If ALT/AST rise above 8x ULN, manage per Grade 4 ALT/AST elevation.

	Nivolumab dosing should not be resumed until ALT/AST resolve to Grade 1 or better. Select patients whose ALT/AST elevations resolve to Grade 2 and have improving but persistent Grade 2 ALT/AST levels for at least 2 weeks on rucaparib may be considered for resumption of nivolumab dosing after discussion with the PI.
Grade 2 ALT/AST elevation:	• Hold nivolumab and monitor liver enzymes every 2 to 3 days. Rucaparib and dosing may be continued. Nivolumab dosing may be resumed once ALT/AST resolve to Grade 1 or better. Select patients whose ALT/AST remain at Grade 2 and are improving numerically for at least 2 weeks on rucaparib may be considered for resumption of nivolumab dosing after discussion with the PI.
Grade 1 ALT/AST elevation	• Continue study treatment and monitor liver enzymes per study protocol.
*DILI definition: ALT or AST > 3 x ULN **and** Bilirubin > 2 x ULN and No other immediately apparent possible causes	• See Section 11.3 for management

11.2.2 Nivolumab Dose Delay Criteria

Dose reductions for nivolumab are not permitted in this study. Nivolumab may be delayed based on observed drug-related toxicities.

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 1 pneumonitis (in the case of Grade 1 pneumonitis, delay should be considered but is not required).
- Any Grade ≥ 2 non-skin, nonlaboratory drug-related AE, except for fatigue
- Grade 3/4 endocrinopathies that cannot be successfully treated with administration of replacement therapy.
- Any Grade ≥ 3 skin drug-related AE.

- AnyGrade 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, AST, ALT
    - Grade 3 lymphopenia does not require a dose delay.
    - AST and ALT elevations should be managed as per Table 6 with dose delays for Grade ≥ 2 drug related toxicities. f a patient has a
    - Any Grade 3 drug-related amylase and/or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The MSK PI should be consulted for such Grade ≥ 3 amylase or lipase abnormalities, patients can be restarted on therapy once the abnormalities have recovered to < Grade 3.
- Any AE, laboratory abnormality, or inter-current illness which, in the judgment of the Investigator, warrants delaying the dose of study medication.

Criteria to Resume Nivolumab

Patients will be permitted to resume therapy at the same dose level(s) following resolution of the AE to Grade ≤ 1 or to baseline within 42 days after the last dose, with the exception of patients who meet criteria for permanent discontinuation. Patients who meet criteria for permanent discontinuation must not receive further study therapy. Exemptions may be considered for those subjects who are determined by the investigator to have received clinical benefit and it is considered safe and to be in the best interest of the subject to resume the treatment after consultation with the PI.

If the decision is to resume study drug dosing, the patient should restart treatment on the next regularly scheduled study drug dosing visit. Skipped doses are not to be replaced.

Patients may resume treatment when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue.
- Elevations in AST/ALT and total bilirubin should be managed per Table 6 as ALT/AST elevations have been observed with rucaparib, and are also a potential side effect of nivolumab.
- 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 re-treatment if discussed with and approved by the MSK PI.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the MSK PI.

- Patients who delay study treatment due to any Grade ≥ 3 amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis may resume nivolumab when the amylase or lipase abnormality has resolved to Grade < 3.
- Dose delay that results in treatment delay of > 42 days requires treatment discontinuation, with exceptions as noted in section below. However, if the toxicity resolves to ≤ Grade 1 or baseline > 42 days after the last dose, but the patient does not otherwise meet the criteria for permanent discontinuation (see Section 11.4), and the Investigator believes that the patient is deriving clinical benefit, then the patient may be eligible to resume the study drug(s) following the approval of the MSK PI.

Nivolumab Permanent Treatment Discontinuation Criteria

Patients meeting any of the following criteria will be required to permanently discontinue nivolumab.

- Any Grade ≥ 3 drug-related myocarditis
- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 6 weeks
- Grade 2 drug-related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm in **Appendix C**). Any Grade 3 or 4 pneumonitis will also require discontinuation.
- Any Grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, and laboratory abnormalities:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction **of any duration** requires discontinuation.
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days associated with clinically significant bleeding requires discontinuation.
    - Drug-related liver function test abnormality should be managed per Table 6 and may not require discontinuation
- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to Grade < 4 after consultation with the MSK PI.



  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy AEs such as adrenal insufficiency, adrenocorticotropic hormone deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the MSK PI.
- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued treatment.
- Any dosing delay lasting > 42 days after the last dose, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a patient with a dosing delay lasting > 42 days after the last dose and with no more than 3 missed doses, the MSK PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed.
  - Dosing delays > 42 days after the last dose, which occur for nondrug-related reasons, may be allowed if approved by the MSK PI. Prior to re-initiating treatment in a patient with a dosing delay lasting > 42 days after the last dose and with no more than 3 missed doses, the MSK PI must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed, and patients must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered.

For nivolumab, please refer to Appendix C for additional guidance for the management of immune related adverse events including dose interruption and discontinuation. There are no dose modifications for nivolumab.

11.2.3 Treatment of Nivolumab-Related Infusion Reactions

Infusion reactions have been infrequently reported during nivolumab infusions. Nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the MSK PI and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (Version 5.0) guidelines.



Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For **Grade 1** symptoms (mild reaction; infusion interruption not indicated; intervention not indicated):

- Remain at bedside and monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions:
    - For patients ≥ 18 years:
        - diphenhydramine 50 mg (or equivalent)
        - acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional study drug administrations.
    - For patients < 18 years:
        - diphenhydramine 1mg/kg (50 mg max)
    - acetaminophen/paracetamol 10 - 15 mg/kg (1000mg max) at least 30 minutes before additional study drug administrations.
    - For **Grade 2** symptoms (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for 24 hours:
    - Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate.
    - For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of Solu-Cortef or equivalent) may be used.
- For **Grade 3 or Grade 4** symptoms (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated):
    - Immediately discontinue infusion nivolumab.



- Begin an IV infusion of normal saline and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

11.3 Potential Drug Induced Liver Injury (DILI)

Drug-induced liver injury (DILI) is described in the US FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation and should be referenced when managing treatment-emergent ALT/AST elevations.

Rucaparib and/or nivolumab treatment must be interrupted if biochemical criteria for suspected DILI are met, according to presence of the following laboratory abnormalities:

ALT or AST > 3 x ULN

and

Bilirubin > 2 x ULN

and

No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

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

While treatment is interrupted, the patient should be evaluated for the presence of confounding factors including malignant disease in the liver, co-administration of other suspect drugs, cholestasis, and viral or autoimmune hepatitis that could have caused the laboratory abnormalities. Other laboratory investigations of liver function such as

international normalized ratio (INR) should be implemented as indicated. Management of liver enzyme elevation is outlined in Table 6.

All cases of possible DILI should be followed until all abnormalities have returned to normal, returned to baseline levels, or an alternative cause is found to explain the combination of the increased transaminases and total bilirubin. Per US FDA Guidance for Industry, Drug Induced Liver Injury: Premarketing Clinical Evaluation, liver enzymes and serum bilirubin should be measured two to three times per week until values have normalized, or the values have stabilized and the patient is asymptomatic. In general, it is not advised that patients be re-challenged with the study drugs if liver enzyme values are greater than five times normal and there is concomitant bilirubin elevation. However, the decision to re-challenge should be made on a case by case basis along with the principle investigator of the study weighing whether other options for treatment are available and benefit received up until that point.

11.4 Correlative studies

All patients enrolled on this study will be required to have archival tissue for correlative testing.

All patients will undergo on treatment biopsy and blood sample collection for research purposes (correlative/companion studies).

Blood samples for research purposes including plasma for cfDNA will be obtained at week 1, 5, 9, 17, 25 and at the date of the end of treatment visit (± 3 days). The timepoints are detailed in Table 3 (Study calendar).

Biopsies for research purposes will be done at Week 8 in all patients enrolled in this study where feasible. Up to 6 cores from each tumor biopsy site should be taken where feasible and safe to do so. A goal of 6 cores should be obtained with a minimum of one formalin-fixed for later paraffin embedding (FFPE), one fresh and one flash frozen in liquid nitrogen. If any extra cores are obtained they will be flash frozen with liquid nitrogen. Biopsy procedures will otherwise be performed in accordance with institutional guidelines. An optional biopsy of a progressing lesions will be offered to all patients at the time of progression.

Sample	Collection Time Point	Facilty
Blood and archival tumor sample for IMPACT (12-245)	Screening	Follow SOP for IMPACT testing

Blood Sample: 4x8ml of peripheral venous blood will be collected in Sodium Heparin tubes with FICOLL	Week 1, 5, 9, 17, 25 and EOT (see study calendar)	Immune Monitoring Core
Blood Sample for cfNDA: 2 X 10 mL STRECK tubes per timepoint	Week 1, 5, 9, 17, 25 and EOT (see study calendar)	Center for Laboratory Medicine
Archival tissue and tumor Biopsy: 6 cores Prioritized: 1 FFPE 1 flash frozen 1 fresh 1 FFPE 1 flash frozen 1 fresh If any extra cores are obtained they will be flash frozen with liquid nitrogen.	Screening and week 8	FFPE: Central Pathology Lab Flash frozen; fresh: Immune Monitoring Core

Samples will be labeled using an adherent, liquid nitrogen proof label with the following information:

1. Procurement date
2. Study IRB number
3. Study patient number
4. Time point (baseline or on-treatment)
5. Anatomical biopsy site

Each FFPE sample is to be placed in a pathology sample container pre-filled with formalin and delivered to the central pathology lab. Each fresh sample is to be placed in RPMI media in a falcon tube and transported on ice (RPMI media should be kept in a fridge and should not be kept longer than two weeks, fresh bottles are available from the Singer lab). Each flash frozen sample is to be placed within an individual cryovial, labeled, and the vial immediately placed in liquid nitrogen for 2 minutes or longer to snap-freeze the tissue.

These vials can be transported in either liquid nitrogen or in dry ice. The fresh and flash frozen samples are to be transported to the Immune Monitoring Core in Zuckerman 1519. Samples are to be handed to a member of the lab.

Tumor Based Biomarkers

Interrogation of immune responses within the tumor microenvironment of sarcomas before and after treatment (archival and biopsy) with rucaparib and nivolumab will include the following correlative studies:

a) Density of immune infiltration and immune checkpoint expression of sarcomas: IHC will be used to assess the number and composition of immune infiltrates in order to define the immune cell subsets present within the tumor and PD-L1 protein expression by IHC before and after exposure to rucaparib and nivolumab.

The IHC assays will be performed by the department of pathology using but are not limited to the following markers: CD3, CD4, CD8, CD25, CD28 CD45RA, CD68, CD69, CCR7, PD-L1, PD-1, CD137, FOXP3, LAG-3, TIM-3, and ICOS.

b) Phenotype and function of TIL in human sarcomas: Multiparameter flow cytometry (MFC) performed on freshly dissociated tumor tissue will be used to characterize the tissue T cell populations.. We will study the functional significance of PD-1 expression on T cells isolated from sarcomas. Using intracellular cytokine staining (ICS) and MFC analysis on freshly isolated TIL, we will identify the T cell cytokine profiles in accordance to their immune checkpoint expression profile (PD-1, LAG-3, TIM-3). A range of cytokines representing key lymphocyte subgroups (e.g., Th1, 2 or 17) such as IL-2, TNF-α, IFN-γ, IL-17 among other inflammatory mediators will be assessed. Functional T cell markers including granzyme B and perforin as well as activation markers such as CD62L, CD44, CD69 will be also included in our analysis.

c) Tumor Biopsy gene expression profiling: Fresh tumor biopsy will be sent to IGO and examined for RNA gene and protein expression by NanoString technology (nCounter® RNA: Protein, PanCancer Immune Profiling Panel) or an alternative platform and/or qRT-PCR to detect expression of immune related genes. This panel includes 770 immune related genes including: 109 genes related to cell surface markers for 24 different immune cell types and populations, 30 genes for commonly studied cancer/testis (CT) antigens, over 500 genes for measuring immune response and 40 reference genes.

d) Neoantigen analysis: Massively parallel sequencing of the whole exome of the tumor tissue and normal blood will be performed for patients who opt in. Genomic DNA will be captured via solution-based hybrid selection and sequenced on the Illumina HiSeq platform

by the Genomics Core at MSKCC. The sequencing data will be aligned by the Bioinformatics Core Tumor, using Somatic Sniper, Somatic Indel Detector and Mutect software.

e) Next generation sequencing for T-cell receptor clonality in tumor-infiltrating lymphocytes (TIL): Samples will be analyzed using high throughput sequencing of the variable β-chain of the T cell receptor (TCR) to characterize the expansion and clonality of the T-cell repertoire in TILs.

f) **Next generation sequencing using MSK-IMPACT assay:** NGS of on-treatment tumor tissue and normal DNA sample (extracted from peripheral blood/saliva etc.) will be performed under #12-245 using the MSK-IMPACT assay to characterize the patient's tumor (somatic) and germline genetic profile related to DNA damage response and homologous recombination deficiency.

g) **Immunohistochemistry for markers of PARP inhibitor sensitivity and resistance**: IHC for SLFN11, PARP and gamma-H2AX.

Tissue microarrays (TMA) will be created using biopsy tissue mounted on poly-L-lysine coverslips, done by central pathology. Deidentified TMAs will be shipped to Enable Medicine for imaging analysis.

Role of Enable Medicine as a Participating Site is as Follows:

- Specimens will be labeled with deidentified study IDs, to only indicate cohort identification and patient subsets.
- Documents will be sent with a simple packing sheet providing an inventory list of the material being sent.
- No participant identifiers will be shared.
- Specimens will be shipped to Enable Medicine, located at 3499 Edison Way, Menlo Park, CA 94025.
- Specimens will be shipped at ambient temperature.
- Specimens are being tracked in a secure MS Excel that has been locked.
- Specimens should be received during normal business hours, M-F.
- Enable Medicine's primary contacts are as follows, and will be notified when shipments go out – and to confirm shipment receipt
    - Enable Medicine Shipment Inbox (samples@enablemedicine.com)
    - Gulpree Kaur, Field Science Director (gulpreet.kaur@enablemedicine.com)
- Preferred Courier is FedEx

Peripheral blood studies

Blood samples will be taken prior to initiation of study therapy and on designated time points post-treatment for the retrospective characterization of circulating candidate biomarkers of response, resistance or disease progression.

Peripheral blood samples for research will be obtained at at week 1, 5, 9, 17, 25 and at the date of the end of treatment visit (± 3 days). The timepoints are detailed in Table 3 (Study calendar).

At each research blood collection time point the following samples will be collected:

- 4x8ml of peripheral venous blood will be collected in Sodium Heparin tubes with FICOLL
- 2 X 10 mL STRECK tubes for cfDNA

Specimens will be placed in a biohazard bag and kept at room temperature.

Samples will be labeled with the following information:

- Procurement date
- Study IRB number
- Study patient number
- Time point (baseline or week-X)

cfDNA STRECK tubes along with completed requisition forms should be transported to Center for Laboratory Medicine, cfDNA lab, Rm. C2-004. cfDNA order MUST be placed in CIS.

- Chintan Patel patel@mskcc.org 646-608-1035

Research blood samples and tumor biopsy samples, along with completed requisition forms, are to be transported to the Immune Monitoring Facility in the Zuckerman Research Building, Room Z-1513. At least 24 hours advance notification prior to biopsy or blood collection must be provided by email to the IMF contacts below or entered in the IMF shared calendar (zzCAL_LAB_Clinical_Trials/Shared Calendar), with clinical site location and contact information from which samples are arriving indicated. Samples must be delivered between the hours of 9 am-4 pm to a member of the lab:

- Erika Ritter <ritter1@mskcc.org> 646-888-2114
- Zhenyu Mu <muz@mskcc.org> 646-888-3106
- Rosemarie Ramsawak <ramsawar@mskcc.org> 646-888-3106
- Luisa Caro <carol@mskcc.org> 646-888-2114

Such assessments will include, but not limited to, circulating nucleic acids (CNAs) and circulating lymphocytes. These samples will be analyzed for the expression of various markers such as, but not limited to, those related to DNA damage response, homologous recombination deficiency, and markers of immune activation and dysfunction.

These samples will be analyzed for:

a.) Immunophenotyping and Functional Analyses:

1. Samples will be analyzed by flow cytometry to study the effects of nivolumab and rucaparib on various peripheral blood immune cell subsets including, but not limited to T cell subsets (activated, memory and regulatory T cells).

2. To explore whether PD-1 blockade will restore T cell activation and function, peripheral blood mononuclear cells (PBMCs) will be isolated and cryopreserved. Assays of the functional status of effector T cells will be performed, including, but not limited to assays for interferon-gamma (IFN-γ) and granzyme B. This assay will use a non-specific stimulus including but not limited to anti-CD3 and anti-CD28 and would allow for the comparison of the effect of nivolumab on T cell function.

b.) Soluble Factors: Baseline and on-treatment serum levels of chemokines, cytokines and other immune mediators will be assessed by techniques that may include but are not limited to ELISA or multiplex assays. Analytes may include, but are not limited to IFN-γ, IL-12, IL-10, soluble MICA, C-reactive protein, soluble PD-1 and soluble PD-L1.

c.) Next generation sequencing for T-cell receptor clonality in peripheral blood:

Samples will be analyzed using high-throughput sequencing of the variable β- chain of the T cell receptor (TCR) to characterize the expansion and clonality of the T-cell repertoire in peripheral blood mononuclear cells.

d) Next generation sequencing of germline DNA extracted from peripheral blood

MSK-IMPACT testing will be performed on germline DNA. This processing and analysis will be performed as per the institutional standard for MSK-IMPACT.

In the course of this research it is possible that some patients whose tumors are analyzed through investigational “next-generation” profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The

consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For MSK, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

e) Plasma for cell free DNA

11.5 Second Course Phase of Therapy

All participants who stop study treatment with SD or better may be eligible for up to an additional 12 cycles (approximately 1 year) of nivolumab treatment if they progress after stopping study treatment from the initial treatment phase. This retreatment is termed the Second Course Phase of this study and is available only if the study remains open and the participant meets the following conditions:

Either

- Stopped initial treatment with study treatment after attaining an investigator-determined confirmed complete response (CR) based on RECIST v 1.1, and
    - Was treated with at least 8 cycles of study treatment before discontinuing treatment, and
    - Received at least 2 treatments with nivolumab beyond the date when the initial CR was declared

OR:

- Had SD, PR, or CR and stopped study treatment after completion of 26 administrations (approximately 2 years) of study treatment for reasons other than disease progression or intolerability.

AND:

- Experienced and investigator-determined radiographic disease progression by RECIST v 1.1 after stopping initial treatment, **and**
  - No new anticancer treatment was administered after the last dose of study treatment, **and**
  - The participant meets all the safety parameters listed in the inclusion criteria and none of the safety parameters listed in the exclusion criteria, **and**
  - The study is ongoing

When initiating the Second Course Phase of therapy, patients may be restarted at the same doses of rucaparib and/or nivolumab they last had received. An objective response or disease progression that occurs during the Second Course Phase for a participant will not be counted as an event for the primary analysis of either endpoint in this study.

Table 7. Second Course of Therapy

	Pre-initiation of Second Treatment Course[a]	$C_{T2}1D1$	$C_{T2}2D1$ (+/- 3d)	$C_{T2}3D1$ (+/- 3d)	$C_{T2}4+D1$ (+/- 3d)	$C_{T2}12$[h]	Off Study
Rucaparib[b]		X	X	X	X	X	
Nivolumab[c]		X	X	X	X	X	
Concurrent Medications	X	X---X				X	X
Physical Exam and vitals[i]	X	X[d]	X	X	X	X	X
Weight	X	X[d]	X	X	X	X	X
Performance Status	X	X[d]	X	X	X	X	X
CBC w/ diff, plts	X	X[d]	X	X	X	X	X
Comprehensive Metabolic Panel	X	X[d]	X	X	X	X	X
TSH, free T4[e]	X		X		X		X
Urine dipstick	X		X		X		
Beta-HCG (serum)	X[f]						
Patient Medication Diary			X	X	X	X	X
Adverse Event Evaluation	X- -X						X
Tumor Measurements	X[g]	CT and/or MRI will be performed every 3 cycles (12 weeks+/-1wk) for the first 3 cycles then every 4 cycles (16 weeks+/-1wk).					

a: Patients must meet eligibility criteria as defined in Section 6.1 and 6.2 to be eligible to enter the second treatment course.
b: Patients will start taking rucaparib at the last dose level they had taken prior to discontinuation of therapy on C $_{T2}$1D1 in a 4-week cycle.
c: Patients will start nivolumab 480mg IV on C1D1. Nivolumab will be given every 4 weeks (+/- 3 days).
d: These C $_{T2}$1D1 evaluations may be performed up to 1 week prior to the start of treatment.
e: These evaluations will take place at baseline then every even cycle until off-study.
f: To be performed within 72 hours of study drug treatment.
g: The most recent scan prior to re-treatment will be used as the new baseline scan. After 12 cycles (if SD or better), the patient will then enter a monitoring phase during which they will be monitored with clinical appointments and imaging every 3 months or as clinically indicated.
h: Treatment will continue for 12 cycles (approximately 1 years) prior to discontinuation.

12.0 CRITERIA FOR REMOVAL FROM STUDY

Patients will be removed from the study when any of the criteria listed below applies. The reason for removal from the study and the date the patient was removed must be documented in the Clinical Research Database system. Patients who come off study before their first radiological assessment from baseline for reasons other than disease progression or treatment related toxicities may be replaced.

All patients who have received at least one dose of both study treatments will be assessable for safety of the combination therapy. Patients evaluable for efficacy analysis will include all patients who have received at least one cycle of treatment with both rucaparib and nivolumab and assessable for response. Patients who are missing an assessment of response post baseline will not be considered evaluable for response unless they missed the assessment

due to progression of disease or treatment related toxicities in which case they will be considered non-responders for that time point.

In the absence of treatment delays due to adverse events, treatment with rucaparib and/or nivolumab may continue until one of the following criteria applies:

- Until a total of 26 cycles (approximately 2 years) of treatment has been administered as long as subjects are receiving benefit from treatment and have not had disease progression or met any criteria for study withdrawal outlined below. Any subject in this study who continues to demonstrate objective clinical benefit at the end of a 2-year treatment duration may continue any component of study treatment after agreement between the principal investigator and treating investigator.
  Note: Any patient who discontinues study therapy after 2 years of treatment and demonstrated objective clinical benefit at the end of a 2-year treatment duration may resume study therapy in the setting of subsequent progression of disease off all therapy.
- Clinical or radiographic disease progression as defined by RECIST 1.1. Patient may be allowed to continue treatment after progression if they are deriving clinical benefit (section 9.4).
- Intercurrent illness that prevents further administration of treatment
- Intolerance of study treatment (as defined in sections 11.3 and 11.4)
- Patient decides to withdraw from the study
- Physician decides to withdraw a patient from the study for a reason not listed here
- Pregnancy in patient
- The patient is lost to follow-up

Due to the mechanism of action, subjects may experience growth in existing tumors or the appearance of new tumors prior to maximal clinical benefit of rucaparib and nivolumab. The patient may be allowed to continue study treatment after initial RECIST 1.1 defined progression if they are assessed by the treating physician to be deriving clinical benefit and tolerating study treatment. The treating physician may consult with the overall study PI for help with assessing the patient. Such patients should discontinue study therapy upon further evidence of progression at the discretion of the treating investigator.



Safety follows up and End of Study visit

Upon permanent discontinuation from the study treatment for any reason, the following procedures will be performed approximately 28 (+7) days after the last dose of study therapy, whichever is later.

- Full medical history, physical exam, assessment of performance status by KPS or ECOG status
- Review of concomitant medications
- Complete vital signs (pulse, blood pressure, temperature, respiratory rate, oxygen saturation) as well as weight
- Urinalysis
- Complete blood count with differential, including lymphocyte and eosinophil count
- Comprehensive metabolic panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate, calcium, total protein, albumin, serum bilirubin, alkaline phosphatase, ASL, AST) phosphorus, magnesium

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or clinically significant laboratory value must be followed until resolution or stabilization of the event.

Reporting of adverse events will occur for up to 30 days for serious adverse events, events of clinical interest and documentation of concomitant medications (within 30 [+7] days after the last administration of rucaparib. For nivolumab reporting of adverse events for up to 100 days post last dose is required.

Long-Term Follow-up Procedures:

All subjects who permanently discontinue study drug for any reason other than withdrawal of full consent will be contacted by clinic visit or telephone to assess survival and initiation of additional sarcoma therapy. Contact for all subjects will be attempted every 12 weeks (±28 days) following the safety follow-up visit until death, subject withdraws full consent, or up to 12 months after the end of treatment.

13.0 CRITERIA FOR OUTCOME ASSESSMENT AND ENDPOINT EVALUABILITY

13.1 Criteria for Therapeutic Response/Outcome Assessment

All patients will undergo a baseline staging CT scan of the chest (with or without contrast), abdomen and pelvis (with or without contrast), and MRI of the affected area if deemed

necessary by the treating physician. Response evaluations will occur at week 8 and every 8 weeks subsequently (± 1-week window) until week 56, and then less frequently at the discretion of the treating investigator.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1 (Primary response criteria).[32] 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 criteria.

In addition, patients will also be evaluated using the Immune-related Evaluation Response Criteria (irRECIST), which ***will not be used*** for treatment decisions (Secondary Response Criteria) and are discussed separately in section 13.1.13.

In subjects who have initial evidence of progressive disease (PD) as per RECIST criteria, it is at the discretion of the investigator to continue a subject on study treatment until confirmation of PD ≥ 4 weeks. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data.

Subjects will receive treatment if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating PD.
- No decline in the Eastern Cooperative Oncology Group (ECOG) performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

13.1.1 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 for non-nodal lesions and short axis for nodal lesions) as >20mm by chest x-ray, as >10mm with CT scan or MRI, or >10mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

To be considered pathologically enlarged and measurable, a lymph node must be > 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable unless there is evidence of progression after radiation therapy.

Non-measurable disease – All other lesions (or sites of disease), including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15mm short axis) are considered non-measurable disease. 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.

Target lesions – All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. 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. The baseline sum diameters will be used as a reference to further characterize any objective 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. Measurements of these lesions are not required, but the presence, absence or in rare cases unequivocal progression of each should be noted throughout follow-up.

13.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up portion of study. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion[23] being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions - Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray - Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

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 or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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.

13.1.3 Primary Response Criteria (RECIST 1.1)

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.

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. (Note: the appearance of one or more new lesions is also considered progressions).

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

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 short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion[23].

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 MSKCC Principal Investigator).

Evaluation of Best Response

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

Table 8. Evaluation of Best Response – RECIST criteria

Target Lesions	Non-Target Lesions	New Lesions	Best Response	Best Response for This Category also Requires:
CR	CR	No	CR	≥ 4 wks. Confirmation
CR	Non-CR/ Non-PD	No	PR	≥ 4 wks. Confirmation
PR	Non-CR/ Non-PD	No	PR	
SD	Non-CR/ Non-PD	No	SD	documented at least once ≥ 4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

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

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

13.1.4 Confirmation of response

Complete or partial response may only be claimed if the criteria for each are met at a subsequent time point (≥4 weeks later) in studies with a primary endpoint that include response rate.

Special note on target lesions that become "too small to measure"

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes, lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs, it is important that a value be recorded on the D2M form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

13.1.5 Not evaluable (NE)

When no imaging/measurement is done at all at a particular time point, the patient is considered not evaluable (NE) at that time point.

13.1.6 Early death

If the patient has no repeat tumor assessments following initiation of study therapy resulting from the death of the patient due to disease or treatment, it is considered early death.

13.1.7 Symptomatic Deterioration

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

13.1.8 Duration of response

Defined as the time measurement criteria are first met for CR/PR until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study).

13.1.9 Duration of stable disease

Measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

13.1.10 Progression-Free Survival (PFS)

PFS is defined as the period from start of study treatment until recurrent or progressive of disease (POD) is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study), death, or date of last study visit involving assessment of disease status.

13.1.11 Overall Survival (OS)

OS is defined as the observed length of life from start of study treatment to death or the date of last contact.

13.1.12 Secondary Response Criteria – Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

In 2013, Nishino et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability.[33] Based on these findings and in order to utilize both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishino et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines.

irRECIST
Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al. are presented below.

I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1.

One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign ‘No Disease’ (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease

Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

The key difference in irRECIST is that the appearance of new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB.

C. Follow-up for New Non-Measurable Lesions

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

<u>Overall Assessments for irRECIST</u>

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA),



the SumD At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB). In the setting where treatment is continued beyond progression further assessments using irRECIST will use the first scan showing progressive disease as the new baseline scan to which all subsequent scans are compared.

Table 8. Overall Assessment by irRECIST

Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with **no target lesions at baseline**, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation • irRECIST can be used in the **adjuvant setting**, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response. • Based on the above, investigators may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.

Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening
Other	**irNE:** used in exceptional cases where insufficient data exist. **irND:** in adjuvant setting when no disease is detected **irNN:**, no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

13.2 Criteria for Study Endpoint Evaluability

Patients evaluable for efficacy analysis will include all patients who have received at least one cycle of treatment with both nivolumab and rucaparib and are assessible for response. Patients who are missing an assessment of response post baseline will not be considered evaluable for response unless they missed the assessment due to progression of disease or treatment related toxicities in which case they will be considered non- responders for that time point. Patients who miss an assessment of response post baseline for any reason

other than progression of disease and treatment related toxicity will be replaced. Patients evaluable for safety analysis will include all patients who have received at least one dose of nivolumab and rucaparib.

14.0 BIOSTATISTICS

14.1 Primary Endpoint

The primary objective of this study is to evaluate the efficacy, as assessed by the best objective response rate (complete response + partial response) by 24 weeks by RECIST 1.1. This trial uses a one-stage design to test the alternative hypothesis that the objective response rate (ORR) is ≥ 0.25 versus the null hypothesis that ORR ≤ 0.05. Based on a one-stage design, the sample size for this study will be 20 patients. If ≥ 3 patients respond by 24 weeks, the treatment will be considered effective. This design has 91% power with 8% type-I error.

The patient population in this study represents patients with locally advanced/metastatic sarcoma that have likely received previous therapy where appropriate. The data supporting the 5% null rate comes from the SARC028 study that evaluated the efficacy of anti-PD-1monotherapy with pembrolizumab among patients with advanced/metastatic soft tissue and bone sarcoma. In the LMS cohort, there were no objective responses. In assessing the efficacy of a combination therapy incorporating anti-PD-1 agent in this study population a response rate of > 5% would be suggestive as having a signal of efficacy given the historical data. A single stage design is being utilized given the heterogeneity of the population, planned equal accrual of the two subtypes, and the relatively fast accrual comparing with the timeframe for primary endpoint assessment.

We expect to accrue approximately 1-2 patients per month and hence expect to finish enrollment in approximately 12-24 months. In the SAR028 study of pembrolizumab in sarcoma, success was defined as an objective response rate of 25% as this was considered to be a clinically meaningful. Therefore, an ORR of 25% is being tested in this study.

14.2 Secondary Endpoints

1. Safety

Adverse events will be graded according to the NCI CTCAE v5.0, presented on an individual basis and summarized using descriptive statistics.



2. Survival

PFS is defined as the period from start of study treatment until recurrent or progression of disease (POD) is objectively documented (taking as reference for progressive disease the smallest measurement recorded on study), death, or date of last study visit involving assessment of disease status. Overall survival (OS) is defined as the time from the start of treatment to the date of death or lost of follow-up, whichever occurs first. PFS rate at 24 weeks, median PFS, and median OS, along with their two-sided 95% confidence intervals, will be estimated using Kaplan-Meier methodology.

3. Best Objective Response Rate by irRECIST

Best objective response rate (complete response + partial response) by 24 weeks by immune-related response criteria (irRECIST) will be estimated as a binomial proportion, together with the two-sided 95% confidence interval.

4. Duration of response per RECIST and irRECIST among the responders.

Duration of response per RECIST and irRECIST among the responders will be displayed using the swimmer plot and summarized with the median (based on the Kaplan Meier curve if any censoring).

14.3 Correlative Endpoints Statistical Considerations

The study is not powered to detect specific hypotheses. Due to the small sample size, the correlative studies will be exploratory and hypothesis generating in nature. These analyses will help better identify patients having the potential to benefit from this therapy and aid in designing future studies.

To evaluate the association between genomic characteristics and selected immune-related biomarkers measured in tumor tissue at baseline with clinical efficacy. Categorical data analysis and logistic regression will be used to evaluate the associations between genomic and immune tumor markers and clinical outcome (eg, response, clinical benefit, time to progression, progression-free survival, and survival). Kaplan-Meier methodology and Cox Proportional Hazards models will be used to evaluate time to event endpoints.



15.0 TOXICITIES/RISKS/SIDE EFFECTS

Risks, toxicities and Treatment Emergent Adverse Events (TEAEs)

Rucaparib and nivolumab dosing likely will produce side effects, and not all side effects may be known. Specific identified risks and potential risks are highlighted below, as well as TEAEs observed in clinical trials. CTCAE Version 5 will be utilized for toxicity evaluation.

See the investigation brochure for complete list of possible adverse events related to rucaparib and nivolumab.

Rucaparib

Common TEAEs for 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 decreased, alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, constipation, decreased appetite, and dysgeusia. Commonly experienced Grade 3 or higher TEAEs included anemia/hemoglobin decreased, asthenia/fatigue, and ALT/AST increased. Results of a more recent integrated safety analysis for rucaparib treatment in over 900 patients with ovarian cancer who received 600 mg BID rucaparib in either 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, ALT/AST increased, decreased appetite, and dysgeusia. The most common TEAEs≥ Grade 3 included anemia/decreased hemoglobin, ALT/AST increased, neutropenia/decreased absolute neutrophil count (ANC), and asthenia/fatigue.

The laboratory abnormalities were consistent with the TEAEs, with decreased hemoglobin (and associated increase in mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]), increased ALT, increased AST, and increased serum creatinine, most commonly occurring. Decreased platelets, neutrophils, leukocytes, lymphocytes, and increased cholesterol were observed to a lesser extent. The transient elevations in ALT/AST with rucaparib treatment 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. 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. 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.

Adverse Events of Special Interest

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs) for rucaparib, as these events have been observed in patients exposed to cytotoxic chemotherapy (e.g., platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib.

Pneumonitis has been reported with PARP inhibitor treatment, including in clinical trials evaluating rucaparib. Currently, however, there is a lack of understanding of a mechanistic link between pneumonitis and PARP inhibitor treatment, and causality assessment is often confounded by lack of a consistent clinical pattern as well as other pre-disposing factors, such as cancer and/or metastases in lungs, underlying pulmonary disease, smoking history, and/or previous chemotherapy and radiotherapy. The following AEs will also be considered AESIs:

- Interstitial lung disease
- Pulmonary fibrosis
- Acute interstitial pneumonitis
- Alveolitis necrotizing
- Alveolitis
- Hypersensitivity pneumonitis
- Ofrganizing pneumonia

AESIs (both serious and non-serious) will be reported to Clovis within 24 hours of awareness and will continue to be reported to Clovis under SAE reporting requirements.

Nivolumab

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested up to 10 mg/kg. There was no pattern in the incidence,

severity, or causality of AEs to nivolumab dose level. Most AEs were low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs. Most high-grade events were manageable with the use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the Management Algorithms **(Appendix C).**

A total of 39 and 306 patients with selected recurrent or treatment-refractory malignancies have been treated in a completed Phase 1 single-dose study (CA209001) and an ongoing Phase 1 multidose study (CA209003), respectively. Because the safety profile from CA209003 to date is consistent with that observed for CA209001, only data from the larger and more recent study, CA209003, is presented below.

In CA209003 (n=306, including 129 patients with NSCLC), as of the 05-Mar-2013 data base lock, drug related AEs of any grade occurred in 75% of patients. The most frequent drug-related AEs occurring in > 5% of patients included fatigue (28%), rash (15%), diarrhea (13%), pruritus (11%), nausea (9%), decreased appetite (9%), hemoglobin decreased (6%) and pyrexia (6%). The majority of events were low grade, with grade 3/4 drug-related AEs observed in 17% of patients. The most common Grade 3/4 drug-related AEs occurring in > 1% of patients were fatigue (2%), pneumonitis (1%), diarrhea (1%), abdominal pain (1%), hypophosphatemia (1%), and lymphopenia (1%). Drug-related serious AEs (SAEs) occurred in 14% of patients; 8% were of Grade 3/4 including pneumonitis (1%) and diarrhea (1%). The spectrum, frequency, and severity of drug-related AEs were generally similar across the dose levels tested. A review of the safety data by tumor type (RCC, NSCLC, mCRPC, CRC, and melanoma) also did not show any clinically meaningful differences in the proportion of patients with AEs noted across tumor type.

Select adverse events with potential immune-related causality, previously termed “immune-related adverse events” or “adverse events of special interest” were also analyzed taking into account multiple events, with rates adjusted for treatment duration. Most events occurred within the first 6 months of therapy; cumulative or novel toxicities were not observed with prolonged drug exposure. Nineteen of 306 patients (6%) experienced grade 3-4 treatment-related select adverse events. Fifty-two of 230 patients (23%) with drug-related adverse events required management with systemic glucocorticoids and/or other immunosuppressive agents. Twenty-one of 52 (40%) resumed nivolumab therapy after toxicity resolved, while others discontinued therapy.

Although tumor progression was the most common cause of mortality, there were 3 drug-related deaths associated with grade 3-4 pneumonitis. Pneumonitis (any grade) occurred in 12 of 306 patients (4%), and grade 3-4 pneumonitis occurred in 4 patients (1%), with clinical presentations ranging from asymptomatic radiographic abnormalities to progressive, diffuse pulmonary infiltrates associated with cough, fever, and/or dyspnea. No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or treatment duration was noted. In 9 of 12 patients, pneumonitis was reversible with treatment discontinuation and/or immunosuppression (glucocorticoids, infliximab, mycophenolate). There were no pneumonitis-associated deaths between November 2011 and March 2013, the point of data



analysis, 79 patients continued to receive nivolumab during this time (median 29 weeks, range 2-69 weeks).

Adverse Event Definition

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product. Examples of AEs include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or grade of the condition
- New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE).

Events that do not meet the definition of an AE include:

- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease or condition present or detected at the start of the study that do not worsen.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

Time Period and Frequency of Detecting AEs and SAEs

AEs and SAEs will be collected from the time the first dose of study treatment is administered until 30 days following discontinuation of study treatment for rucaparib and from time of consent to 100 days post last dose for nivolumab regardless of initiation of a new cancer therapy or transfer to hospice. For, rucaparib after the 30-day reporting window after discontinuation of assigned treatment, only SAEs assessed as related to study drug(s) and all AESIs, irrespective of causality, need to be reported.

After discontinuation of study treatment, the investigator will monitor all AEs/SAEs that are ongoing until resolution or stabilization of the event or until the subject is lost to follow-up. At any time after treatment discontinuation the investigator may report any adverse event that they believe possibly related to study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported according to the internal and external reporting criteria.

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements) including those that worsen from baseline, and events felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as an AE or SAE, in accordance with the definitions provided.

The following laboratory abnormalities should be documented and reported appropriately:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.
- It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., anemia versus low hemoglobin value).

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

Investigational Scan Considerations

CT scans of the chest/abdomen/pelvis obtained at screening (if sooner than the next standard of care scan) are considered investigational. All other disease assessment scans will be per standard of care. The additional dosimetry that patients will be exposed to for the investigational scans is approximately 2 rem per scan.

Patients on study will have a biopsy at week 8 and may have an optional biopsy at the time of progression of disease. Patients undergoing investigational CT guided biopsies are exposed to an additional 0.626 Gy (+/- 0.132) dermatologically, an additional 29.9 mSv in for scan done in helical mode and an additional 18.9 mSv for scans done in axial mode.

It is estimated that each patient will have up to 1 CT scan for research purposes while on study, and up to 2 additional scans for CT-guided biopsies.

The informed consent will include the necessary risk language on contrast use and low-level radiation.

15.1 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant’s last investigational treatment/intervention. Any event that occur after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

<u>The following are not considered SAEs and therefore do not need to be reported as such:</u>

1. Pre-planned or elective hospitalization including social and/ or convenience situations (e.g., respite care)
2. Hospital visits of less than 24 hours duration (e.g., patient presents to the emergency room, but is not admitted to a ward)
3. Overdose of either study drug or concomitant medication unless associated with an SAE. However, the event should still be captured as a nonserious AE on the appropriate eCRF page
4. Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an AE or an SAE;
5. Events that meet the SAE criteria and occur after informed consent but before the first dose of study drug, which are considered unrelated to screening procedures.

15.1.6 Pregnancy Testing, Prevention and Lactation Reporting

Neither study drug should be used by pregnant women. Studies to evaluate the potential for embryotoxicity and teratogenicity have not been performed.

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

medical condition).

The need for a screening pregnancy test depends on whether a female subject is of childbearing potential or non-childbearing potential.

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

(1) Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in

women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

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

OR

Has a congenital or acquired condition that prevents childbearing.

A female of child-bearing potential is defined as any female who does not meet the criteria of non-childbearing potential as described in the previous paragraph.

If a female subject is of childbearing potential, she must have a serum β-HCG or urine pregnancy test performed within 72 hours of the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Subjects with positive pregnancy test result must be excluded from the study.

Male patients must not make semen donations during treatment and for 7 months following the last dose of study drug(s). Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 6 months days after the last dose.

(1) practice abstinence† from heterosexual activity;

OR



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

Acceptable methods of contraception are‡:

- Single method (one of the following is acceptable):
  - intrauterine device (IUD)
  - vasectomy of a female subject's male partner
  - contraceptive rod implanted into the skin
- Combination method (requires use of two of the following):
  - diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
  - cervical cap with spermicide (nulliparous women only)
  - contraceptive sponge (nulliparous women only)
  - male condom or female condom (cannot be used together)
  - hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin- only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 6 months after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

If a female subject becomes pregnant while receiving investigational therapy or within 6 months after the completion of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to Clovis and BMS to facilitate outcome follow-

up. If pregnancy is confirmed, subject must stop study treatment immediately. Information on the status of the mother and child will be forwarded to Clovis and BMS. Any premature termination of the pregnancy will be reported. If the partner of a male subject becomes pregnant, Clovis and BMS contact information will be provided for the partner to contact the companies directly, as per MSKCC policy.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a subject exposed to the study drug should be recorded and reported as an SAE.

15.1.7 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

15.2. External SAE Reporting

Corvus SAE Reporting: Rucaparib

All Serious Adverse Events (“SAE”) required to be reported pursuant to the Protocol shall be provided to Clovis within twenty-four (24) hours of the first learning of the event. The MSK CTMS SAE report form will always be completed as thoroughly as possible with all available details of the SAE, signed by the investigator, and forwarded to Clovis within the designated time frames. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying Clovis of the SAE and completing the form. The form will be updated when additional information is received. The investigator will always provide an assessment of causality at the time of the initial report

SAE Reports will be sent to Clovis at the email address below. Notwithstanding anything to the contrary herein, Institution will have the primary responsibility of reporting adverse events (“AE”) to regulatory authorities.

- drugsafety@clovisoncology.com

BMS SAE Reporting: Nivolumab

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).

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- 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.
- If the BMS safety address is not included in the protocol document (e.g., multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

MSK SAE form will be sent to BMS with the BMS Protocol number on the SAE form or on the cover sheet with the SAE form transmission.

- In accordance with local regulations, 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 will be reported on the MSK site form.

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

1. BMS Pregnancy Surveillance Form or,
2. MSK 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.

Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, **or** approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

For any pregnancy that occurs in a female partner of a male study participant, BMS contact information will be provided for the partner to contact the company directly, as per MSKCC policy.

16.0 PROTECTION OF HUMAN PARTICIPANTS

16.1 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals/entities described in the Research Authorization form. A Research Authorization form must be approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with others at the time of study publication.

The consent indicates that samples and genetic information collected may be shared with other qualified researchers and placed in online databases. An example of an online database is the NIH dbGAP database, which is monitored by the National Institutes of Health, and may be made accessible to investigators approved by the U.S. government. Such information will not include identifying information such as name. It is also stated in the Research Authorization that research data (e.g. genomic sequence) may be shared with regulators. The requirements for submission of genotype/phenotype data into the NIH dbGAP or any other public database will be followed as per the IRB SOP for Genomic Data Sharing.

16.2 Data Management

A clinical research associated (CRA) and clinical research coordinator (CRC) will be assigned to the study. The responsibilities of the CRA/CRC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secure database, Medidata. Source documentation will be available to support the computerized patient record.

16.3 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.4 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan, where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials."

There are several different mechanisms by which clinical studies are monitored for data, safety and quality. At a departmental/PI level there exists procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Deputy Physician-In-Chief, Clinical Research.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant/or by the end of the year one if no accruals and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual.

16.5 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

Participating sites that are conducting specimen analysis must submit the following documents to MSK before specimens can be shipped to the site:

- Participating Site 1572
- Conflict of Interest forms for Participating Site Investigators on the 1572

Participating sites that are conducting specimen analysis should submit this protocol to their IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

16.5.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and approved by the MSKCC IRB/PB.

16.5.2 Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC, approval from the MSKCC IRB/PB is required prior to the action. A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

16.5.3 Document maintenance

The MSKCC PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

17.0 REFERENCES

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18.0 APPENDICES

Appendix A. Deleterious or suspected deleterious germline or somatic mutations present in the following genes for correlative analysis

Mismatch Repair (MMR)	Nucleotide Excision Repair (NER)	Homologous Recombination (HR)	Fanconi Anemia (FA)	DNA Damage Checkpoint	Base Excision Repair (BER)
MLH1	ERCC2	ABRAXAS1	FANCA	ATM	MUTYH
MSH2	ERCC3	BARD1	FANCC	ATR	PARP1
MSH3	ERCC4	BRCA1		CHEK1	NTHL1
MSH6	ERCC5	BRCA2		CHEK2	
PMS1	POLE	BRIP1		TP53BP1	
PMS2	POLD1	MRE11A		MDC1	
		NBN		BABAM1	
		PALB2			

		RAD21 RAD50 RAD51 RAD51B RAD51D RAD52 RAD54L RECQL RECQL4 RTEL1 XRCC2			

Abbreviations: MMR: mismatch repair; NER: Nucleotide excision repair; HR: Homologous recombination, FA: Fanconi anemia

Appendix B. Medications to be used with caution in combination with Rucaparib

CYP Enzyme	**Sensitive Substrates**
CYP1A2	Tizanidine, theophylline, alosetron, caffeine, duloxetine, melatonin, ramelteon, tasimelteon
CYP2C9	Celecoxib
CYP2C19	S-mephenytoin, omeprazole
CYP3A	Alfentanil, sirolimus, tacrolimus, avanafil, cuspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomiptapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

CYP Enzyme	**Substrate**
CYP2C9	Warfarin (monitor INR regularly per standard clinical practice)

Drug	Comments
Digoxin	Rucaparib marginally increases digoxin AUC, monitor digoxin levels after starting rucaparib and then regularly per standard practice
Metformin	Metformin renal elimination and hepatic uptake may be decreased
BRCP substrates	e.g. rosuvastatin (exposure may be increased)

Abbreviations: CYP = cytochrome P450; This table is prepared to provide examples of clinical sensitive or moderate sensitive index substrates and is not intended to be an exhaustive list. Data compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Appendix C. Immune-Related Adverse Events Management Guidance for Investigators

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

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

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

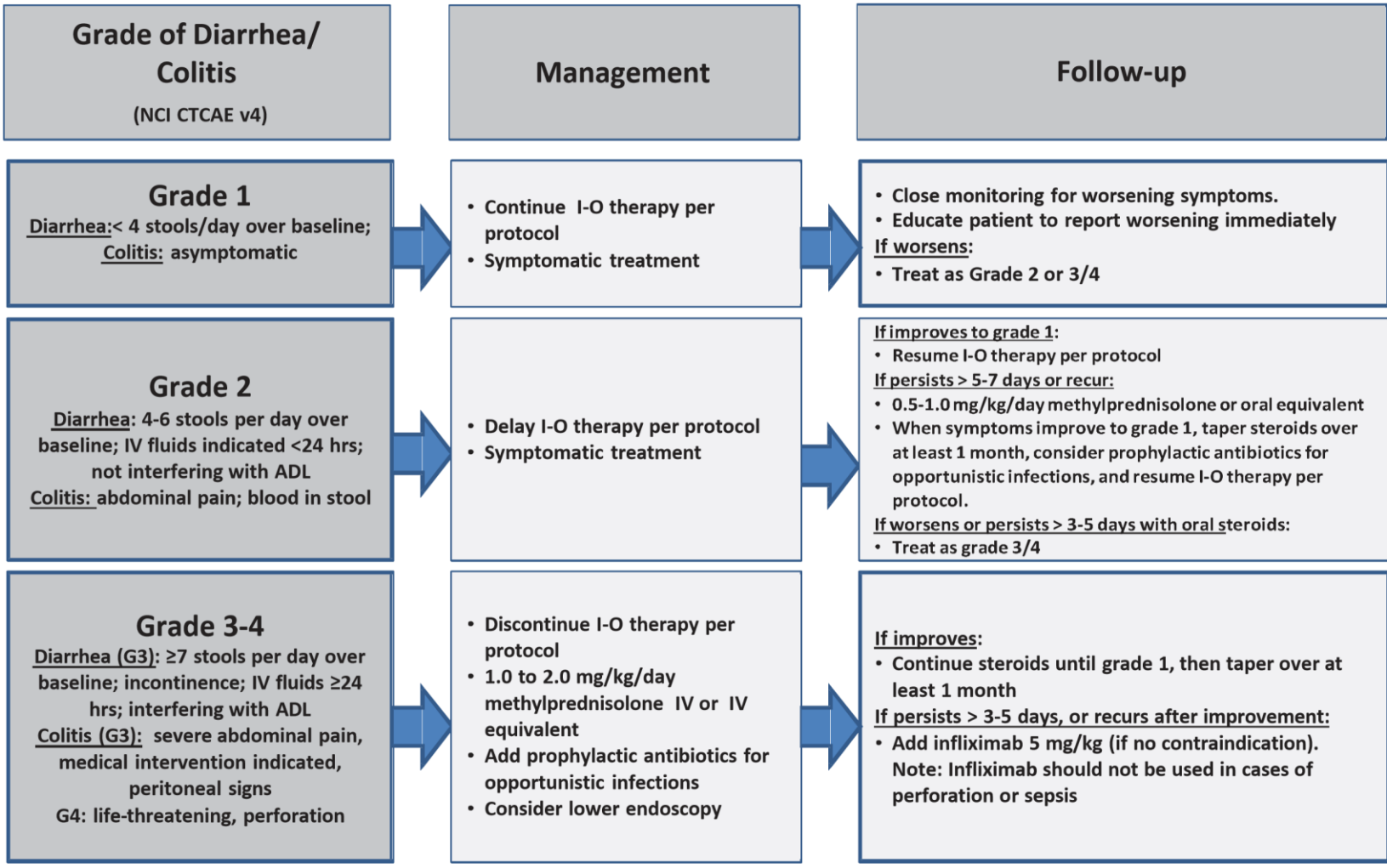
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

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

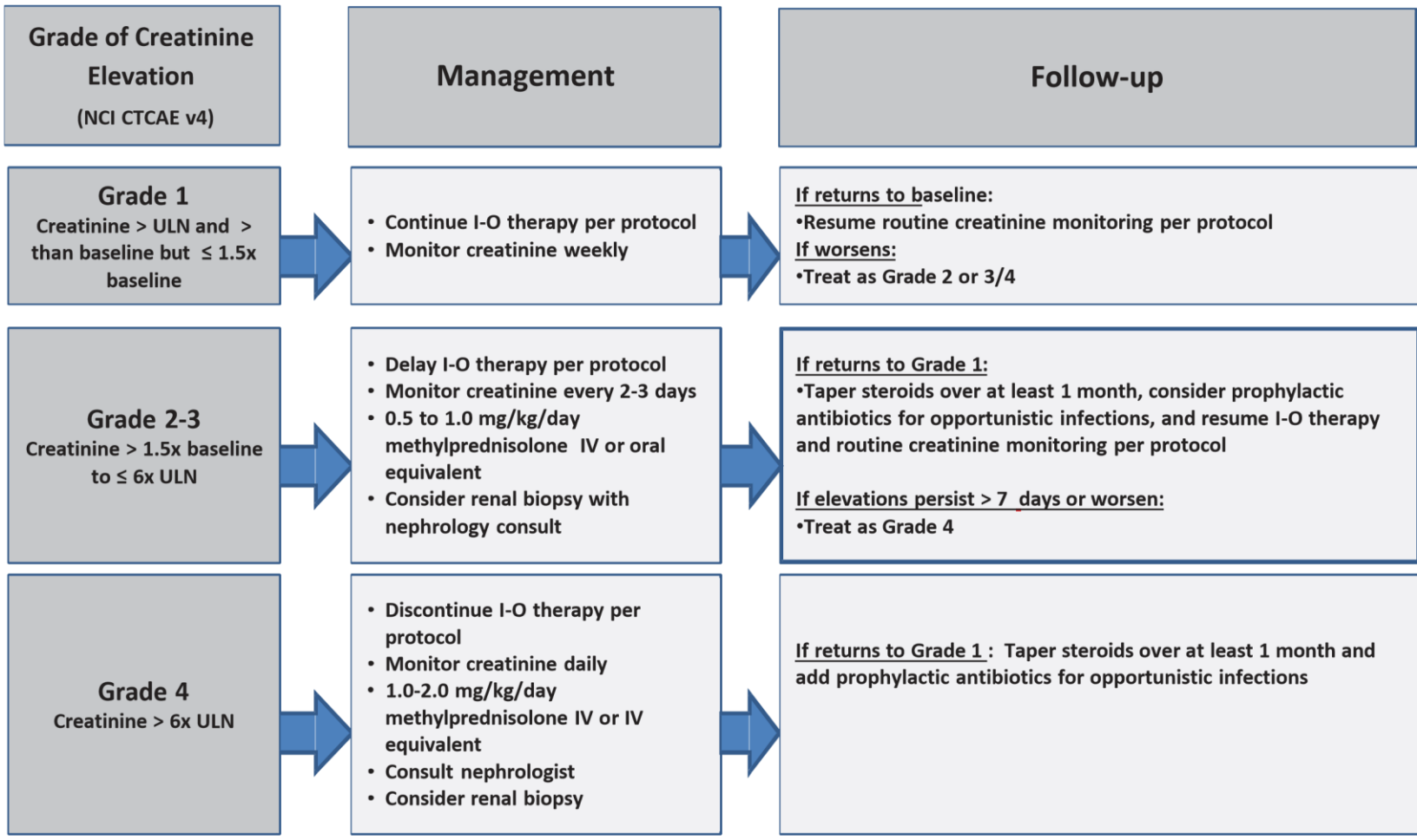




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Renal Adverse Event Management Algorithm

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



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

Pulmonary Adverse Event Management Algorithm

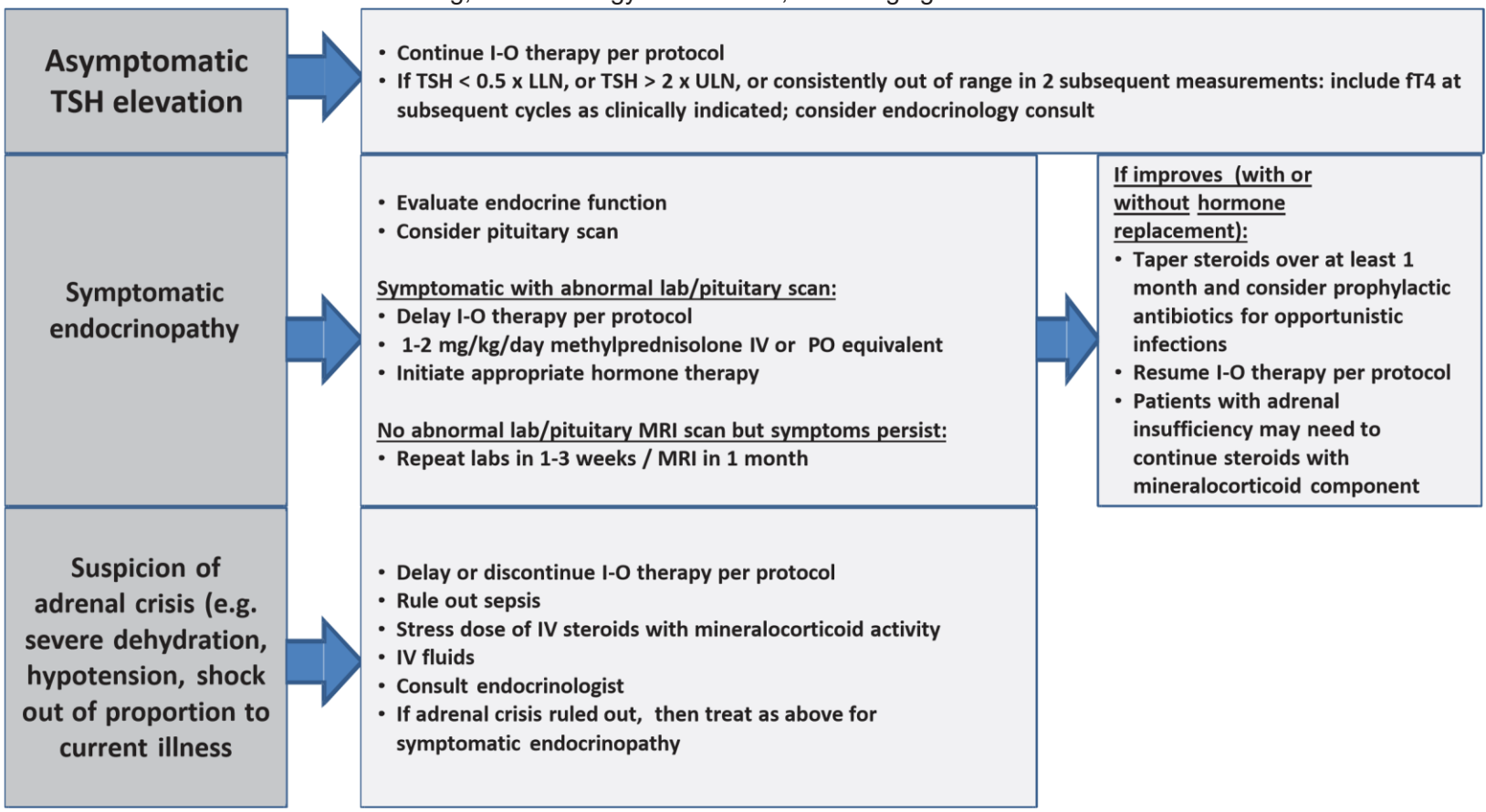
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days If improves: • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics If not improving after 2 weeks or worsening: • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	If improves to baseline: • Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: • Add additional immunosuppression

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

Endocrinopathy Adverse Event Management Algorithm

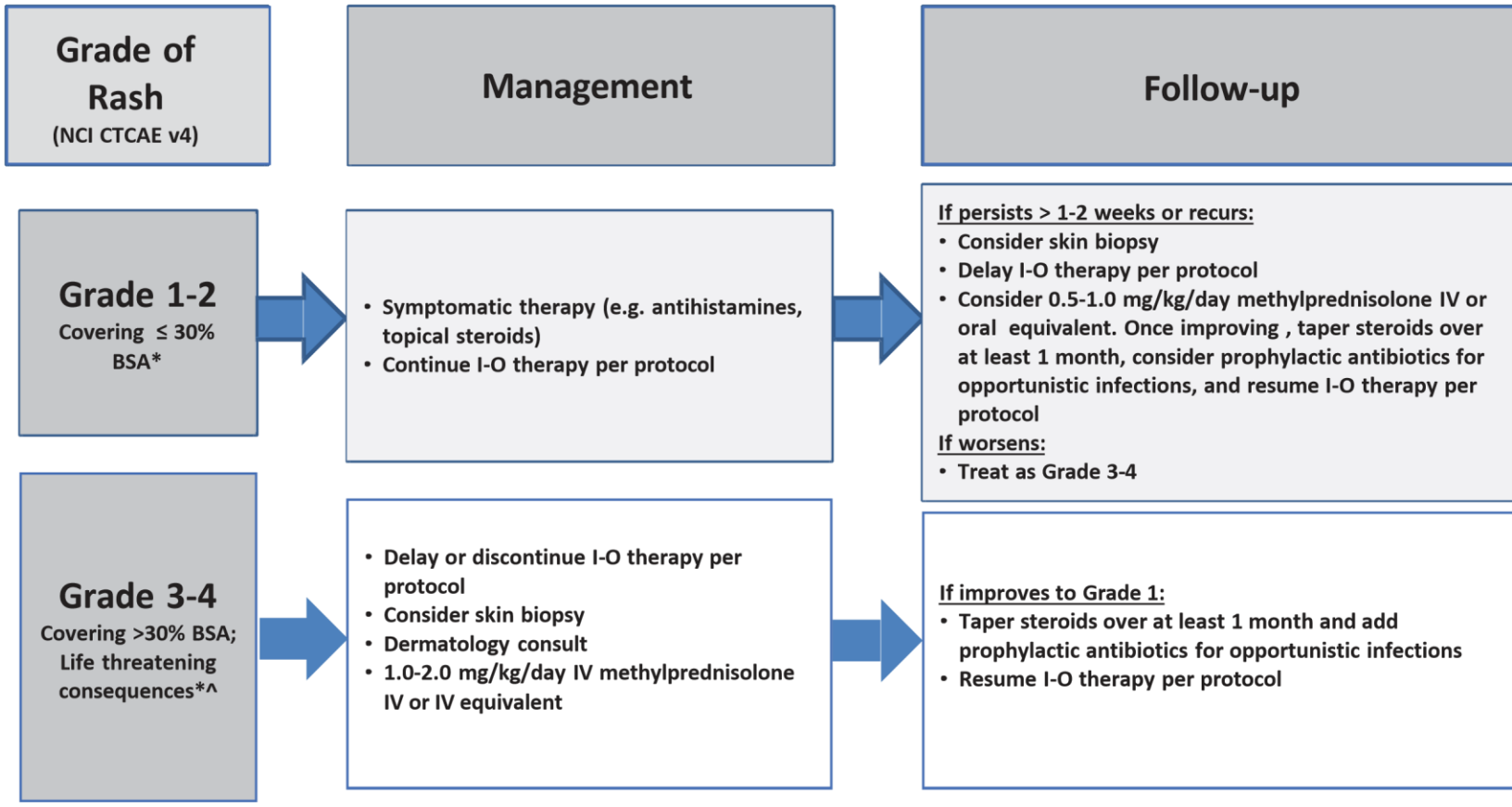
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



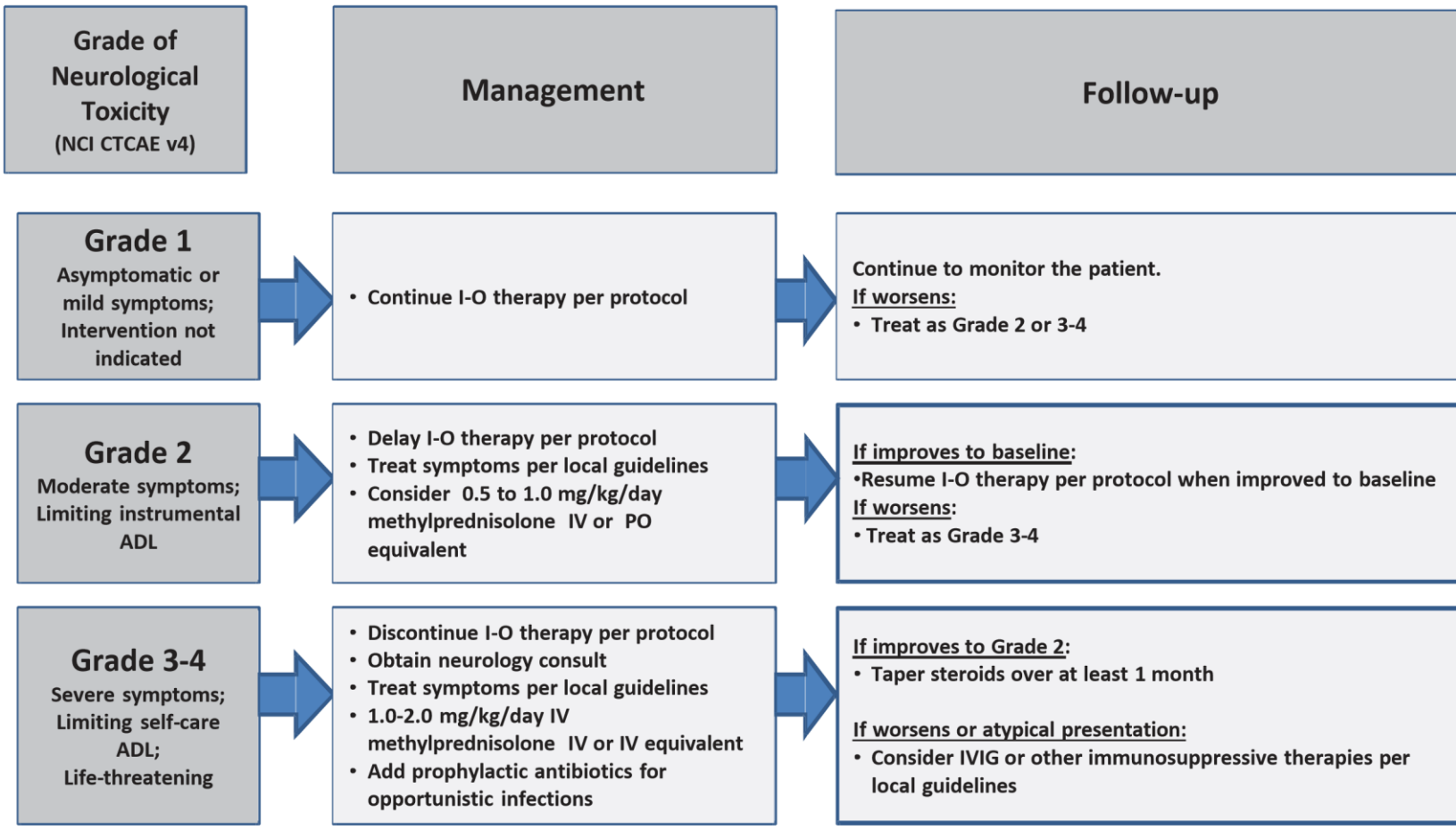
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v5 for term-specific grading criteria.

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

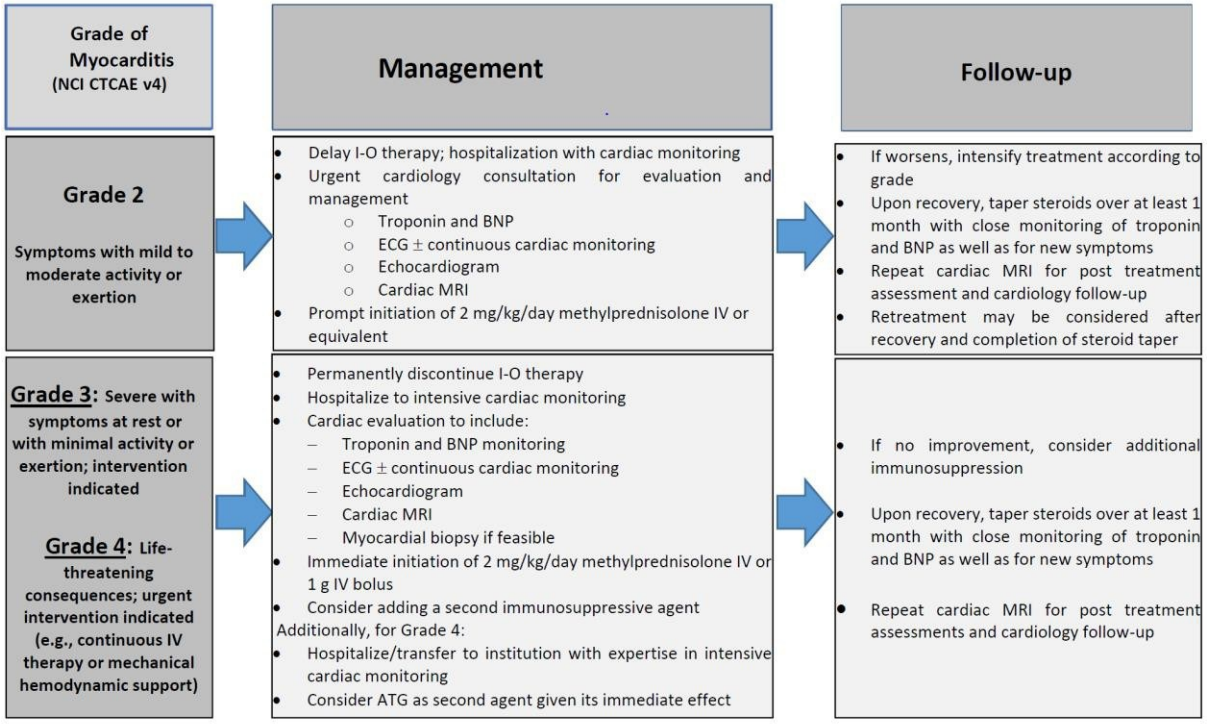
Neurological Adverse Event Management Algorithm

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



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

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging