DF/HCC Protocol #: 16-263

TITLE: A phase II study with a safety lead-in of nivolumab in combination with bevacizumab or in combination with bevacizumab and rucaparib for the treatment of relapsed epithelial ovarian, fallopian tube or peritoneal cancer

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NCI-Supplied Agent(s): N/A
Other Agent(s):
Nivolumab (Bristol-Myers Squibb)
Rucaparib (pharmaand GmbH)
Bevacizumab or biosimilar (commercial)

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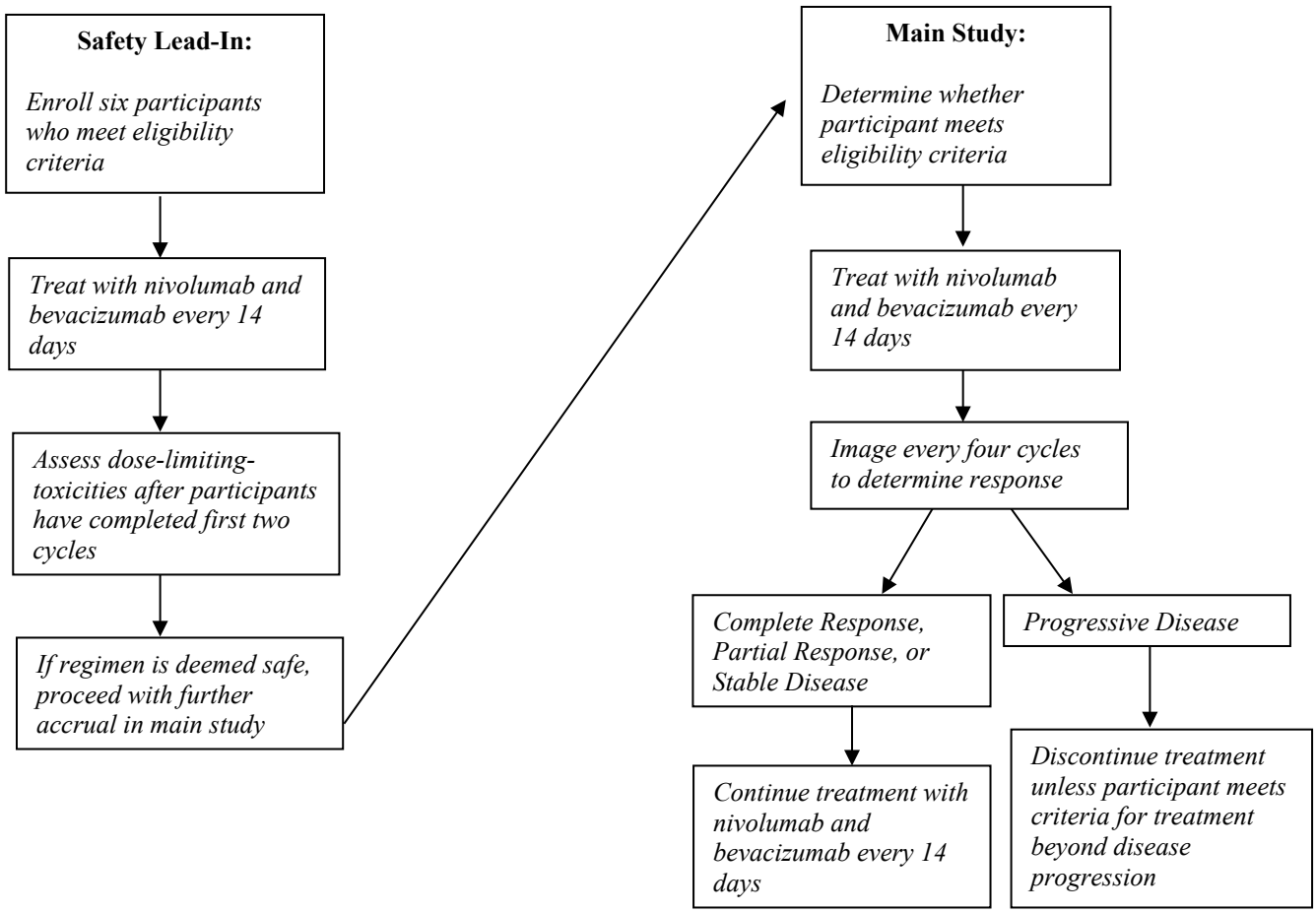
SCHEMA (COHORT 1)

1 cycle = 14 days



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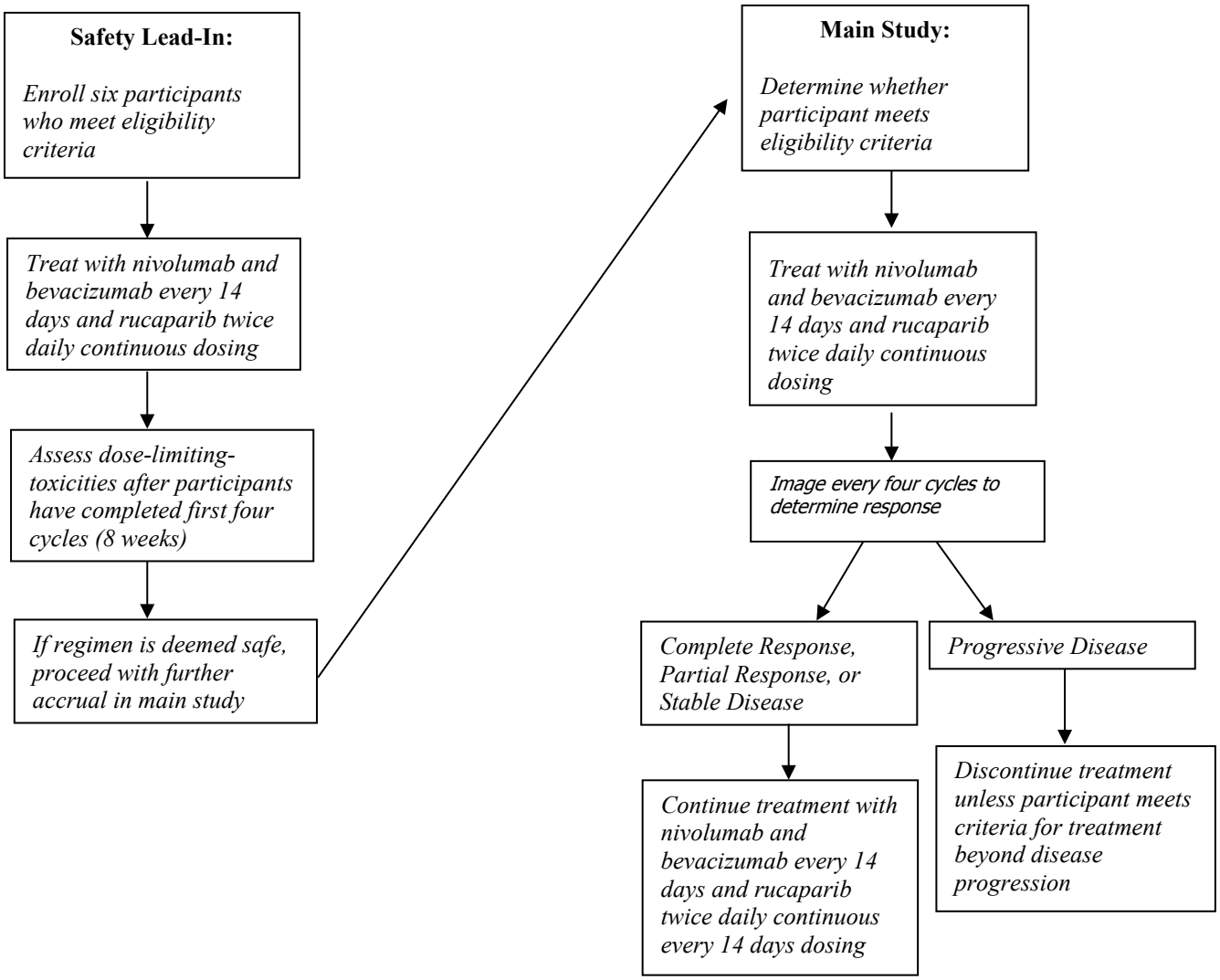

SCHEMA (COHORT 3)

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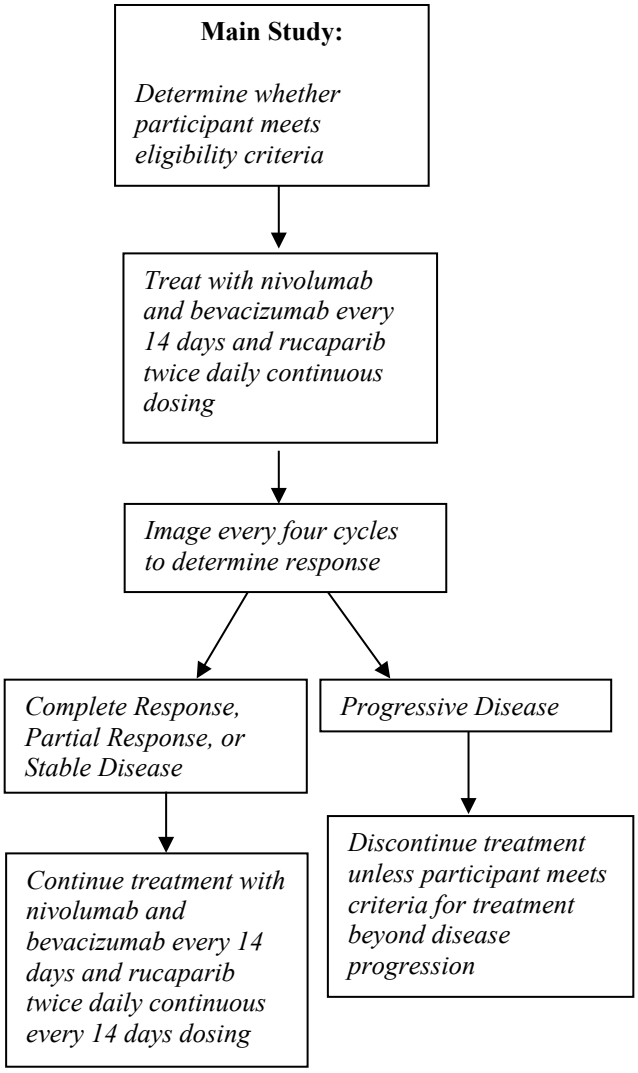

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1. OBJECTIVES

1.1 Study Design

This is a phase II two-arm study with a safety lead-in. Cohort 1 will look at the combination of nivolumab, an intravenous monoclonal antibody and inhibitor of the immune checkpoint PD-1, and bevacizumab, an intravenous monoclonal antibody against VEGFA and inhibitor of angiogenesis, in patients with relapsed epithelial ovarian, fallopian tube or peritoneal cancer. Cohort 2 and cohort 3 will look at the combination of nivolumab, bevacizumab, and rucaparib, an oral small molecule inhibitor of PARP enzymes, including PARP-1, PARP-2, and PARP-3, also in patients with relapsed epithelial ovarian, fallopian tube or peritoneal cancer. Patients on all cohorts will receive treatment with nivolumab and bevacizumab every 14 days with one cycle consisting of one treatment and undergo restaging every four cycles. Patients on cohort 2 and cohort 3 will also receive rucaparib twice daily as continuous dosing. Patients in cohorts 1 and 2 will be enrolled following a two-stage design with continuation of enrollment to the second stage if sufficient anti-tumor activity is seen in the first stage. Patients in cohort 3 will be enrolled in a single stage designed for assessment of safety and tolerability.

1.2 Primary Objectives

Cohort 1: The primary objective is to investigate the objective response rate of nivolumab and bevacizumab using RECIST 1.1 criteria or modified GCIG CA-125 criteria.

Cohort 2: The primary objective is to investigate the objective response rate of the combination of nivolumab, bevacizumab, and rucaparib using RECIST 1.1 criteria or modified GCIG CA-125 criteria.

Cohort 3: The primary objective is to investigate the safety and tolerability of the combination of nivolumab, bevacizumab, and rucaparib based upon maintenance of dosing without drug modifications within the first 100 days of dosing.

1.3 Secondary Objectives

1. To investigate the safety and observed toxicities of the combination of nivolumab and bevacizumab or the combination of nivolumab, bevacizumab, and rucaparib in women with relapsed ovarian, fallopian tube, or primary peritoneal cancer.
2. To investigate the percentage of patients progression-free at 6 months, duration of response, and overall response in women with relapsed ovarian, fallopian tube, or primary peritoneal cancer receiving nivolumab and bevacizumab or the combination of nivolumab, bevacizumab, and rucaparib. In patients in Cohort 3, additional secondary measures of clinical activity will include objective response rate by RECIST 1.1 or modified GCIG CA-125 criteria.
3. To investigate immune-related objective response rate and immune-related progression-free survival (irPFS) in women with relapsed ovarian, fallopian tube, or primary peritoneal cancer receiving nivolumab and bevacizumab or the combination of nivolumab, bevacizumab, and rucaparib.
4. To investigate the association of tumoral PD-L1 in pre-treatment (archival or pre-treatment biopsy) with anti-tumor activity of the combination of nivolumab and bevacizumab or the

combination of nivolumab, bevacizumab, and rucaparib in women with relapsed ovarian, fallopian tube, or primary peritoneal cancer

1.4 Exploratory Objectives

Exploratory translational objectives include:

a. Evaluation of gene expression immune profiles in association with anti-tumor activity of combination nivolumab and bevacizumab or the combination of nivolumab, bevacizumab, and rucaparib
b. Evaluation of somatic mutational burden and alterations in homologous recombination pathway genes and association with anti-tumor activity of combination nivolumab and bevacizumab or the combination of nivolumab, bevacizumab, and rucaparib
c. Evaluation of serum cytokines pre-, on-, and post-treatment, and association with anti-tumor activity of combination nivolumab and bevacizumab or the combination of nivolumab, bevacizumab, and rucaparib

2. BACKGROUND

2.1 Ovarian Cancer

Epithelial ovarian cancer is the third most common and the most lethal gynecologic malignancy, with an incidence of 21,980 new cases and approximately 14,270 deaths estimated in 2014 (Siegel *et al.,* 2014). This disease typically presents at an advanced stage, with a high risk of recurrence following first-line platinum-based chemotherapy. In the recurrent setting, treatment options for managing relapsed epithelial ovarian cancer (EOC) include platinum-based regimens, liposomal doxorubicin, paclitaxel, gemcitabine, bevacizumab, olaparib, and others. Bevacizumab, an inhibitor of VEGF-A, is active as a single agent, is generally well-tolerated without the usual side effects of cytotoxic chemotherapy, and has reported response rates of approximately 16-21% as monotherapy (Cannistra *et al.,* 2007; Burger *et al.,* 2007). In relapsed EOC bevacizumab has also been studied in combination with cytotoxic chemotherapy with reported response rates of 27% and 79% in the platinum-resistant and platinum-sensitive settings, respectively (Pujade-Lauraine *et al*., 2014; Aghajanian *et al.,* 2012). While there are many options for the treatment of relapsed disease, the response rates are generally low, remission durations are short, and resistance invariably develops. More effective therapy for relapsed EOC represents an important unmet need.

2.2 PD-1 Blockade as Immunotherapy in Oncology

PD-1 (or CD279), a 55-kilodalton Type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include immunoglobulin super family members CD28, CTLA-4, ICOS, and BTLA. PD-1 is highly expressed on activated T cells and B cells.

PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems (Freeman *et al.,* 2000; Latchman *et al.,* 2001; Carter *et al.,* 2002). The interaction of PD-1 with

its ligands, PD-L1 and PD-L2, expressed on antigen-presenting cells (APCs) and DCs, transmits negative regulatory stimuli to down-modulate the activated T-cell immune response. The absence or inhibition of PD-1 in murine models has resulted in the development of various autoimmune phenotypes and autoimmune diseases (Sharpe *et al.,* 2007). Taken together, these results suggest that inhibition of PD-1 binding to its ligands has the potential to activate T-cell responses. Since these responses are variable and dependent upon various host genetic factors, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Tumors can express tumor-specific antigens as a result of mutational burden, and ongoing immune surveillance is believed to control the development of many tumors. Tumor progression may depend on the acquisition of mechanisms that permit them to evade an effective immune response. One such mechanism of evasion may be the expression of ligands, which engage inhibitory receptor(s) on anti-tumor T-cells of many tumors. PD-L1 expression has been found on a number of tumors and may be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response (Dong *et al.,* 2002; Wintterle *et al.,* 2003; Dong *et al.,* 2003). Expression of INF-γ by T cells is known to induce PD-L1 expression in tumors. (Pardoll *et al.*, 2012). PD-L1 expression has been associated with poor prognoses in renal (Thompson *et al.,* 2004; Thompson *et al.,* 2005; Thompson *et al.,* 2006), esophageal (Ohigashi *et al.,* 2005), gastric (Wu *et al.,* 2006) ovarian (Dong *et al.,* 2003), pancreatic (Nomi *et al.,* 2007), and lung cancer (Zitvogel *et al.,* 2006). PD-1 engagement on T-cells by PD-L1-positive APC or PD-L1-positive tumor cells in the tumor microenvironment may limit effective immune responses. Conversely, PD-L1 expression may be a positive prognostic factor as it may indicate infiltration of tumor-specific T cells that secrete IFN-γ, which upregulates PD-L1 expression. Consistent with this hypothesis is the co-localization of lymphoid cell infiltrates and PD-L1 staining observed in human melanoma lesions (Taube *et al.,* 2012).

Studies in multiple tumor models using a chimeric murine anti-mouse PD-1 antibody showed that PD-1 blockade has anti-tumor activity (Iwai *et al.,* 2005). Blocking PD-1 in PD-L1-positive tumors may reverse the inactivation of tumor-specific effector T-cells at the tumor site, as well as activate anti-tumor responses that are limited by PD-L1 expression on "host" DC or APC. The anti-tumor effects of anti-PD-1 observed in several murine models suggest that both PD-L1-positive and PD-L1-negative tumors may be targeted using this approach. In addition, in several tumor models in which anti-PD-1 has proved ineffective, PD-1 blockade can be combined with vaccines or other immunomodulatory antibodies for improved therapeutic efficacy (Hirano *et al.,* 2005; Li *et al.,* 2009; Curran *et al.,* 2010).

2.3 PARP inhibitors in ovarian cancer

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) are a class of drugs which target the DNA repair pathway. PARPi's have now been demonstrated to have activity in ovarian cancer in a number of different settings, including in relapsed disease (Audeh *et al.,* 2010; Gelmon *et al.*, 2011) as well as in a maintenance setting following response to platinum-based chemotherapy (Ledermann *et al.*, 2012; Ledermann *et al.*, 2014; Mirza *et al.*, 2016; Pujade-Lauraine *et al.*, 2017; Coleman *et al.*, 2017). PARPi's appear to be particularly active in the setting of pre-existing defects in double-strand DNA repair, although activity has been observed

in patient populations without evidence of homologous recombination deficiency (Mirza *et al.*, 2016; Coleman *et al.,* 2017). Three PARPi's (rucaparib, olaparib, and niraparib) are currently approved by the US FDA for therapy in ovarian cancer in different clinical settings.

Combination therapy with PARPi's has been an area of growing interest to increase activity and overcome drug resistance. Initial studies investigated the potential of combining PARPi's with chemotherapy; a particular challenge in this setting has been the overlapping toxicity of myelosuppression (Matulonis *et al.*, 2017). As such, combinations of PARPi's with targeted or biologic therapies have been of growing interest, where overlapping myelosuppressive toxicities may be avoided. A Phase 2 study combining the anti-angiogenic cediranib with the PARPi olaparib demonstrated significant activity in women with platinum-sensitive ovarian cancer compared to olaparib alone (Liu *et al.*, 2014), and Phase 3 trials of this combination are ongoing. Additional ongoing trials are investigating the combination of olaparib and bevacizumab following initial platinum-based therapy for ovarian cancer and the combination of niraparib and bevacizumab in relapsed disease. Similarly, there has been interest in combining PARPi's with immune checkpoint inhibitors, and recent data have demonstrated activity of combination pembrolizumab and niraparib in women with platinum-resistant ovarian cancer, including in women without a BRCA mutation (Konstantinopoulos *et al.*, 2018).

2.4 IND Agents

2.4.1 Nivolumab

Mechanism of Action

Nivolumab (also referred to as BMS-936558, MDX1106, ONO-4538) is a fully 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. (Sharpe *et al.,* 2007) 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.

Summary of Preclinical Studies

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family, such as CD28 inducible co-stimulator (ICOS), cytotoxic T lymphocyte antigen-4 (CTLA-4), and B and T lymphocyte attenuator (BTLA) (*Nonclinical Study Report: Medarex Study No. MDX1106-025-R*, 2006; *Nonclinical Study Report: Medarex Study No. MDX1106-028-R*, 2007). Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro (Velu *et al.,* 2009; *Nonclinical Study Report: Medarex Study No. MDX1106-023-R*, 2006; *Nonclinical Study Report: Medarex Study No. MDX1106-032-R*, 2006). Fluorescent-activated cell sorter (FACS) analysis confirmed that nivolumab binds to transfected CHO and activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1, but not to rat or rabbit PD-1 molecules (*Nonclinical Study Report: Medarex Study No. MDX1106-025-R*, 2006).

PD-1 inhibition in a mixed lymphocyte reaction (MLR) resulted in a reproducible concentration-dependent enhancement of IFN-γ release in the MLR up to 50 μg/mL. No effect was observed with a human IgG4 isotype control or CD4+ T cells and dendritic cell (DC) controls (Want *et al.,* 2014).

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well-tolerated at doses up to 50 mg/kg, administered weekly for five weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. Nivolumab-related findings were limited to a reversible decrease of 28% in triiodothyronine (T3) among the females administered 27 doses of 50 mg/kg. No corresponding changes in the level of thyroxin (T4), thyroid-stimulating hormone (TSH), or histologic changes in the thyroid were observed (*Nonclinical Study Report: Medarex Study No. SUV00025/MDX1106-024-R*, 2006; *Nonclinical Study Report: Medarex Study No. WIL-552003/MDX1106-025-R*, 2007).

An enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted (*BMS-936558: Intravenous Study).* Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC(0-168 h)] 117,000 μg•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice (Habicht *et al.,* 2007).

Summary of Clinical Studies

Nivolumab has demonstrated clinical activity either as monotherapy or in combination with ipilimumab in several tumor types, including non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC). The majority of responses were durable and exceeded six months (BMS-936558 (nivolumab) Investigator Brochure, 2014). The FDA has approved the use of nivolumab to treat patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy as well as patients with unresectable or metastatic refractory melanoma.

Nivolumab was investigated in a phase II study of 18 with platinum-resistant ovarian cancer (PROC) (Haminishi *et al., 2014).* Eligibility for this study required at least two prior lines of chemotherapy including a taxane. This was a heavily treated group with 11 of the 18 patients having received four or more prior lines of chemotherapy. Despite extensive prior treatment, a preliminary response rate of 18% and disease control rate of 44% were reported in this study, which compare favorably to results observed with single agent cytotoxic chemotherapy in this clinical setting.

Clinical Pharmacokinetics

Single-dose Pharmacokinetics of Nivolumab

Single-dose PK of nivolumab was studied in 39 subjects with cancer (*Clinical Study Report: Study No. MDX1106-01*, 2011). The single-dose pharmacokinetics (PK) of nivolumab was linear and dose-proportional in the range of 0.3 mg/kg to 10 mg/kg. The mean terminal T-HALF of nivolumab ranged between 17 and 25 days across the dose range of 0.3 mg/kg to 10 mg/kg. Geometric mean total clearance varied from 0.13 mL/h/kg to 0.19 mL/h/kg, while mean volume of distribution varied between 83 mL/kg and 113 mL/kg across doses. The clearance and half-life of nivolumab are consistent with that of IgG4.

Multiple-dose Pharmacokinetics of Nivolumab

The multiple-dose PK of nivolumab given Q2W was determined from MDX1106-03 study as well as by population PK (PPK) using data from 669 subjects across nivolumab studies. (*Clinical Study Report: Study No. MDX1106-03*, 2013) Multiple-dose PK of nivolumab following Q2W dosing was linear with dose-proportional increase in Cmax and AUC(TAU) in the studied range of 0.1 mg/kg to 10 mg/kg. Nivolumab accumulation with Q2W dosing frequency was in the range of 2.9 to 3.3 based on AUC(TAU), 2.0 to 2.4 based on Cmax, and 3.1 to 4.8 based on Cmin. A PPK model was developed by nonlinear mixed effect modeling using data from 669 subjects. Nivolumab concentration-time data were well described by a linear, 2-compartment, 0-order IV infusion model with first-order elimination. Nivolumab PK was found to be linear, dose independent, and time invariant. The geometric mean of terminal T-HALF was 25.6 days and the typical clearance was 8.8 mL/h, which are consistent with those of full human immunoglobulin antibodies. Clearance of nivolumab is independent of dose in the dose range (0.1 mg/kg to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights.

Flat (Standardized Dose) of Nivolumab

Nivolumab monotherapy has been extensively studied in a number of tumor types including NSCLC, MEL, RCC, and CRC with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of subjects in these studies have been characterized by population pharmacokinetic (PPK) analysis of data collected these studies, together with PK data from several phase 1, 2, and 3 clinical studies of nivolumab monotherapy in solid tumors. Population PK (PPK) analyses have shown that the PK of nivolumab are linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg, and are similar across tumor types. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients.

Using the PPK model, nivolumab steady-state trough, peak and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) were predicted for a flat nivolumab dose of 240 mg

Q2W and compared to those following administration of 3 mg/kg Q2W in NSCLC subjects. A dose of 240 mg nivolumab is identical to a dose of 3 mg/kg for subjects weighing 80 kg, which is the approximate median body weight of NSCLC subjects in the 3 Phase 2 and 3 BMS clinical studies of nivolumab monotherapy. The geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Across the various tumor types in the BMS clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. Thus a flat dose of 240 mg every 2 weeks is planned for investigation in this study.

Safety Profile

Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues. A variety of preferred terms (PTs) have been used to describe similar kinds of organ-related AEs, with the result being that AE frequency tables organized by PTs can lead to underestimation of the frequency of similar kinds of organ-related AEs. To address this issue, select AE categories were created. Select AE categories group together the most common and impactful PTs by organ category. These categories include the following: pulmonary, GI, hepatic, skin, endocrine, hypersensitivity/infusion reaction, and renal AEs. It is useful to consider the management of nivolumab-related AEs by organ category as the diagnostic work-up often requires excluding other potential diagnoses and, when appropriate, instituting specific management principles as outlined in the subsequent subsections and Appendix B.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 4,000 subjects treated to date. All available data suggest that nivolumab monotherapy has a consistent AE profile across tumor types. Across all studies conducted to date, treatment-related AEs have included pulmonary toxicity, renal toxicity (including acute renal failure), endocrine abnormalities, GI toxicity, dermatologic toxicity (including rash), and hepatotoxicity. Most AEs were low-grade (Grade 1-2) with relatively few related high-grade (Grade 3-4) AEs. The safety profile is generally consistent across completed and ongoing clinical trials, with no maximum tolerated dose (MTD) reached at any monotherapy dose tested up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level.

In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Safety management algorithms for organ-specific AEs are found in Appendix B. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized. Once the AE has begun to improve,

corticosteroids can be tapered over approximately three weeks to six weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms.

The safety profile of nivolumab combination therapy varies with the agent combined with nivolumab, but is generally consistent with the safety profiles observed with either agent alone and, in some cases, the frequency of AEs may be greater than that observed with either agent alone.

For nivolumab monotherapy and combination therapy, the majority of AEs have been managed successfully with supportive care and, in more severe cases, a combination of dose delay, permanent discontinuation, and/or initiation of systemic corticosteroids. Most high-grade events were manageable with use of corticosteroids or hormone replacement therapy (endocrinopathies) as instructed in the management guidelines provided in Appendix B.

It is rare for a patient receiving immunosuppression for nivolumab-related AEs to develop an opportunistic infection. Patients with inflammatory events of any organ category expected to require more than four weeks of corticosteroid or other immunosuppressive agents to manage the AE should be considered for antimicrobial/antifungal prophylaxis, per institutional guidelines, to prevent opportunistic infections such as *P. jiroveci* (formerly *P. carinii*) and fungal infections. Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate. In addition, a concomitant opportunistic infection should be considered in the differential diagnosis if a patient develops recurrent AEs in the setting of ongoing or prior immunosuppressive use. Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

Clinical Safety of Nivolumab Monotherapy in Combined Advanced Malignancies

A total of 39 and 306 subjects with selected recurrent or treatment-refractory malignancies have been treated in a completed phase I single-dose study (MDX1106-01) and a completed phase I multidose study (MDX1106-03), respectively (*Clinical Study Report: Study No. MDX1106-01*, 2011; *Clinical Study Report: Study No. MDX1106-03*, 2013). The safety data observed from the smaller MDX1106-01 study is similar to the larger and more recent MDX1106-03 study.
As an overview, review of the safety data by tumor type (RCC, NSCLC, mCRPC, CRC, and melanoma) did not show any clinically meaningful differences in the proportion of subjects with AEs noted across tumor types. Overall, the safety profile of nivolumab monotherapy was generally manageable and was consistent with the mechanism of action of nivolumab. No MTD was reached at doses tested up to 10 mg/kg Q2W. The nature, frequency, and severity of any causality and treatment-related safety events were similar across tumor types.

Key safety findings for the subjects in MDX1106-03 are summarized here (*Clinical Study Report: Study No. MDX1106-03*, 2013; *Addendum 1 to Final Clinical Study Report for MDX1106-03*). Drug-related AEs (any grade) were reported in 75.2%, and drug-related Grade 3-4 AEs were reported in 17.0% of subjects. The most frequently reported drug-related AE was

fatigue (28.1%). Other drug-related Grade 3-4 AEs reported in more than two subjects were pneumonitis (1.3%), lymphopenia (1.3%), diarrhea (1.0%), abdominal pain (1.0%), CD4 lymphocytes decreased (1.0%), and hypophosphatemia (1.0%). The most frequently reported drug-related SAE was pneumonitis (seven subjects, 2.3%). Drug-related Grade 3-4 pneumonitis was reported in four patients (1.3%). The most frequently reported drug-related select AE categories (any grade) were skin (24.5%), GI (14.1%), and endocrine (9.5%). AEs belonging to the pulmonary and renal select AE categories were unexpected, drug-related toxicities associated with the use of nivolumab. AEs belonging to select AE categories were generally manageable and reversible with the use of immunosuppressants.

The majority of the deaths reported during MDX1106-03 were due to disease progression. Three subjects (1.0%) died due to study drug toxicity at the time of database lock; two out of three subjects died within 100 days of last dose of nivolumab, and one died more than 100 days after the last dose of nivolumab. The reported causes of death for these three subjects were: non-drug-related cardiopulmonary arrest due to complications from Grade 5 sepsis (drug-related), drug-related sepsis, and drug-related respiratory failure secondary to pneumonitis and progressive disease. After database lock for the final clinical study report, two subjects were reported to have died; both were subjects with NSCLC treated with 3 mg/kg nivolumab. The reported causes of death for these two subjects were: drug-related pneumonitis, and non-drug-related infection after experiencing drug-related Grade 3 pneumonitis Although not considered to be the primary cause of death in all five subjects described above, pneumonitis was considered a contributory factor in each case (Weber *et al.,* 2013).

Clinical Safety of Nivolumab Monotherapy in Platinum Resistant Ovarian Cancer

In the phase II study of nivolumab monotherapy in PROC, safety analyses were reassuring with limited treatment-related serious adverse events (Hamanishi *et al.,* 2014). Among the 18 patients the most common treatment-related adverse events were rash, hypothyroidism, fever, arthralgia and lymphocytopenia. For each of these toxicities, the grade 3-4 incidence was low with one occurrence reported for each toxicity except for two occurrences reported for hypothyroidism. In addition, there were two patients with reported treatment-related serious adverse events (all grade 3). For the first patient disorientation, gait disorder and fever were reported; for the second patient fever and deep venous thrombosis were reported. There were no treatment-related deaths reported in this study.

Clinical Safety of Nivolumab in Combination with Bevacizumab

The safety of nivolumab in combination with bevacizumab has been evaluated in the context of NSCLC in two phase I studies, CA209-130 and CA209-012 (Kanda *et al.,* 2014; Rizvi *et al.,* 2014).

The first study, CA209-130, enrolled a total of 24 patients and evaluated combinations of chemotherapy, nivolumab, and bevacizumab for patients with newly diagnosed stage IIIB/IV NSCLC who were unsuited to radical radiotherapy or patients with recurrent NSCLC (Kanda *et al.,* 2014). In this study there were six patients who were initially treated the combination of carboplatin, paclitaxel, nivolumab, and bevacizumab for six treatment cycles followed by maintenance continuation of nivolumab and bevacizumab. In this group of six patients, no DLTs

were observed. There was one SAE reported, a patient with grade 2 epistaxis. The combination was tolerable with grade 3-4 AEs limited to hematologic toxicities.

The second study, CA209-012, included evaluation of nivolumab, alone or in combination with bevacizumab, as switch maintenance therapy after first-line treatment of advanced NSCLC (Rizvi *et al.,* 2014). In this study there were 12 patients who received the combination of nivolumab and bevacizumab until disease progression or development of unacceptable toxicity. The most commonly reported treatment-related AEs were fatigue, pneumonitis, rhinorrhea, cough and diarrhea. Grade 3 treatment-related AEs occurred in four patients (33%) treated with this combination; there were no grade 4 treatment-related AEs reported. Four patients (33%) discontinued protocol therapy due to treatment-related AEs.

Across all tumor types including ovarian cancer, all available data indicates that nivolumab monotherapy has a tolerable and consistent AE profile. The data for the combination of nivolumab in combination with bevacizumab is limited to NSCLC and is also reassuring. A safety lead-in is embedded within this study to further characterize the toxicities associated with the combination of nivolumab and bevacizumab in ovarian cancer prior to proceeding with full enrollment.

2.4.2 Bevacizumab

Bevacizumab is a monoclonal antibody against VEGF-A that has clinical activity in various contexts in the treatment of ovarian cancer included as monotherapy in relapsed disease, front-line maintenance therapy, and in combination with chemotherapy for both platinum-sensitive and platinum-resistant disease (Cannistra *et al.,* 2007; Burger *et al.,* 2007; Perren *et al.,* 2011, Burger *et al.,* 2011; Aghajanian *et al.,* 2012, Pujade-Lauraine *et al.,* 2014).

Bevacizumab was studied as monotherapy for relapsed disease in two phase II single-arm studies (Cannistra *et al.,* 2007; Burger *et al.,* 2007). The first study enrolled 44 patients of whom the majority (84%) was platinum resistant and approximately half had received three prior lines of chemotherapy. In this study the response rate was 16% and all responses were partial. Regarding toxicities, treatment-related grade 3-4 AEs included proteinuria, hypertension, bleeding, and wound-healing complications. SAEs included a GI perforation rate of 11% and arterial thromboembolism rate of 7% (Cannistra *et al.,* 2007). The second study enrolled 62 patients of whom 42% were platinum resistant. This study enrolled less heavily pretreated patients with a maximum of two prior cytotoxic regimens. The response rate was 21% of which two were complete responses. Grade 3-4 AEs included hypertension, thromboembolism, proteinuria, and GI events. There were no perforations, fistulae, or arterial thromboembolic events (Burger *et al.,* 2007).

With evidence of efficacy as monotherapy in relapsed disease, bevacizumab was also studied with chemotherapy in two large phase III phase randomized trials in the front-line setting (Perren *et al.,* 2011; Burger *et al.,* 2011). ICON7 studied bevacizumab 7.5mg/kg and randomized participants to receive either standard chemotherapy with bevacizumab followed by bevacizumab maintenance or standard chemotherapy alone (Perren *et al.,* 2011). The primary outcome of this study was progression-free survival. Analysis at 42 months of follow-up showed that participants treated with bevacizumab did experience longer PFS, 24.1 months compared to

22.4 ($P = 0.04$). The observed toxicities were in keeping with the earlier studies and included hypertension, proteinuria, GI toxicities, bleeding, abscess and fistula formation. GOG-218 also studied the incorporation of bevacizumab at 15mg/kg into the primary treatment of ovarian cancer but with a somewhat different study design (Burger *et al.,* 2011). In this three-arm placebo-controlled study, women were randomized to standard chemotherapy with bevacizumab followed by bevacizumab maintenance, standard chemotherapy with bevacizumab followed by placebo, or standard chemotherapy with placebo followed by placebo. The primary endpoint again was PFS with a significant improvement in PFS observed in the group that received bevacizumab both incorporated with front-line chemotherapy and continued as maintenance compared to the group that did not receive bevacizumab, 14.1 months and 10.3 months respectively ($P < 0.001$). The toxicity profile in GOG-218 was comparable to that in ICON7.

Finally, bevacizumab has been studied in relapsed ovarian cancer both platinum-sensitive and platinum-resistant disease in two large randomized trials. (Aghajanian *et al.,* 2012, Pujade-Lauraine *et al.,* 2014) In the OCEANS study, participants with platinum-sensitive disease were randomized to either carboplatin and gemcitabine with bevacizumab followed by bevacizumab maintenance or carboplatin and gemcitabine with placebo followed by placebo. (Aghajanian *et al.,* 2012)The primary outcome was again PFS and the group that received bevacizumab demonstrated superior outcome with PFS of 12.4 months compared to 8.4 months ($P < 0.0001$). The AURELIA study randomized participants with platinum-resistant ovarian cancer to either chemotherapy with bevacizumab or chemotherapy alone. (Pujade-Lauraine *et al.,* 2014) In this study protocol-specified therapy continued until either disease progression or the development of unacceptable toxicities. Patients who were randomized to the chemotherapy alone arm were allowed to cross over to bevacizumab monotherapy at time of progression. The use of bevacizumab again resulted in superior PFS, 6.7 months compared to 3.4 months ($P < 0.001$). In both OCEANS and AURELIA, hypertension and proteinuria were more commonly observed among patients treated with bevacizumab.

2.4.3 Rucaparib

Rucaparib is a potent small molecule inhibitor of PARP) enzymes, including PARP-1, PARP-2, and PARP-3. Rucaparib has been developed for the treatment of cancer associated with homologous recombination deficiency (HRD), defined by the presence of a deleterious mutation in the breast cancer gene (BRCA) 1 (BRCA1), breast cancer gene 2 (BRCA2), or another homologous recombination repair (HRR) gene, and/or high percentage of tumor genome with loss of heterozygosity (tumor genomic loss of heterozygosity [LOH]), which is a phenotypic consequence of HRD. Rucaparib is approved in the United States (US) for maintenance treatment of adult patients with deleterious BRCA mutation (germline and/or somatic)-associated recurrent epithelial ovarian (EOC), fallopian tube (FTC), or primary peritoneal (PPC) cancer who are in a complete or partial response to platinum-based chemotherapy. Rucaparib has also been approved in the European Union (EU) as monotherapy treatment of adult patients with platinum-sensitive, relapsed or progressive, BRCA-mutated (germline and/or somatic), high-grade EOC, FTC, or PPC who have been treated with 2 or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy.

The efficacy of rucaparib was investigated in ARIEL3 (NCT01968213), a double-blind,

multicenter clinical trial in which 564 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who were in response to platinum-based chemotherapy were randomized (2:1) to receive rucaparib tablets 600 mg orally twice daily (n=375) or placebo (n=189). Treatment was continued until disease progression or unacceptable toxicity. All patients had achieved a response (complete or partial) to their most recent platinum-based chemotherapy. Randomization was stratified by best response to last platinum (complete or partial), time to progression following the penultimate platinum therapy (6 to ≤ 12 months and > 12 months), and tumor biomarker status.

Tumor tissue samples were tested using a clinical trial assay (CTA) (N=564) and an investigational Foundation Medicine tissue test (n=518). Of the samples evaluated with both tests, tumor *BRCA* (t*BRCA*) mutant status was confirmed for 99% (177/178) of t*BRCA*-positive patients determined by the CTA. Blood samples for 94% (186/196) of the t*BRCA* patients were evaluated using a central blood germline *BRCA* test. Based on these results, 70% (130/186) of the t*BRCA* patients had a germline *BRCA* mutation and 30% (56/186) had a somatic *BRCA* mutation. The efficacy results are based on the t*BRCA* (germline or somatic) subgroup.
The major efficacy outcome was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 (v1.1). Overall survival (OS) was an additional outcome measure.

Of the 564 enrolled patients, 196 patients (35%) had a t*BRCA* mutation. Among the patients who had a t*BRCA* mutation, the median age was 58 years (range: 42 to 81) for patients receiving rucaparib and 59 years (range: 36 to 84) for those on placebo; the majority were White (84%); and 100% had an ECOG performance status of 0 or 1. All patients had received at least two prior platinum-based chemotherapies (range: 2 to 5). A total of 33% of patients were in complete response (CR) to their most recent therapy. The progression-free interval to penultimate platinum was 6-12 months in 41% of patients and > 12 months in 59%. Prior bevacizumab therapy was reported for 22% of patients who received rucaparib and 17% of patients who received placebo. Measurable disease was present at baseline in 32% of patients.

ARIEL3 demonstrated a statistically significant improvement in PFS for patients randomized to rucaparib as compared with placebo in patients who had a t*BRCA* mutation. Results from a blinded independent radiology review were consistent.

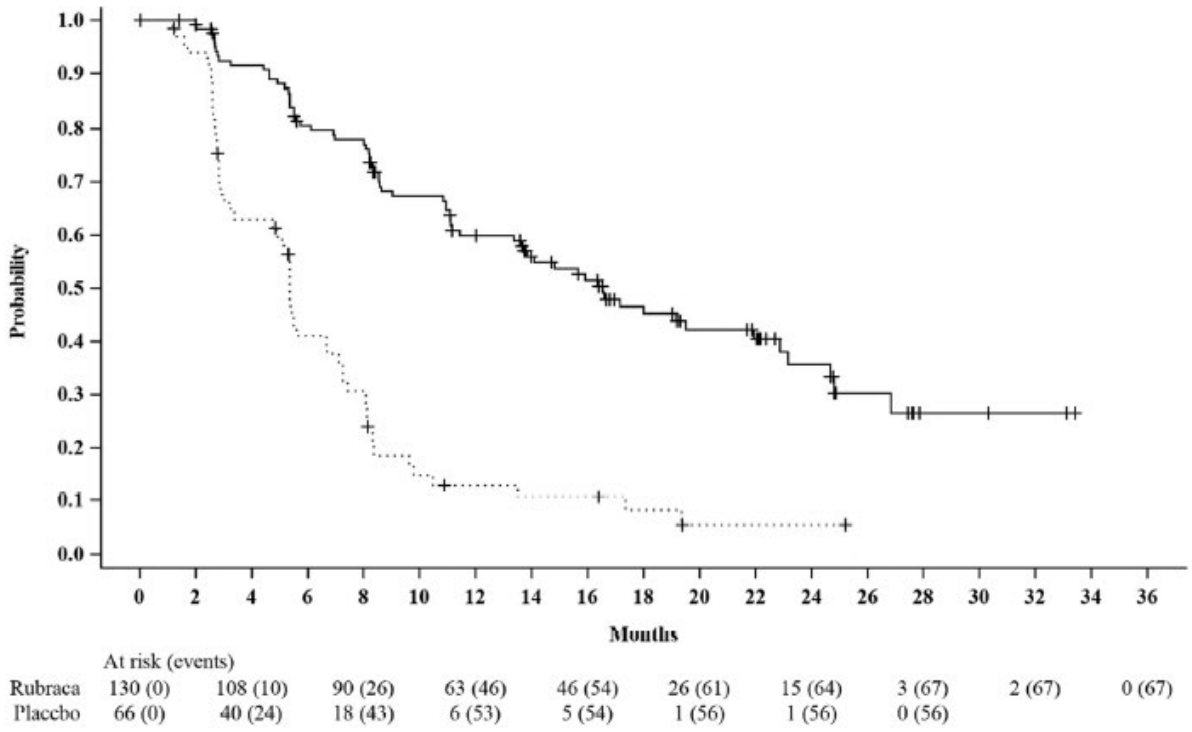
Efficacy results for patients with a t*BRCA* mutation are summarized below.

Efficacy Results in Patients with t*BRCA*-mutated Ovarian Cancer – ARIEL3 (Investigator Assessment)[a]

	Rubraca N=130	Placebo N=66
Progression Free Survival		
Number of events, n (%)	67 (52%)	56 (85%)
Median in months (95% CI)	16.6 (13.4-22.9)	5.4 (3.4-6.7)
HR (95% CI)	0.23 (0.16, 0.34)	
p-value	< 0.0001	

[a] t*BRCA* includes all patients with a deleterious germline or somatic *BRCA* mutation, as determined by the CTA.

Kaplan-Meier Curves of Progression-Free Survival in ARIEL3 as Assessed by Investigator: t*BRCA* Group



A final OS analysis was conducted after 130 events were observed. Exploratory OS results showed a HR of 0.83 (95% CI: 0.58, 1.19) in the t*BRCA* subgroup with a median OS of 45.9 months (95% CI: 37.7, 59.6) for patients treated with rucaparib and 47.8 months (95% CI: 43.2, 55.8) for patients on placebo.

The most common adverse events reported with rucaparib have primarily been mild to moderate in severity, and include gastrointestinal disorders (nausea, vomiting, diarrhea, constipation, and abdominal pain), asthenia/fatigue, decreased appetite, and dysgeusia. The most common grade 3 or higher adverse events include anemia, increase in transaminases, neutropenia, and fatigue.

Summary of Preclinical Studies

Pharmacological assessment demonstrated that rucaparib is a potent and selective inhibitor of

PARP-1, PARP-2, and PARP-3 and has robust and durable in vitro and in vivo activity in multiple BRCA1/2-mutant cell lines and xenograft models. Rucaparib was also active in a BRCA wild-type model, consistent with in vitro data suggesting that rucaparib is active in cells with other defects in homologous recombination through synthetic lethality. In vitro screens suggested that rucaparib has a limited potential for off-target effects. Safety pharmacology studies suggest that when given orally, rucaparib poses a low risk for causing neurobehavioral and cardiac effects in patients.

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

Oral dosing of rucaparib in single and repeat dose toxicity studies in rats and dogs resulted in toxicity to the hematopoietic, lymphopoietic, and gastrointestinal systems. These toxicities were generally both reversible upon recovery and predictive of toxicities observed in patients. Rucaparib was shown to be clastogenic in an *in vitro* chromosomal aberration assay suggesting potential genotoxicity in humans. Reproductive and development toxicity studies in rat showed that rucaparib caused maternal toxicity and was embryo-toxic. Although no rucaparib related effects on sperm total count, density, motility, or morphology were identified, based on published studies, PARP inhibitors have the potential to impair spermatogenesis and reduce fertility.

Clinical Pharmacokinetics

An overview of data are provided below and described in detail in the rucaparib IB.

Assessment of rucaparib PK in cancer patients showed an approximate dose-proportional exposure after once daily (QD) or BID dosing, rapid absorption with maximum plasma concentration (Cmax) achieved within 1.5 to 6 hours, and distribution into tissue. The oral bioavailability was 36% and terminal half-life (T1/2) ranged from 9.23 to 33.6 hours. Rucaparib was moderately bound to human plasma proteins in vitro.

At a dose of 600 mg BID rucaparib, steady-state was achieved after approximately 1 week. At the target clinical dose of 600 mg, a high-fat meal increased the Cmax and area under the plasma concentration-time curve from 0 to 24 hours (AUC0-24h) of rucaparib by 20% and 38%, respectively, and delayed the median time to occurrence of Cmax (Tmax) by approximately 2.5 hours as compared with these parameters under fasted conditions. The effect of food on rucaparib PK is not considered to be clinically significant, thus rucaparib can be taken with or without food.

Population PK Analyses

Drug interactions with rucaparib as a substrate were assessed in a population PK analysis. CYP2D6 phenotypes (poor metabolizers, intermediate metabolizers, normal metabolizers, and ultra-rapid metabolizers) and CYP1A2 phenotypes (normal metabolizers and hyperinducers) did not significantly impact the steady-state exposure of rucaparib at 600 mg BID. Current smokers had overlapping rucaparib exposures as compared to nonsmokers and former smokers. Collectively, the results suggest that CYP1A2 and CYP2D6 play a limited role in rucaparib metabolism in vivo, and no rucaparib dose adjustment is needed when concomitantly administered with CYP inhibitors.

Concomitant treatment with proton pump inhibitors (PPIs) showed no clinically significant effect on rucaparib PK. No dose modification of rucaparib is required for patients who are receiving concomitant treatment with a PPI. Results from Study CO-338-044 evaluating potential drug-drug interactions (DDI) with rucaparib, indicated that rucaparib, at 600 mg BID, moderately inhibited CYP1A2, weakly inhibited CYP2C9, CYP2C19, and CYP3A, and showed no clinically significant effect on Pgp. Caution should be exercised in the concomitant use of drugs that are substrates of the above CYP enzymes with narrow therapeutic windows.

Safety Profile

An overview of data are provided below and described in detail in the rucaparib IB.

Integrated Safety Analysis

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 (AESIs)

An overview of data are provided below and described in detail in the rucaparib IB.

Myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) are considered adverse events of special interest (AESIs), as these events have been observed in patients exposed to cytotoxic chemotherapy (eg, platinum and anthracyclines) used for treatment of ovarian cancer as well as with PARP inhibitors, including rucaparib. Patients in rucaparib clinical studies diagnosed with MDS or AML had significant confounding risk factors including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation (8, 9). Based on these confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib.

Adverse events of pneumonitis have 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. In order to gather the necessary information to enable a thorough evaluation and assessment to better understand whether or not there is a relationship between pneumonitis and rucaparib treatment, pneumonitis has been classified as an AESI.

On 01 May 2023, pharmaand Schweiz GmbH (Pharma&) acquired the rights to and assumed regulatory responsibility for rucaparib from Clovis Oncology, Inc (Clovis).

2.5 Study Rationale

Preclinical and early-phase clinical data suggest that immune modulation represents a treatment strategy that is worthy of further investigation in relapsed EOC. One method by which tumor cells may evade immune surveillance is by activation of the programmed cell death (PD-1) pathway, mediated by expression of PD-1 on the surface of T lymphocytes, which conveys an inhibitory signal after binding to its ligand PD-L1 on the surface of tumor cells. This mechanism seems applicable to ovarian cancer and it is noteworthy that higher tumoral expression of PD-L1 is associated with inferior prognosis (Hamanishi *et al.,* 2007) .

Both nivolumab and bevacizumab show activity as monotherapies in previously treated relapsed EOC with single-agent response rates of approximately 16-18% (Hamanishi *et al.,* 2014; Cannistra *et al.,* 2007; Burger *et al.,* 2007). Regarding the safety of the combination, the toxicity profiles of these targeted agents do not seem to overlap and safety analyses of the combination in phase I studies in NSCLC did not reveal any unexpected toxicity signals (Kanda *et al.,* 2014; *Rizvi et al.,* 2014).

In addition to these encouraging early-phase clinical efficacy and safety data, there is reason to believe that there is cross-talk between immune checkpoint regulation mediated by the PD-1 pathway, and VEGF-induced angiogenesis. It is increasingly appreciated that VEGF is not only involved in stimulating angiogenesis, but plays an immune suppressive function as well. In particular, VEGF has been shown to impair dendritic cell (DC) function and maturation, which has been postulated to inhibit effective antigen presentation by DCs in humans, as well as in murine models (Motz *et al.,* 2011; Takahashi *et al.,* 2004; Gabrilovich *et al.,* 1996). Furthermore, inhibition of tumor derived VEGF in murine models of angiogenesis has been shown to improve DC numbers and function. Importantly, it has been shown that tumor-derived VEGF-A is a potent inducer of PD-L1 expression in preclinical murine models (Curiel *et al.,* 2003), thus establishing the potential for in vivo cross-talk between the angiogenic and immune checkpoint pathways. These preclinical data make it reasonable to hypothesize that there may be synergy in simultaneously blocking both VEGF as well as PD-1 in patients with relapsed EOC.

Other clinical studies have demonstrated that PARP inhibitors and bevacizumab can be combined with minimal overlapping toxicities (ongoing AVANOVA study; Dean et al., Br J Cancer 2012), and both pre-clinical and clinical studies suggest that anti-angiogenics and PARP inhibitors could potentially have synergistic effects (Liu et al., Lancet Oncol 2014; Bindra et al., Oncogene 2007; Chan et al., Cancer Res 2010). Similarly, pre-clinical studies also suggest that PARP inhibitors alone can have immunoregulatory effects (Huang et al., Biochem Biophys Res Comm 2015; Jiao et al., Clin Cancer Res 2017), and that, in combination with immune checkpoint inhibitors, can have synergistic effects (Higuchi et al., Cancer Immunol Res 2015). These studies provide rationale for exploring the combination of PARP inhibitors with immune checkpoint inhibitors in recurrent ovarian cancer. Based on these multiple mechanisms of synergy between these three classes of agents, it is possible a “triplet combination” of nivolumab, bevacizumab, and rucaparib could lead to even greater activity in women with recurrent ovarian cancer.

2.6 Rationale for Cohort 3

22 total patients were enrolled to Cohort 2 of the study; 5 patients were enrolled to the initial safety lead-in including rucaparib 600mg orally twice daily, nivolumab 240mg IV q2weeks, and bevacizumab 10mg/kg IV q2weeks. This dose level was deemed not tolerable after 2 patients developed a DLT (1 grade 3 hematuria, 1 grade 3 LFT elevation). Enrollment proceeded at the protocol-specified DL -1 of rucaparib 500mg orally twice daily, nivolumab 240mg IV q2weeks, and bevacizumab 10mg/kg IV q2weeks. A total of 17 patients were enrolled at this dose level to the first stage of this Cohort per protocol (1 patient was not evaluable for response and was replaced). While the clinical activity in this cohort met the pre-specified criteria to proceed to

stage 2 of this two-stage design (4 partial responses were observed), 13 of the 17 patients had discontinuation of at least one of the study medications, with multiple patients requiring multiple dose reductions of rucaparib, suggesting poor tolerability of the regimen when rucaparib is dosed at 500mg twice daily. Notably, no concerns regarding safety or tolerability were observed with the combination of nivolumab 240mg IV q2weeks and bevacizumab 10mg/kg IV q2weeks dosing regimen, as reported in Cohort 1 of this study (Liu et al., JAMA Oncol 2019).

A "triplet" regimen of combined PARP inhibition, PD-1 inhibition, and an anti-angiogenic agent remains of interest in ovarian cancer, due to potential for synergistic activity, as detailed in Section 2.5. Clinical data have supported the potential for significant activity, particularly in patients with platinum-sensitive disease. In the MEDIOLA study, Drew and colleagues reported an 87.1% response rate with a median PFS of 14.7 months and a median duration of response of 11.1 months in women with BRCA wild-type platinum-sensitive recurrent ovarian cancer to the combination of the PARP inhibitor olaparib, the PD-L1 inhibitor durvalumab, and the anti-angiogenic agent bevacizumab (Drew et al., ESMO 2020 Virtual Congress). 58% of patients had a platinum-free interval of 6 to 12 months, and activity was observed regardless of genomic instability status, as assessed by Foundation Medicine next generation sequencing.

Given the potential activity of this triplet combination but challenges with tolerability with rucaparib dosed at 600mg twice daily or 500mg twice daily, we therefore propose a cohort to assess the safety and tolerability of this triplet combination when rucaparib is dosed at 300mg twice daily, with a secondary assessment of efficacy in a platinum sensitive population.

2.7 Correlative Studies Background

Exploratory correlative studies aim to identify potential predictive biomarkers of nivolumab plus bevacizumab therapy in subjects with ovarian cancer. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (adverse event) data. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with ovarian cancer or immunotherapy plus antiangiogenic treatment.

Correlative studies include evaluation of tumoral PD-L1 expression, evaluation of tumoral genomic signatures, homologous recombination deficiency (HRD) status, mutational status, and serum biomarker profiling.

<u>Evaluation of tumoral PD-L1 expression</u>

Given their mechanism of action, tumoral PD-L1 expression has been predicted to be a possible biomarker of response to PD-1/PD-L1 blockade. Studies have suggested higher response rates to mediators of PD-1/PD-L1 blockade in patients with PD-L1 expressing tumors (Topalian *et al.*, 2012; Weber *et al.*, 2013; Herbst *et al.*, 2014). However, some patients without PD-L1 expression within their tumors have still exhibited significant response to PD-1/PD-L1 blockade.

Tumor PD-L1 overexpression has shown to be a negative prognostic factor in patients with ovarian cancer (Hamanishi *et al*., 2007). However, because of the fact that the PD-L1/PD-1 interaction promotes immune escape in human ovarian cancers (Lavoue *et al*., 2013), high PD-

L1 expression in ovarian tumors may be present in patients that better respond to anti-PD-1 therapy when compared to patients with low tumor PD-L1 expression. In this context, the analysis of PD-L1 expression in tumor samples can help elucidate whether expression of PD-L1 in ovarian cancer is predictive of response to anti-PD-1 therapy.

Evaluation of tumoral genomic signatures

Genomic analyses of tumor biopsies may provide with a comprehensive tumor immunoprofiling of ovarian cancer. In 2011, the cancer genome atlas research network (TCGA) described four phenotypes of ovarian cancer based on gene expression analysis: immunoreactive, differentiated, proliferative, and mesenchymal (TCGA, 2011). Among these, the mesenchymal group was associated with shorter OS, while the immunoreactive group showed the highest TILs and a link between anti-tumor B-cell activity and longer survival (Iglesia *et al*, 2014).

Gourley and colleagues described a three-group gene expression-based classification of ovarian cancer: immune, proangiogenic, and immune/proangiogenic. The immune subgroup was accompanied by superior survival compared to the other groups. However, the addition of bevacizumab significantly reduced clinical outcome in the immune subgroup while showed a trend toward PFS benefit in the proangiogenic group in a post-hoc analysis of data from the ICON7 trial (Gourley *et al.*, 2014). Additionally, the ESTIMATE score (described by Yoshihara *et al.*, 2013), which utilizes gene expression signatures to infer the fraction of stromal and immune cells in tumor samples, may also allow for classification of ovarian cancers based upon degree of immune infiltration.

Analysis of these tumor-associated normal cells in tumor tissues may provide insights into tumor biology and aid in the development of prognostic and predictive models. We therefore propose to explore the correlation of tumoral genomic signatures with clinical outcomes in patients receiving combination of nivolumab with bevacizumab.

Evaluation of mutational and HRD status

Genomic BRCA mutations, as well as total mutational burden, have been associated with response to in patients with high grade serous ovarian cancer (Birkbak et al. PLOSone 8:e80023, 2013). In addition, hyper mutated ovarian tumors may be associated with high immune infiltration. This study will investigate whether mutational load may identify subjects that better respond to nivolumab plus bevacizumab therapy. The mutational and HRD status of patients with ovarian cancer will be assessed to evaluate the impact of genomic alterations on susceptibility to the combination of nivolumab and bevacizumab of tumor biopsies may provide with a comprehensive tumor immunoprofiling of ovarian cancer.

Evaluation of serum biomarkers

A pre-existing pro-inflammatory cytokine profile as well as an increase of pro-inflammatory cytokines during therapy may represent a pharmacodynamic biomarker of response to anti-PD-1 treatment (Zaretsky *et al*., 2015). In addition, high VEGF levels in the peripheral blood are almost invariably associated with poor outcomes (Zhu, et al, Nat Rev Clin Oncol, 2011), which

is indicative of its prognostic biomarker value. An increase of soluble VEGF and soluble VEGF receptors may both indicate pharmacodynamic effect and toxicity of bevacizumab therapy. For example, circulating levels of neuropilin-1, VEGF-A, and genetic variants in VEGFA or its receptors are proposed as biomarker candidates for therapy with bevacizumab (Lambrechts, et al, JCO, 2013). Furthermore, PlGF changes may have pharmacodynamic biomarker value and the increase of PIGF can mediate resistance to bevacizumab (Duda, et al, Oncologist, 2010). Finally, pre-existing high levels of soluble VEGFR-1 can also be considered as a negative predictor biomarker of response to bevacizumab in cancer (Duda, et al, ISRN Cell BIol, 2012). Therefore, exploratory investigation of serum biomarkers of response to combined nivolumab and bevacizumab will also be incorporated in this study.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologic or cytologic confirmation of epithelial ovarian cancer, fallopian tube or peritoneal cancer. All histologies (including serous, mucinous, endometrioid, clear cell, MMMTs, and mixed histologies) are eligible. All tumor grades are eligible.

3.1.2 Participants must have received a first-line platinum-based chemotherapy regimen

3.1.3 Participants must have relapsed disease despite standard therapy.

3.1.4 For Cohorts 1 and 2: Participants with platinum-resistant or platinum-sensitive disease (within 12 months) are eligible. Platinum-resistant disease is defined as relapse within 6 months after the last dose of platinum-based chemotherapy. Platinum-sensitive disease is defined as relapse greater than 6 months after the last dose of platinum-based chemotherapy. Participants with platinum-sensitive disease who have experienced relapse within 6 to 12 months after the last dose of platinum-based chemotherapy are eligible. Participants with primary platinum-refractory disease (defined as progression during or relapsed within 2 months of their initial platinum-based chemotherapy) are not eligible.

For Cohort 3: Particpants must have platinum-sensitive disease and have experienced relapse within 6 to 12 months (i.e., 180 to 365 days) after the last dose of platinum-based chemotherapy.

3.1.5 Participants must have received no more than 3 prior chemotherapy or cytotoxic regimens. There is no limit to the number of prior hormonal therapies.

3.1.6 Participants must have measurable disease by RECIST 1.1 criteria.

3.1.7 Participants who have received prior bevacizumab are eligible unless there is evidence of unacceptable toxicity due to prior bevacizumab exposure.

3.1.8 Participants may not have received any prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

3.1.9 Participants must have stopped any hormonal therapy at least 1 week prior to treatment with nivolumab and bevacizumab. Participants may continue on hormone replacement therapy administered for post-menopausal symptoms.

3.1.10 Age ≥ 18 years

3.1.11 Estimated life expectancy of greater than 6 months.

3.1.12 ECOG performance status of 0 or 1 (Appendix A)

3.1.13 Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to registration:

- WBC ≥ 2,000/μL
- Absolute neutrophil count ≥ 1,500/μL
- Platelets ≥ 100,000/mcL
- Hemoglobin ≥ 9.0 g/dL
- Serum creatinine less than or equal to the institutional ULN or creatinine clearance (CrCl) ≥ 60 mL/min (calculated using the Cockgroft-Gault formula) for participants with serum creatinine levels above institutional ULN
- AST (SGOT) / ALT (SGPT) ≤ 3 × institutional ULN
- Total bilirubin ≤ 1.5 × institutional ULN (except participants with Gilbert Syndrome, who can have total bilirubin ≤ 3.0 × institutional ULN with direct bilirubin that is within institutional ULN)
- Coagulation parameters (INR, aPTT) ≤ 1.25 × institutional ULN

3.1.14 Patients with treated limited stage basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the breast or cervix are eligible. Patients with stage IA endometrial cancer are eligible if the following conditions are met: without vascular or lymphatic invasion AND no serous, clear cell or grade 3 histology. Patients with early stage I or II cancers treated with curative intent who have no evidence of recurrent cancer 3 years following diagnosis and judged by the investigator to be at low risk of recurrence are eligible.

3.1.15 Participants must have biopsiable disease and be willing to undergo pre-treatment biopsy, or have an archival tumor sample obtained < 20 months prior to study entry.

3.1.16 Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. Additionally, women under the age of 62 who are not surgically sterile must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL to document postmenopausal status.

Nivolumab, bevacizumab, and rucaparib may each cause fetal harm or risk to human pregnancy. For this reason, WOCBP must agree to use appropriate method(s) of contraception for 6 months after the last dose of study treatment, per FDA recommendations on use of contraception following bevacizumab. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Patients receiving rucaparib should immediately discontinue rucaparib if they should become pregnant or suspect they are pregnant

3.1.17 WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study treatments.

3.1.18 Women must not be breastfeeding

3.1.19 Ability to understand and the willingness to sign a written informed consent document.

3.1.20 **Specific criteria for Cohorts 2 and 3**

3.1.20.1 Patients must have undergone germline BRCA testing and must **not** have a deleterious or suspected deleterious BRCA mutation. Where tumor testing has been performed, patients with a deleterious or suspected deleterious somatic BRCA mutation are also not eligible.

3.2 Exclusion Criteria

3.2.1 Patients with primary platinum-refractory disease are ineligible. Primary platinum-refractory disease is defined as relapse less than 2 months after initial platinum-based chemotherapy.

3.2.2 Patients with platinum-sensitive disease with relapse greater than 12 months after the last dose of platinum-based chemotherapy are ineligible.

3.2.3 Participants who have had chemotherapy or radiotherapy within 3 weeks prior to entering the study or those who have not recovered from adverse events due to agents administered more than 3 weeks earlier.

3.2.4 Participants may not be receiving any other investigational agents nor have participated in an investigational trial within the past 4 weeks.

3.2.5 Participants must agree not to use natural herbal products or other "folk remedies" while participating in this study.

3.2.6 Patients with a history of allergic reactions attributed to bevacizumab or to compounds of similar chemical or biologic composition to nivolumab or bevacizumab are excluded.

3.2.7 Patients are excluded if they have active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 6 months after treatment is complete and within 28 days prior to the first dose of nivolumab and bevacizumab administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

3.2.8 Patients with any of the following cardiovascular diseases are excluded:

3.2.8.1 History of myocardial infarction within six months
3.2.8.2 Unstable angina
3.2.8.3 Angina pectoris that requires the use of anti-anginal medication
3.2.8.4 History of documented congestive heart failure (NYHA classification of III or IV) or documented cardiomyopathy
3.2.8.5 Valvular disease with documented compromise in cardiac function
3.2.8.6 If cardiac function assessment is clinically indicated or performed:
LVEF less than normal per institutional guidelines, or < 55%, if threshold for normal not otherwise specified by institutional guidelines
Patients with the following risk factor should have a baseline cardiac function assessment:
- Prior treatment with anthracyclines

3.2.8.7 Any prior history of hypertensive crisis or hypertensive encephalopathy
3.2.8.8 Patients may not have any evidence of pre-existing inadequately controlled hypertension (defined as a systolic BP of >140 mmHg or a diastolic BP of >90 mmHg), and must have a normal blood pressure (≤140/90 mmHg) taken in the clinic setting by a medical professional within 2 weeks prior to starting study.
3.2.8.9 Clinically significant peripheral vascular disease
3.2.8.10 Vascular disease including aortic aneurysm or dissection
3.2.8.11 History of stroke, transient ischemic attack or subarachnoid hemorrhage
3.2.8.12 Ventricular arrhythmias except for benign premature ventricular contractions
3.2.8.13 Cardiac conduction abnormality requiring a pacemaker
3.2.8.14 Known history of QT/QTc prolongation or torsades de pointes

3.2.8.15 QTc prolongation > 470 msec or other significant ECG abnormality noted during screening

3.2.9 Grade 2 or higher proteinuria (2+ or higher protein on urinalysis or urine protein:creatinine (UPC) ratio ≥ 1.0; if both tests are performed, UPC should be used to evaluate eligibility) or hematuria.

3.2.10 Participants may not have evidence of a bowel obstruction, abdominal fistula, or intra-abdominal abscess within 6 months of study entry. Participants with current signs or symptoms suggestive of bowel obstruction including early or partial obstruction are ineligible. Participants with a history of gastrointestinal perforation at any time point are ineligible.

3.2.11 Non-healing wound, ulcer or bone fracture.

3.2.12 Serious active infection requiring intravenous antibiotics and/or hospitalization at study entry.

3.2.13 Current dependency on IV hydration or TPN.

3.2.14 Any patient with a history of major depressive episode, bipolar disorder, obsessive/compulsive disorder, schizophrenia, a history of suicide attempt or ideation, or homicide/homicidal ideation as judged by the investigator and/or based on recent psychiatric assessment may not participate in this study without discussion with and agreement of the study PI.

3.2.15 Uncontrolled current illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.16 Patients are excluded if they have an active, known or suspected autoimmune disease other than the following: vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger.

3.2.17 Patients are excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration, with the exception of a brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen). Participants are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption).

3.2.18 Patients are excluded if they test positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.

3.2.19 Patients are excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

3.2.20 Evidence of prior or current coagulopathy or bleeding diathesis.

3.2.21 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting nivolumab and bevacizumab

3.2.22 History of severe infusion reactions to monoclonal antibody therapy

3.2.23 **Specific criteria for Cohorts 2 and 3**

3.2.23.1 Patients who have received a prior PARP inhibitor are not allowed to enroll to Cohort 2 of the trial

3.2.23.2 Patients are excluded from Cohort 2 and Cohort 3 should they have pre-existing duodenal stent and/or any gastrointestinal disorder or defect that would, in the opinion of the investigator, interfere with absorption of rucaparib.

3.3 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial. This disease does not affect men.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

N/A

4.4 Registration Process for Other Investigative Sites

N/A

5. TREATMENT PLAN

5.1 Treatment Regimen

Cohort 1

Each cycle will be 14 days with nivolumab and bevacizumab administered on day 1 of each cycle. Treatment will be administered on an outpatient basis. Expected toxicities and potential risks for nivolumab and bevacizumab are described in Section 7 (Adverse Events: List and Reporting Requirements). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The treatment dose of nivolumab is 240 mg. The starting dose for bevacizumab is 10 mg/kg. No dose reductions or escalations will be allowed for nivolumab. One dose reduction will be allowed for bevacizumab. Dosing delays and modifications are described in Section 6 (Dosing Delays/Dose Modifications). In cases where cycles may be shortened or extended, a minimum of 12 days must pass between consecutive infusions of nivolumab and bevacizumab.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Nivolumab	No premedication or hydration necessary. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according	240 mg	IV over 30 minutes before bevacizumab	*Day 1*	*14 days*

	to Protocol Section 5.3 & 6.7				*(2 weeks)*
Bevacizumab	No premedication or hydration necessary	10 mg/kg (dosing weight may be actual body weight or per institutional guidelines)	IV over 30 minutes (though infusion duration may vary per institutional guidelines) after nivolumab. Begin bevacizumab infusion 30 minutes after conclusion of nivolumab infusion.	*Day 1*	

Cohort 2

Each cycle will be 14 days with nivolumab and bevacizumab administered on day 1 of each cycle. Rucaparib will be taken twice daily by the patient on a continuous schedule. Treatment will be administered on an outpatient basis. Expected toxicities and potential risks for nivolumab, bevacizumab, and rucaparib are described in Section 7 (Adverse Events: List and Reporting Requirements). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The treatment dose of nivolumab is 240 mg. The starting dose for bevacizumab is 10 mg/kg. The starting dose for rucaparib is 600mg twice daily. No dose reductions or escalations will be allowed for nivolumab. One dose reduction will be allowed for bevacizumab. Up to three dose reductions will be allowed for rucaparib. Dosing delays and modifications are described in Section 6 (Dosing Delays/Dose Modifications). In cases where cycles may be shortened or extended, a minimum of 12 days must pass between consecutive infusions of nivolumab and bevacizumab.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Nivolumab	No premedication or hydration necessary. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an	240 mg	IV over 30 minutes before bevacizumab	*Day 1*	

	acute infusion reaction is noted, subjects should be managed according to Protocol Section 5.3 & 6.7				*14 days (2 weeks)*
Bevacizumab	No premedication or hydration necessary	10 mg/kg (dosing weight may be actual body weight or per institutional guidelines)	IV over 30 minutes (though infusion duration may vary per institutional guidelines) after nivolumab. Begin bevacizumab infusion 30 minutes after conclusion of nivolumab infusion.	*Day 1*	
Rucaparib	No premedications or hydration necessary	600 mg	PO	*BID days 1 through 14*	

An initial safety lead-in of 6 patients shall be enrolled to this cohort at a dose of rucaparib 600mg twice daily prior to expansion to full enrollment. Should two or more patients experience a DLT at this dose level, a second safety cohort of 6 patients will be enrolled to this cohort at a dose of rucaparib 500mg twice daily.

Cohort 3

Each cycle will be 14 days with nivolumab and bevacizumab administered on day 1 of each cycle. Rucaparib will be taken twice daily by the patient on a continuous schedule. Treatment will be administered on an outpatient basis. Expected toxicities and potential risks for nivolumab, bevacizumab, and rucaparib are described in Section 7 (Adverse Events: List and Reporting Requirements). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

The treatment dose of nivolumab is 240 mg. The starting dose for bevacizumab is 10 mg/kg. The starting dose for rucaparib is 300mg twice daily. No dose reductions or escalations will be allowed for nivolumab. One dose reduction will be allowed for bevacizumab. One dose reduction will be allowed for rucaparib. Dosing delays and modifications are described in Section 6 (Dosing Delays/Dose Modifications). In cases where cycles may be shortened or extended, a minimum of 12 days must pass between consecutive infusions of nivolumab and bevacizumab.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Nivolumab	No premedication or hydration necessary. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 5.3 & 6.7	240 mg	IV over 30 minutes before bevacizumab	*Day 1*	*14 days (2 weeks)*
Bevacizumab	No premedication or hydration necessary	10 mg/kg (dosing weight may be actual body weight or per institutional guidelines)	IV over 30 minutes (though infusion duration may vary per institutional guidelines) after nivolumab. Begin bevacizumab infusion 30 minutes after conclusion of nivolumab infusion.	*Day 1*	
Rucaparib	No premedications or hydration necessary	300 mg	PO	*BID days 1 through 14*	

5.2 Pre-Treatment Criteria

5.2.1 Cycle 1, Day 1

If screening labs are performed greater than 3 days prior to Cycle 1 Day 1, labs must be repeated on Cycle 1 Day 1 and must meet eligibility criteria. The patient may not start on study treatment until Cycle 1 Day 1 labs meet eligibility criteria. If screening labs are performed within 3 days prior to Cycle 1 Day 1, and meet eligibility criteria, labs do not need to be repeated on Cycle 1

Day 1 unless the investigator believes they are likely to have changed significantly.

5.2.2 Subsequent Cycles

Treatment may proceed if the following criteria are met:

- ECOG performance status of 2 or less
- No evidence of life-threatening medical problems
- Criteria for dose modification or hold of study-specific medications should be followed, per Section 6

5.2.3 Criteria to Re-challenge

Patients who elect to stop treatment with Nivolumab after 2 years of therapy (as outlined in Section 5.5) and subsequently progress can be re-challenged if they meet the following selected eligibility criteria:

- Laboratory values defined in section 3.1.13.
- No interim diagnosed malignancy as defined in section 3.1.14.
- No interim systemic therapy. (Interim palliative radiation for selective supplemental treatment may be allowed after discussion with the Overall PI.)
- Patients with brain metastases must meet criterion 3.2.7.
- Patients must also meet eligibility criteria as defined in sections 3.1.16, 3.1.17, and 3.1.18 and exclusion criteria as defined in sections 3.2.5, 3.2.8, 3.2.10, 3.2.11, 3.2.12, and 3.2.13.
- Patients must be reconsented to any consent form changes during the interim.

For patients who elected to also stop Bevacizumab (Cohort 1) or Bevacizumab/Rucaparib (Cohort 2 or Cohort 3) at the time of stopping treatment Nivolumab who wish to be re-challenged may not have had any interim events meeting exclusion criteria defined in section 3.2.21.

Patients who discontinue therapy due to disease progression or adverse events may not be re-challenged.

5.3 Agent Administration

5.3.1 Nivolumab Administration

Nivolumab is to be administered as a 30-minute (± 10 minute) IV infusion. For details on prepared drug storage, preparation, and administration, please refer to the Nivolumab Investigator Brochure (IB).

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at 240 mg. It is not to be administered as an IV push or bolus injection. Nivolumab injection will be infused diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. The total infusion volume should not exceed 120 mL. Care must be taken to

assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

5.3.2 Bevacizumab Administration

Bevacizumab will be given at 10 mg/kg in 100 cc NS, with dosing weight calculated by actual body weight or per institutional standards. It should be given intravenously over 30 minutes, though infusion duration may vary per institutional guidelines. Bevacizumab will be given 30 (+/- 10) minutes after conclusion of nivolumab infusion.

For details on prepared drug storage, preparation, and administration, please refer to the Bevacizumab Investigator Brochure (IB) and/or pharmacy reference sheets.

5.3.3 Rucaparib Administration

Rucaparib should be taken orally twice daily 12 hours apart with or without food. Rucaparib cannot be chewed, crushed or dissolved. If a dose of rucaparib is missed by more than four hours from the scheduled time, the participant should omit that dose and take the next dose at its scheduled time. Vomited doses should not be replaced.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Prohibited treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as noted in Section 3.2.17 and 5.4.2, or to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy, or standard or investigational agents for treatment of cancer) or natural herbal products or other “folk remedies”. Supportive care for disease-related symptoms may be offered to all subjects on the trial.

5.4.2 Permitted therapy

Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the case report form (CRF). All medications (prescriptions or

over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue indefinitely or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Participant has completed 2 years of treatment with nivolumab (treatment may continue beyond 2 years per investigator and participant discretion). Participant may continue on bevacizumab alone (Cohort 1) or bevacizumab/rucaparib (Cohort 2 or Cohort 3) per investigator discretion should nivolumab be stopped. (Note: If the patient subsequently progresses re-challenge is allowed after discussion with the Overall PI, please see section 5.2.3 for re-challenge criteria.)

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

In December 2022, Clovis Oncology communicated that, due to financial considerations and bankruptcy filing, they will not be able to provide the study agent rucaparib for use in this study beyond the supply currently available and allocated for this study. Participants in Cohorts 2 and 3 who are receiving rucaparib may therefore no longer be able to continue on rucaparib once this available rucaparib supply has been exhausted. Participants affected by this drug supply issue will be able to continue study treatment with nivolumab and/or bevacizumab following rucaparib discontinuation per investigator and participant discretion.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Joyce Liu at [redacted]

5.6 Duration of Follow Up

After removal from protocol therapy, participants will be followed until death.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

5.8 Treatment Beyond Disease Progression

Accumulating evidence indicates that a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD). Subjects treated with nivolumab will be permitted to continue treatment beyond initial PD as assessed by the investigator's clinical judgment and local standards of care as long as they meet the following criteria:

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases)

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment.

All decisions to continue treatment beyond initial progression must be discussed with the overall principal investigator. Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts. Decisions to continue treatment beyond initial progression will be documented in the study records.

A radiographic assessment/ scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with combination nivolumab and bevacizumab.

For the subjects who continue on study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Study treatment should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

For statistical analyses, this will need to be described in patient population information. (e.g. subjects who continue treatment beyond initial investigator-assessed, RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event as these immune responses may be used in determining advancement to the second stage).

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Dose holds and modifications can be made separately for each study medication (nivolumab, bevacizumab, or rucaparib), depending upon the observed adverse event and the attribution. Dose holds can be made independently for each study medication surrounding clinical procedures (e.g. port placement) as appropriate per standard of care guidelines. Dose holds may also be made at the discretion of the treating physician with the approval of the overall PI if clinically indicated for medical reasons other those described in this section. For patients in Cohort 2 and Cohort 3, cycles are numbered continuously with each cycle being 14 days in length; rucaparib dosing may be re-initiated mid-cycle, but bevacizumab and nivolumab dosing should occur/be resumed on day 1 of each cycle only.

6.1 Nivolumab Dose Modifications

Nivolumab dose reductions or dose escalations are not permitted. When blood counts have recovered or toxicities have resolved as described in section 6.3 and 6.8, nivolumab will be resumed at full dose.

6.2 Bevacizumab Dose Modifications

Bevacizumab dose escalations are not permitted. One dose reduction is permitted:

Dose Level	Bevacizumab Dose
0	10 mg/kg every 2 weeks
-1	5 mg/kg every 2 weeks

- All dose reductions are permanent.
- A maximum of 1 dose bevacizumab reduction is possible. Patients requiring more than 1 dose reduction must discontinue study treatment. Patients who are deriving clinical benefit and experience bevacizumab-related toxicities necessitating discontinuation of bevacizumab may be allowed to continue on nivolumab alone (or combination nivolumab/rucaparib for patients in Cohort 2 or Cohort 3) after discussion with the study PI.
- If patients have not recovered blood counts or resolved toxicities to required levels within 6 weeks, patients must discontinue study treatment.

6.3 Rucaparib Dose Modifications

Cohorts 1 and 2: Dose reductions of rucaparib are permitted, as per the table below. The dose of rucaparib should not be lowered below 300mg twice daily.

Dose Level	Rucaparib Dose
0	600mg twice daily
-1	500mg twice daily
-2	400mg twice daily
-3	300mg twice daily

Cohort 3: Dose reduction of rucaparib is permitted, as per the table below.

Dose Level	Rucaparib Dose
0	300mg twice daily*
-1	200mg twice daily*

*A dose level of 250mg twice daily may be implemented for select patients as described in the following paragraphs.

For select patients who have not experienced significant adverse events after receiving combination nivolumab, bevacizumab, and rucaparib for at least 100 days, dose escalation of rucaparib to 400mg twice daily may be considered in the setting of stable disease or disease progression after discussion with the overall Study PI.

As communicated by Clovis Oncology in December 2022, available supply of rucaparib 200mg tablets for this study is no longer available outside of supply already distributed to the participating study sites. Additionally, all available 300mg tablets for this study will expire in March of 2023. A significant supply of 250mg tablets is available that will expire in January of

2024. No other tablet sizes are available for distribution for this study. Because of these drug availability issues, additional considerations to the dose reductions and modifications for rucaparib include:

- For patients receiving rucaparib 300mg twice daily requiring a dose reduction after January 10, 2023, patients should be dose reduced to 250mg twice daily. Patients who require dose reduction beyond 250mg twice daily will need to be discontinued from rucaparib therapy. At the discretion of the treating investigator and the patient, patients receiving rucaparib 300mg twice daily will have the option of continuing on rucaparib at 250mg twice daily or discontinuing rucaparib therapy when the supply of rucaparib 300mg tablets is exhausted.
- Patients receiving rucaparib 200mg twice daily after January 10, 2023 may continue on rucaparib 200mg twice daily dosing until drug supply of 200mg tablets are exhausted. At the discretion of the treating investigator and the patient, patients who are deriving clinical benefit and tolerating rucaparib 200mg twice daily well have the option of either dose escalation of rucaparib to 250mg twice daily or discontinuing rucaparib therapy when the supply of rucaparib 200mg tablets is exhausted.

6.3.1 Hematologic toxicity

Patients experiencing hematologic toxicities related to rucaparib should be managed by the following table. Use of hematopoietic agents is not allowed on trial.

Table 6.3.1: Dose Modification and Management of Hematologic Adverse Events

Hematologic Event	Dose Modification
Absolute neutrophil count ≥ 1000/mcL **AND** Platelets ≥ 100,000/mcL **AND** Hemoglobin ≥ 8 mg/dL	Maintain dose level
Absolute neutrophil count < 1000/mcL **OR** Platelets < 100,000/mcL **OR** Hemoglobin < 8 mg/dL	Hold treatment until absolute neutrophil count ≥ 1000/mcL, platelets ≥ 100,000/mcL, and hemoglobin ≥ 8 mg/dL. Treatment may be restarted at one dose level lower. Patients whose counts have not recovered to absolute neutrophil count ≥ 1000/mcL, platelets ≥ 100,000/mcL, and hemoglobin ≥ 8 mg/dL within 28 days should be discontinued from rucaparib.
Grade 4 hematologic AE related to rucaparib that does not resolve to absolute neutrophil count ≥ 1000/mcL, platelets ≥ 100,000/mcL, and hemoglobin ≥ 8 mg/dL despite maximum supportive care after 28 days.	Permanently discontinue rucaparib.

Patients who have treatment held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery. If counts do not improve to CTCAE grade 1 or better despite drug cessation for 4 weeks, patients should be referred to a hematologist for

further assessment. A bone marrow analysis should be considered per hematology assessment.

6.3.2 Non-hematologic toxicity

Patients experiencing non-hematologic toxicities related to rucaparib should be managed by the following table. Guidelines for management of AST/ALT elevations are provided separately in Section 6.3.3, and should be followed instead of the table below.

Table 6.3.2: General Management of Rucaparib-related Non-Hematologic Toxicity

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Any ≥ grade 3 non-hematologic (excluding grade 3 fatigue or easily correctable asymptomatic grade 3 laboratory abnormalities)	Hold rucaparib until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower[1]. If symptoms do not resolve to ≤ grade 1 within 28 days, rucaparib should be discontinued.
Any grade 2 non-hematologic AE or grade 3 fatigue that persists despite maximal support.	Hold rucaparib until toxicity resolves to ≤ grade 1. Treatment may be restarted at either the same dose or one dose level lower, per investigator discretion[1]. If symptoms do not resolve to ≤ grade 1 within 28 days, rucaparib should be discontinued.
1. Grade 3 or 4 non-hematologic AE that does not resolve to grade 0-2 within 28 days despite maximum supportive care after treating patient at the lowest reduced dose level.[2] 2. Grade 3 or 4 non-hematologic AE lasting > 28 days despite maximum supportive care and treatment being held.	Permanently discontinue rucaparib.

[1]Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the Study Chair if evidence of clinical benefit.
[2]For thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic. For weight loss events, treatment may be resumed or continued at the discretion of the investigator if the weight stabilizes after an initial weight loss.

6.3.3 AST/ALT elevation (Cohorts 2 and 3 only)

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. For patients on cohort 2 or cohort 3 who experience an ALT/AST elevation, management should be as follows. For patients who have discontinued bevacizumab therapy for other reasons, rechallenge may occur with rucaparib monotherapy. (Please note that, as cycles are counted continuously, rechallenging with rucaparib/bevacizumab may result in initiating rucaparib therapy mid-cycle and subsequently treating with bevacizumab on Day 1 of the subsequent cycle):

- Grade 4 ALT/AST elevation:
    - If accompanied by elevation in bilirubin, discontinue from study and initiate management of potential immune-related hepatitis as clinically appropriate.
    - If no accompanying elevation in bilirubin, hold study drugs and initiate management of potential immune-related hepatitis as clinically appropriate. Monitor liver enzymes every 2-3 days. If immune-related hepatitis is not suspected and transaminases resolve spontaneously to grade 1 or better without empiric or other therapy directed towards immune-related hepatitis, rechallenge with rucaparib at the next lower dose level together with bevacizumab may be considered after discussion with the overall PI. Nivolumab may not be re-instituted until combination rucaparib/bevacizumab 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/bevacizumab dosing, re-initiation of nivolumab may be considered after discussion with the PI.
- 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 immune-related hepatitis as clinically appropriate. If ALT/AST resolves to Grade 2, rucaparib and bevacizumab 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. 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/bevacizumab 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 and bevacizumab 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/bevacizumab 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 bevacizumab 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/bevacizumab 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.

6.3.4 Cholesterol elevation

Cholesterol elevations to Grade 3 or higher have been observed with rucaparib. Patients experiencing elevation in cholesterol may be started on an HMG-CoA reductase inhibitor (commonly known as a statin) as clinically appropriate. Please refer to Section 8.3.8 regarding drug-drug interactions and statins.

Patients experiencing a Grade 3 or higher cholesterol elevation should have rucaparib held and should initiate treatment with a statin if not already initiated, or have adjustments made to their cholesterol management regimen if a statin has already been initiated. Dosing may resume at the same or a reduced dose of rucaparib, per the investigator's discretion once cholesterol elevation has resolved to Grade 2 or better.

6.4 Treatment Modification for Nivolumab-Related Adverse Events

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs of selected categories. See Investigator Brochure and Appendix B for management algorithms.

Of note, treatment with nivolumab dosing should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:
    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
    - Patients in Cohort 2 and Cohort 3 receiving concomitant rucaparib who experience a Grade 2 elevation in serum creatinine that is not accompanied by elevation in BUN may continue with nivolumab and bevacizumab with close interval monitoring of serum creatinine. Patients who experience a Grade 2 elevation in serum creatinine that has demonstrated close concordance with rucaparib administration (resolution with rucaparib hold and recurrent elevation with rucaparib resumption) may also be continued on nivolumab and bevacizumab.
- Any Grade 3 skin, nivolumab-related AE
- Any Grade 3 nivolumab-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
    - Grade 3 lymphopenia or leukopenia does not require dose delay.
    - For patients receiving nivolumab and bevacizumab alone, if a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity. For patients receiving combination nivolumab, bevacizumab, and rucaparib, please see Section 6.3.3 for further details regarding management.
    - For patients receiving nivolumab and bevacizumab alone, if a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity. For patients receiving combination nivolumab,

bevacizumab, and rucaparib, please see Section 6.3.3 for further details regarding management.
    - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The investigator should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
    - Patients in cohort 2 and cohort 3 experiencing Grade 3 or higher cholesterol elevation attributed to rucaparib alone may continue with nivolumab and bevacizumab dosing. Rucaparib dosing should be managed as per Section 6.3.4.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

6.5 Criteria to Resume Treatment Following Nivolumab-Related Adverse Events

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- For subjects in Cohorts 2 or 3 with AST/ALT elevation, nivolumab dosing may be resumed as per Section 6.3.3.
- For subjects in Cohort 1:
    - Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
    - Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment after discussion with and approval from the principal investigator.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after discussion with and approval from the principal investigator.

If treatment is delayed or interrupted for >6 weeks, the subject must be permanently discontinued from nivolumab therapy. Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI must be consulted. Patients who are clinically benefitting from study treatment who require dose interruption for >6 weeks may be considered for continuation for resumption of nivolumab treatment after discussion with the study PI.

6.6 Nivolumab Management Algorithms

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in the nivolumab IB and in Appendix B of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

6.7 Treatment Discontinuation Criteria for Nivolumab-Related Adverse Events

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, and infusion reactions, and endocrinopathies:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, 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 those noted below:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
    - For patients in Cohort 1: Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
        - AST or ALT > 5 x ULN
        - Total bilirubin > 3 x ULN
        - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
        - For patients in Cohort 2 and Cohort 3, management of LFT abnormalities should be as per Section 6.3.3.
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
    - 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 lymphopenia or leucopenia
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH 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 after discussion with and approval from the principal investigator.
  - For patients in Cohort 2 and Cohort 3: Grade 4 ALT/AST abnormalities without accompanying bilirubin abnormality that are attributed to rucaparib alone and spontaneously resolve without treatment for immune-related hepatitis, as outlined in Section 6.3.3.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing delays or interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted or delayed
  - Dosing interruptions or delays lasting > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the PI must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
  - Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the PI, presents a substantial clinical risk to the subject with continued nivolumab dosing

6.8 Treatment of Nivolumab Related Infusion Reactions

Since 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, hypo- or hypertension, bronchospasm, or other symptoms of allergic-like reactions.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE 4.0 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 subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (Moderate reaction requires 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 subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid 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. Monitor subject closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone 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 of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 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. Subject 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 subject until recovery from symptoms.

In the 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).

6.9 Treatment Modification for Bevacizumab-Related Adverse Events

Event	CTCAE Version 4 Grade	Action to be Taken

Allergic reactions, Infusion-related reactions, or Anaphylaxis	Grade 1-2	• Infusion of bevacizumab should be interrupted for subjects who develop dyspnea or clinically significant hypotension. • For infusion-associated symptoms not specified above, infusion should be slowed to 50% or less or interrupted. Upon complete resolution of the symptoms, infusion may be continued at no more than 50% of the rate prior to the reaction and increased in 50% increments every 30 minutes if well tolerated. Infusions may be restarted at the full rate during the next cycle. • Subjects who experience bronchospasm (regardless of grade) should discontinue therapy.
	Grade 3-4	• Discontinue therapy
Thromboembolic Event (Arterial); arterial ischemia -Cardiac ischemia -Myocardia infraction -CNS ischemia (TIA, CVA) -Any peripheral or visceral arterial ischemia/thrombosis	Grade 2-4	• Discontinue Therapy
Thromboembolic Event (Venous)	Grade 3 or asymptomatic Grade 4	• Hold treatment of both bevacizumab and nivolumab. If the planned duration of full-dose anticoagulation is ≤ 2 weeks, treatment should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is > 2 weeks, treatment may be resumed with bevacizumab during full-dose anticoagulation if all of the following criteria are met: -The subject must not have pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels or other conditions) -The subject must not have had hemorrhagic events while on study -The subject must be on a stable anticoagulation regimen prior to restarting

		treatment. • If thromboemboli worsen/recur upon resumption of study therapy, discontinue treatment.
	Symptomatic Grade 4	• Discontinue therapy.
Hypertension	Grade 1 (SBP 120-139 mmHg or DBP80-89 mmHg)	• Consider increased BP monitoring and start anti-hypertensive medication if appropriate.
	Grade 2 asymptomatic (SBP 140-159 mmHg or DBP 90-99 mm Hg)	• Begin anti-hypertensive therapy and continue treatment.
	Grade 2 symptomatic (SBP 140-160 mmHg or DBP 90-100 mm Hg) Grade 3 (≥ SBP 160 mmHg or ≥ DBP 100 mmHg)	• Start or adjust anti-hypertensive medication • Hold treatment until symptoms resolve **AND** BP < 160/90mmHg. • For HTN that is refractory requiring delay of > 6 weeks, discontinue treatment.
	Grade 4 (Hypertensive crisis or malignant hypertension)	• Discontinue treatment.
Heart Failure or LV dysfunction	Grade 3 or 4	• Discontinue treatment.
Proteinuria (Proteinuria should be monitored by dipstick prior to every dose of bevacizumab. If dipstick ≥ 2+ proteinuria, urine protein:creatinine (UPC) ratio should be obtained)	If UPC < 2.0	• Continue treatment.
	If UPC ≥ 2.0	• Hold treatment until UPC < 2.0 • Discontinue treatment if UPC does not recover to < 2.0 after 6 weeks of treatment interruption.
	Nephrotic syndrome	• Remove from treatment.

Hemorrhage (intracranial or pulmonary)	Grade 1	• Patients receiving full-dose anticoagulation should be removed from study. • For patients not on full-dose anticoagulation, hold treatment until ALL of the following criteria are met: -the bleeding has resolved and Hb is stable -there is no bleeding diathesis that would increase the risk of therapy -there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence
	Grade 2-4	• Discontinue treatment
Hemorrhage (any other organ systems)	Grade 3	• Patients receiving full-dose anticoagulation should be removed from study. • For patients not on full-dose anticoagulation, hold treatment until ALL of the following criteria are met: -the bleeding has resolved and Hb is stable -there is no bleeding diathesis that would increase the risk of therapy -there is no anatomic or pathologic condition that could increase the risk of hemorrhage recurrence • Patients who experience recurrence of grade 3 hemorrhage should discontinue treatment.
	Grade 4	• Discontinue treatment.
RPLS (Reversible Posterior Leukoencephalopathy syndrome) or **PRES** (Posterior Reversible Encephalopathy Syndrome)		• Discontinue treatment.
Wound dehiscence requiring medical or surgical intervention		• Discontinue treatment.
Perforation (GI, or any other organ)		• Discontinue treatment.
Fistula (GI, pulmonary, or any other organ)		• Discontinue treatment.
Obstruction of GI tract	Grade 2 requiring medical intervention	• Hold treatment until complete resolution.
	Grade 3 and 4	• Hold treatment until complete resolution. • If surgery is required, patient should be discontinued from study therapy.
Other unspecified bevacizumab-related	Grade 3	• Hold treatment until symptoms resolve to ≤ grade 1.

AEs (except controlled nausea/vomiting).	Grade 4	• Discontinue treatment. • Upon consultation with the overall principal investigator, resumption of study treatment if patient is benefitting from therapy, and the grade 4 toxicity is transient, has recovered to ≤ grade 1, and is unlikely to recur with retreatment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events Lists

7.1.1.1 Adverse Event List for Nivolumab

Categorization of AEs Potentially Associated with Nivolumab

In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, the Sponsor identified select AEs based on the following 4 guiding principles:

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (e.g., corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these are grouped into endocrine, GI, hepatic, pulmonary, renal, and skin select AE categories, respectively. The list of AEs belonging to select AE categories may evolve as more safety information becomes available in the nivolumab program.

Hypersensitivity/infusion reactions were also analyzed along with the select AE categories because multiple AE terms may be used to describe these events, and therefore, pooling of terms provides a more complete characterization of the events. Hypersensitivity/infusion reactions do not, otherwise, meet criteria to be considered select AEs.

Serious Adverse Events Reported from Clinical Trials with Nivolumab Monotherapy

As of May 2014, the following serious AEs have been reported in clinical studies in which nivolumab was given as monotherapy. The frequency of ADRs is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000). There are no very common or very rare SAEs associated with nivolumab monotherapy. For further information, including SAEs that are rarely associated, please reference the IB.

The following **common SAE** is associated: pneumonitis

The following **uncommon SAEs** by system organ class are associated:

- Endocrine: Adrenal insufficiency, Hypothyroidism
- Gastrointestinal: Abdominal pain, Colitis, Diarrhea, Nausea, Pancreatitis, Vomiting
- General and Administrative Site Conditions: Mucosal inflammation, Pyrexia
- Hepatobiliary: Abnormal hepatic function
- Immune system: Hypersensitivity
- Injury, Poisoning and Procedural Complications: Infusion-related reaction
- Metabolism and Nutrition: Dehydration, Hyperglycemia
- Renal and Urinary: Acute renal failure, Tubulointerstitial nephritis
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, Hypoxia, Interstitial lung disease, Lung infiltration, Respiratory failure

Nonserious Adverse Events Reported from Clinical Trials with Nivolumab Monotherapy

As of May 2014, the following nonserious AEs have been reported in clinical studies in which nivolumab was given as monotherapy. The frequency of ADRs is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000).

The following **very common** nonserious AEs are associated: Fatigue, Nausea, Pruritus
The following **common** nonserious AEs are associated: Arthralgia, Asthenia, Cough, Decreased appetite, Diarrhea, Pyrexia, Rash

A complete list of adverse events observed with nivolumab are detailed in the Investigator's Brochure (IB).

7.1.1.2 Adverse Event List for Bevacizumab

Bevacizumab is FDA-approved in conjunction with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of platinum-resistant ovarian cancer and together with platinum-based chemotherapy for the treatment of platinum-sensitive ovarian cancer. Bevacizumab is associated with a number of toxicities, including hypertension, headache, epistaxis, hoarseness, proteinuria, thromboembolic events (venous and arterial), arthralgia, myalgia, infection, impaired healing, bleeding events, gastrointestinal perforation, fistula formation, myelosuppression, and allergic or infusion reactions.

Please refer to the FDA package insert for a comprehensive list of adverse events.

7.1.1.3 Adverse Event List for Rucaparib

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.

A complete list of adverse events observed with rucaparib are detailed in the Investigator's Brochure (IB).

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3 (Serious Adverse Event).

- **Attribution** of the AE:
  - 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.

7.3 Serious Adverse Event (SAE)

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

NOTE: The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

7.4 Expedited Adverse Event Reporting

7.4.1 Investigators **must** report to the Overall PI any serious adverse event (SAE) that occur during the screening period and within 100 days of the last dose of study treatment on the local institutional SAE form. For participants enrolled on study but never treated with study drug, SAEs should be collected for 30 days from the date of enrollment.

7.4.2 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4.3 Reporting to BMS

SAEs, whether related or not related to study drug, and pregnancies must also be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

[redacted]

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 to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

7.4.4 Reporting to Pharma&

All SAEs and AESIs occurring on patients in Cohort 2 and Cohort 3, regardless of relationship to study drug, must be reported to Pharma&within 24 hours of knowledge of the event, during the study through 28 days after receiving the last dose of study treatment, according to the procedures below. After the 28-day specified window, only SAEs considered to be treatment-related and all AESIs, regardless of treatment relationship, should be reported. It is important that the investigator provide an assessment of relationship of the SAE or AESI to study treatment at the time of the initial report.

AESIs of pneumonitis or similar events (ie, interstitial lung disease, pulmonary fibrosis, acute interstitial pneumonitis, alveolitis necrotizing, alveolitis, hypersensitivity pneumonitis, and organizing pneumonia) should be reported up to, but not beyond, the [28-day Follow-up Visit (28 days after the last dose of investigational product). After the 28-day Follow-up Visit, only pneumonitis or similar events meeting the criteria for an SAE and assessed as potentially related to investigational product should be reported to Pharma&.

The Pharma& or the Sponsor-Investigator's study-specific Serious Adverse Event (SAE)/Adverse Events of Special Interest (AESI) Report Form must be used for reporting SAEs and AESIs. The contact information for reporting of SAEs and AESIs can be found on the SAE/AESI Reporting Form and Pregnancy Report Forms.

[redacted]

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

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

For studies conducted under an Investigator IND in the US, any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information. BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:

[redacted]

All SAEs should simultaneously be faxed or e-mailed to BMS at:

[redacted]

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or other agents administered in this study can be found in Section 7.1.

8.1 Nivolumab

8.1.1 **Description**

Nivolumab is also referred to as BMS-936558-01 or BMS-936558. Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains. The physical and chemical properties of nivolumab are provided in Table 8.1.1 below. The geometric mean of terminal T-HALF was 25.6 days and the typical clearance was 8.8 mL/h, which are consistent with those of full human immunoglobulin antibodies.

Table 8.1.1: Nivolumab Physical and Chemical Properties

BMS Number	BMS-936558-01
Other Names	Nivolumab, BMS-936558, MDX1106, ONO-4538, anti-PD-1
Molecular Weight	146,221 daltons
Appearance	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present
Solution pH	5.5 to 6.5

8.1.2 **Form**

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and Nivolumab Injection, 40 mg/4 mL (10 mg/mL)

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween™ 80), pH 6.0 and includes a 0.7-mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

PRODUCT INFORMATION TABLE:

Product Description:(Other names = MDX-1106, ONO-4538, anti-PD-1)

Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01)*	100 mg/Vial (10	Carton of 5 or 10 vials	10-cc Type 1 flint glass vials	Clear to opalescent, colorless to	**BMS-936558-01 Injection**

Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	mg/mL).	stoppered with butyl stoppers and sealed with aluminum seals.	pale yellow liquid. May contain particles	must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

Nivolumab may be labeled as BMS-936558-01 Solution for Injection.

8.1.3 **Storage and Stability**

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL)
Vials of nivolumab injection must be stored at 2˚to 8˚C (36˚to 46˚F) and protected from light, freezing, and shaking.

If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.

If stored in a glass front refrigerator, vials should be stored in the carton.

Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures.

Diluted Nivolumab Injection in the IV Bag

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°to 8°C, 36°to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20˚to 25˚C, 68˚to 77˚F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

8.1.4 **Compatibility**

Nivolumab injection will be infused diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL.

8.1.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

8.1.6 **Availability**

Nivolumab is an investigational agent and will be supplied free of charge from Bristol-Myers Squibb.

8.1.7 **Preparation**

- Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.
  *Note: Mix by **gently** inverting several times. **Do not** shake.*
- Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection
- Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*

Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL.

Note: Nivolumab infusion should not exceed a total infusion volume of 120 mL.

Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.

- Attach the IV bag containing the nivolumab solution to the infusion set and filter.
- At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Please refer to section 3.2.3 of the current Investigator Brochure. Due to parameters surrounding the use time of nivolumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP].

8.1.8 **Administration**

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2° to 8°C (, 36° to 46°F) and used within 4 for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20° to 25°C, 68° to 77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for diluted solutions of BMS-936558-01 injection in the IV bag should be inclusive of the includes the product administration period.

Nivolumab will be given every two weeks at a dose of 240 mg to be administered as a 30 minute IV infusion.

Subjects may be dosed no less than 12 days from the previous dose of drug. There are no premedications recommended for nivolumab on the first cycle. There will be no dose modifications allowed.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Protocol Section 6.7.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

<u>Nivolumab Injection, 100 mg/10 mL (10 mg/mL) and 40 mg/4 mL (10 mg/mL)</u>

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses and infusion time. It is not to be administered as an IV push or bolus injection. Nivolumab injection will be infused diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl) phthalate) IV components, or glass bottles have been observed.

8.1.9 **Ordering**

It is possible that sites may have more than one clinical study on the same drug ongoing at the same time. It is imperative that only drug product designated for this protocol be used for this study

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately. If commercial investigational product is used, it should be stored in accordance with the appropriate local labeling

Initial Orders

- Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.
- Nivolumab will be supplied in 100 mg vials.
- The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.
- Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing

Re-Supply

- Drug re-supply request form should be submitted electronically 2 weeks before the expected delivery date. Deliveries will be made Tuesday through Friday.
- When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

Drug Excursions

- Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

Expired and unused supplies of nivolumab will be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.2 Bevacizumab

8.2.1 Description

Bevacizumab (Avastin ® or biosimilar product) is a recombinant, humanized, monoclonal antibody with high affinity for binding to vascular endothelial growth factor receptor (VEGF). Bevacizumab is an IgG1 antibody that contains human framework regions and the complementarity determining regions of a murine antibody that binds to VEGF.

8.2.2 Form

Bevacizumab is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for intravenous infusion. It is supplied in 100 mg and 400 mg preservative-free, single-use vials to deliver 4 mL or 16 mL of Avastin (25 mg/mL).

8.2.3 Storage and Stability

Bevacizumab vials [100 mg (NDC 50242-060-01) and 400 mg (NDC 50242-061-01)] are stable at 2−8°C (36−46°F). Vials should be protected from light and should not be frozen or shaken. Diluted bevacizumab solutions may be stored at 2−8°C (36−46°F) for up to 8 hours. They should be stored in the original carton until time of use.

8.2.4 Compatibility

The 100 mg product is formulated in 240 mg α,α-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and water for injection, USP. The 400 mg product is formulated in 960 mg α,α-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and water for injection, USP [24]. No incompatibilities between bevacizumab and polyvinylchloride or polyolefin bags have been observed.

8.2.5 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.2.6 Availability and Ordering

Bevacizumab is a commercially available agent.

8.2.7 Preparation and Administration

Bevacizumab may be prepared per institutional guidelines. It should be given intravenously over 30 minutes, though infusion duration may vary per institutional

guidelines.

8.2.8 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocol Development for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

8.2.9 Destruction and Return

At the end of the study, unused supplies of bevacizumab should be returned according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.3 Rucaparib

8.3.1 Description

Rucaparib is a potent small molecule inhibitor of poly-adenosine diphosphate (ADP) ribose polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3.

8.3.2 Form

Rucaparib is supplied as, , 200mg, 250mg, and 300mg . film coated tablets: The physical appearances of the tablets are unique in order to ensure proper identification....: 200 mg (blue, round, debossed with C2), 250 mg (white, rounded diamond shape, debossed with C25), 300 mg (yellow, oval, debossed with C3)

8.3.3 Storage and Stability

Rucaparib tablets are provided in HDPE bottles and should be stored in the provided containers between 15°C and 30°C.

8.3.4 Handling

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

8.3.5 Availability and Ordering

Rucaparib is an investigational agent and was supplied free of charge by Clovis for use in this clinical trial prior to its acquisition by Pharma& as of 01 May 2023.

8.3.6 **Accountability**

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent (investigational or free of charge) using the NCI Drug Accountability Record or another comparable drug accountability form. (See the CTEP website at http://ctep.cancer.gov/protocol Development for the "Policy and Guidelines for Accountability and Storage of Investigational Agents" or to obtain a copy of the drug accountability form.)

8.3.7 **Destruction and Return**

Expired and unused supplies of rucaparib will be destroyed according to institutional policies. Destruction will be documented in the Drug Accountability Record Form.

8.3.8 **Drug-drug Interactions**

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 with narrow therapeutic windows (see IB, 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 increase metformin renal elimination and decrease liver uptake of metformin, caution is advised when metformin is co-administered with rucaparib. In addition, rucaparib is an inhibitor of the BCRP with 50% inhibitory concentration (IC50) value suggesting potential BCRP inhibition and increased exposures of medicinal products that are BCRP substrate (eg, rosuvastatin).

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Biomarker Studies

A variety of factors that could potentially predict clinical response to nivolumab plus bevacizumab will be investigated in peripheral blood and in tumor specimens taken from all subjects prior to treatment and as outlined in Biomarker Sampling Schedule table in Section 10. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (adverse event) data. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with ovarian cancer or immunotherapy plus antiangiogenic treatment.

9.1.1 Tumor Tissue Specimens

9.1.1.1 Pre-treatment biopsy

Tumor biopsy specimens will be obtained from consenting subjects prior to treatment with nivolumab plus bevacizumab. All participants who do not have an archival sample that was obtained within 20 months of study entry must undergo pre-treatment biopsy, as the expression of PD-L1 degrades over time and could not be reliably assessed in samples older than 20 months. Pre-treatment biopsy is encouraged but is not mandatory for participants who have available archival tissue that was obtained within 20 months of study entry. Biopsies from bone lesions are not suitable for tumor specimens since the decalcification process is not compatible with several planned biomarker analyses.

The investigator, in consultation with the radiology staff, must determine the degree of risk associated with the procedure and find it acceptable. Biopsies may be done with local anesthesia or conscious sedation. Institutional guidelines for the safe performance of biopsies should be followed. Excisional biopsies may be performed to obtain tumor biopsy samples. Invasive procedures that require general anesthesia should not be performed to obtain a biopsy specimen. However, if a surgical procedure is performed for a clinical indication, excess tumor tissue may be used for research purposes with the consent of the subject.

A minimum of 2 and up to 5 cores of a 16 to 18 gauge size should be collected under institutional guidelines for biopsy procedures. Biopsies should be immediately placed in 10% formalin and subsequently embedded in paraffin under standard procedures.

These tumor samples may also be assessed for the expression of other immune or ovarian cancer-related genes, RNAs and/or proteins, as well as the presence of immune cell populations

using a variety of methodologies inclusive of, but not limited to immunohistochemistry (IHC), qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH). Various molecular markers with potential predictive value for the treatment of ovarian cancer with nivolumab plus bevacizumab may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, tumor infiltrating lymphocytes (TILs) or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. Tissue from the resected solitary lesions may be assessed for residual tumor cells and for markers expected to accompany tumor shrinkage in this study, including, but not limited to TILs and subsets thereof.

9.1.1.2 Archival tumor sample

Archival tumor samples will be obtained in participants not undergoing biopsy, consisting of a formalin-fixed paraffin embedded (FFPE) tumor tissue block or at least 20 unstained slides (charged) of 4 uM thickness. Five of these fresh cut slides will need to be refrigerated at around 4° Celsius to be used for PD-L1 testing as described in section 9.1.1.3.

9.1.1.3 Tissue biomarkers

All tumor tissue samples will be assessed for expression of PD-L1 by immunohistochemistry. Additionally, tissue samples may also be assessed for the expression of other immune or ovarian cancer-related genes, RNAs and/or proteins, as well as the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to qRT-PCR, genetic mutation detection and next generation sequencing. Various molecular markers with potential predictive value for the treatment of ovarian cancer with nivolumab plus bevacizumab may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, tumor infiltrating lymphocytes (TILs) or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. Tissue from the resected solitary lesions may be assessed for residual tumor cells and for markers expected to accompany tumor shrinkage in this study, including, but not limited to TILs and subsets thereof.

9.1.1.3.1. Shipping Samples (Cohort 1)

Three slides will be shipped ambient to HTG Molecular for macrodissection, if required, and RNA sample profiling using the HTG EdgeSeq Immuno-Oncology Assay. A sample submission form will be provided to each site that will be emailed to [redacted] prior to sending samples. A copy of the submission form must be included with the shipped samples. Please send the samples to:

HTG Molecular
[redacted]

NOTE: All samples should be shipped overnight Monday – Thursday except for holidays. No

samples will be sent on Fridays as the lab will not be open to receive them over the weekend.

Five slides will be shipped to Mosaic for PD-L1 testing. These fresh cut slides will need to be refrigerated at around 4° Celsius to be used for PD-L1 testing. A shipping manifest will be provided to each site that will be emailed to both [redacted] prior to sending samples. A copy of the manifest must be included with the shipped samples. Please send the samples to:

Attention: [redacted]

NOTE: Samples should be shipped overnight Monday – Friday except for holidays.

9.1.1.3.2. Shipping Samples (Cohort 2 and Cohort 3)

Tumor blocks and/or slides should be shipped to the following address. As per Section 9.1.1.3.1, five fresh cut slides will need to be refrigerated at around 4° Celsius to be used for PD-L1 testing. A shipping manifest will be provided and should be emailed to [redacted] prior to sending samples. A copy of the manifest must be included with the shipped samples. Please send the samples to:

[redacted]

NOTE: Samples should be shipped overnight Monday – Thursday except for holidays.

9.1.2 Germline mutational analysis

A sample of peripheral blood (~7 mL) will be collected prior to initiation of treatment. Next generation sequencing will be performed to evaluate for mutations within genes of homologous recombination and other DNA repair pathways. Recent work has suggested that tumors with BRCA deficiency have a higher neoantigen load, increased population of tumor-infiltrating lymphocytes, and increased expression of PD-1/PD-L1 (Strickland et al., Oncotarget, 2016). Of note, as germline mutational analysis will not be performed in a CLIA setting, results will not be returned to the patient. Please see Appendix C for processing information.

9.1.2.1 Shipping Samples (Cohort 1)

Whole blood samples and 10 slides will be sent to Q2 Solutions for next generation sequencing. A sample manifest should be sent via email to [redacted] to notify Q2 that samples are being shipped. Please reference

study #CA209-323 and quote 25799 on the shipping label and include a copy of the samples manifest in the shipment. Please send samples to:

Q2 Solutions | EA Genomics

[redacted]

NOTE: Samples may be sent overnight Monday – Friday except for holidays.

9.1.2.2 Shipping Samples (Cohort 2 and Cohort 3)

Whole blood samples should be sent to the address below. A sample manifest should be sent via email to [redacted]. A copy of the sample manifest should be included with the shipment. Please send the samples to:

[redacted]

NOTE: Samples should be shipped overnight Monday – Thursday except for holidays.

9.1.3 Exploratory serum biomarkers

Blood samples for exploratory serum biomarker analyses (~6 mL for each timepoint) will be drawn at the time points indicated in Biomarker Sampling Schedule table. Blood samples will be processed to collect serum and then put in frozen storage. Samples may be assessed by ELISA, seromics and/or other relevant multiplex-based protein assay methods for immune or ovarian cancer-related factors that will predict for nivolumab benefit or correlate with treatment efficacy. Numerous potential serum-based biomarkers are currently under investigation for their potential to predict or correlate with efficacy to nivolumab or bevacizumab, including but not limited to levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors and microRNAs (such as, but not limited to, soluble CD25, soluble PD-1, soluble LAG-3, CXCL-9, VEGF, and VEGF receptors). Please see Appendix D for processing information.

9.1.3.1 Shipping Samples (Cohort 1)

Serum biomarker PKs collected on Day 1 Cycles 1-3 and off treatment will be shipped to Myriad RBM overnight for biomarker analysis and can be batch shipped. The sample tubes (when possible) should be placed in 9”x9” cryoboxes, rather than bags, to minimize damage to the samples. The shipment should be prepared according to biohazard regulations and shipped frozen, in a Styrofoam container with sufficient dry ice to maintain temperature (less than -80 °C) for at least 48 hours. Shipment notification emails including a completed MRBM Sample

Submission Form (SSF) and electronic sample manifest (Excel) should be sent to [redacted] A copy of bot the MRMB Sample Submission Form and electronic sample manifest must be sent with the samples. Please send the samples to:

Myriad RBM, Inc.
[redacted]

NOTE: Preferably samples are shipped Monday-Wednesday to arrive Tuesday-Thursday except for holidays. No one will be on site to receive samples over weekends.

9.1.3.2 Shipping Samples (Cohort 2 and Cohort 3)

Samples should be collected and batch shipped to the address below. A sample manifest should be sent via email to [redacted]. A copy of the sample manifest should be included with the shipment. Please send the samples to:

[redacted]

NOTE: Samples should be shipped overnight Monday – Thursday except for holidays.

10. STUDY CALENDAR AND BIOMARKER SAMPLING SCHEDULE

Baseline evaluations are to be conducted within 2 weeks prior to start of protocol therapy. Scans, Echocardiograms, and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

NB: One cycle is 2 weeks in length

STUDY CALENDAR										
Procedures	**Screen**	**Cycle 1**		**Cycle 2**		**Cycle 3**	**Cycle 4 +**	**Nivolumab Discontinuation[l]**	**Off-Tx**	**Follow-Up**
		Day 1	**Day 8**	**Day 1**	**Day 8**	**Day 1**	**Day 1**			
Treatment Nivolumab		X		X		X	X			
Treatment Bevacizumab		X		X		X	X	X[l]		
Treatment Rucaparib[k]		Oral dosing twice daily						X[l]		
Demographics	X									
Medical history	X									
Concurrent meds	X	X		X		X	X	X	X	
Physical exam	X	X		X		X	X	X	X	
Vital signs [a]	X	X		X		X	X	X	X	
Height	X									
Weight	X	X		X		X	X	X	X	
Performance Status	X	X		X		X	X	X	X	
Blood tests [b,j]	X	X	X	X	X	X	X	X	X	
Coagulation parameters (INR, aPTT)	X									
TSH (with Free T4)	X	X					X [c]	X	X	
EKG	X									
U/A or urine protein:creatine ratio[o]	X	X		X		X	X	X	X	
Hepatitis B and C testing [d]	X									
Echocardiogram[i]	X									
Adverse event evaluation		X		X		X	X	X	X	X [e]
Tumor restaging	X	Tumor measurements are repeated every 4 cycles (+/- 1 week), e.g, C5D1, C9D1, C13D1, etc.[n]						X[m]		
Oxygen saturation [f]		X		X		X	X		X	
Pregnancy Test [g]	X	X [g]					X [g]			X [g]
CA-125	X	CA-125 is performed every 4 weeks (2 cycles) (+/- 1 week)						X	X	
Survival Assessment										X [h]
a: Temperature, blood pressure, pulse, respiratory rate, oxygen saturation										

b: CBC with differential, sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, LDH, SGPT [ALT], SGOT [AST], total bilirubin, alkaline phosphatase, amylase, lipase. Patients in cohort 2 and cohort should have a fasting lipid panel performed every 6 weeks (every 3 cycles); if patients have permanently discontinued rucaparib, the fasting lipid panel may be omitted.
c: Thyroid function testing should be done every 6 weeks (every 3 cycles).
d: Hepatitis B and C testing (HBV sAg and HCV Ab or HCV RNA) should be done within 28 days prior to first dose
e: Follow for 100 days following last receipt of study treatment.
f: Oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) should be assessed at each on-study visit prior to dosing
g: Serum or urine pregnancy testing is required for women of childbearing potential within 24 hrs of study enrollment or randomization. Serum or urine pregnancy test should be repeated every 3 cycles. After discontinuation from nivolumab these should be repeated at approximately 30days and approximately 70 days
h: Every 3 months until death
i: Echocardiogram should be done at baseline for patients who have has prior treatment with anthracyclines.
j: Patients enrolled to cohort 2 and cohort 3 should have weekly CBC with differential through the first two cycles (e.g., on Cycle 1 Day 1 and Day 8 and on Cycle 2 Day 1 and Day 8).
k: For patients in cohort 2 and cohort 3 only
l: Patients will be treated on nivolumab for up to 2 years (treatment may continue beyond 2 years per investigator and patient discretion), after 2 years patients have the option to continue on bevacizumab alone or discontinue both drugs should nivolumab be stopped. Patients who discontinue nivolumab and continue on bevacizumab alone (Cohort 1) or bevacizumab/rucaparib (Cohort 2 and Cohort 3) will follow the main study calendar. Patients discontinuing all drugs will need to be evaluated every 12 weeks (+/- 1 week), as defined in the "Nivolumab Discontinuation" column, in order to be re-challenged. If the patient subsequently progresses re-challenge is allowed after discussion with the Overall PI and meeting the criteria outlined in section 5.2.3.
m: Patients who discontinue all drugs will undergo tumor restaging every 8-12 weeks, this can be done more frequently at the discretion of the treating physician.
n: Patients continuing study treatment for a minimum of 1 year may have the interval of repeated tumor measurements expanded to every 6 cycles (e.g. every 12 weeks) +/- 1 week.
o: Urine studies may be omitted if patients have permanently discontinued bevacizumab if clinically appropriate per investigator discretion

BIOMARKER SAMPLING SCHEDULE

Samples [a]	**Screen**	**Cycle 1 Day 1**	**Cycle 2 Day 1**	**Cycle 3 Day 1**	**Off Treatment**
Serum biomarkers		X	X	X	X
Tumor biopsy or archival tissue sample [b]	X				
Whole blood		X			

[a] All biomarker samples may be obtained +/- 3 days from the indicated timepoint. Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 biomarkers must be obtained prior to receiving nivolumab/bevacizumab study treatment.
[b] Pre-treatment biopsy must be obtained within 2 weeks prior to start of protocol therapy on all participants who do not have an archival sample obtained within the last 20 months. Biopsy is optional but strongly encouraged in participants where an archival sample obtained within the prior 20 months is available.

All serum biomarkers and whole blood samples will need to be labelled with the following information:

- Study number
- Subject number
- Time point
- Sample Type

For all tumor biopsy and archival tissue samples please collect the following information:

- Copy of de-identified pathology report
- Original block ID
- Collection method
- Date of biopsy

- Site/organ of biopsy
- Site of collection (primary or metastatic)

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 4 cycles (approximately 8 weeks). In addition to a baseline scan, confirmatory scans should also be obtained (not less than 4) weeks following initial documentation of objective response. The next planned scans may be used as the confirmatory scans.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009] and as per immune-related RECIST criteria (irRC). 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.

11.1.1 Definitions

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

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

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable if progression has been observed in the lesions following completion of the radiation course.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice

thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. 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.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. 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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in 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 thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of 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.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. FDG-PET assessment alone should not be used to document response or progression.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later data and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the

study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

11.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*

CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants 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.

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 Immune related Response Criteria (irRC)

Immune related response criteria using unidimensional measurements may be used to describe tumor shrinkage (Nishino *et al.*, 2014). This methodology is the same as described above for RECIST except:

- New lesions do not automatically denote disease progression
- The measurement of longest diameter of new measurable lesions are included in the sum of the measurements of the original target lesions.

The same method of assessment and the same technique should be used to characterize each identified and reported target lesion(s) at baseline and throughout the trial.

irRECIST criteria are defined as follows:

- Overall immune-related complete response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. All measurable lymph nodes also must have a reduction in short axis to <10 mm.
- Overall immune-related partial response (irPR): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions decreases >= 30%.
- Overall immune-related stable disease (irSD): Sum of the diameters (longest for non-nodal lesions, shortest for nodal lesions) of target and new measurable lesions neither irCR, irPR, (compared to baseline) or immune-related progressive disease (irPD, compared to nadir).
- Overall immune-related progressive disease (irPD): Sum of the diameters(longest for non-nodal lesions, shortest for nodal lesions)of target and new measurable lesions increases >= 20% (compared to nadir), confirmed by a repeat, consecutive observation at least 4weeks from the date first documented.

New measurable lesions: Incorporated into tumor burden (ie, added to the target lesion measurements). A lymph node has to be >= 15 mm in short axis to be a measurable new lesion and its short axis measurement is included in the sum. Up to 2 new lesions per organ and up to 5 new lesions in total can be added to the measurements.

New non-measurable lesions: Do not define progression but preclude irCR.

Overall responses derived from changes in index, non-index, and new lesions are outlines in the following table.

Overall Response Derived from Changes in Index, Non-index and New Lesions

Measurable response	Non-measurable response		Overall response using irRECIST[b]
Index and New Measurable Lesions (Tumor Burden)[a]	Non-Index Lesions	New, nonmeasurable Lesions	
Decrease 100%	Absent	Absent	irCR
Decrease 100%	Stable	Any	irPR
Decrease 100%	Unequivocal progression	Any	irPR
Decrease ≥30%	Absent/stable	Any	irPR
Decrease ≥30%	Unequivocal progression	Any	irPR
Decrease <30% and increase <20%	Absent/stable	Any	irSD
Decrease <30% and increase <20%	Unequivocal progression	Any	irSD
Increase ≥20%	Any	Any	irPD

a. Decrease assessed relative to baseline.
b. Response (irCR and irPR) and progression (irPD) must be confirmed by a second, consecutive assessment at least 4 weeks apart.

Best immune related responses are classified as immune related CR (irCR – disappearance of all lesions) or immune related PR (irPR (≥30% reduction from baseline).

Immune-related progression-free survival (irPFS) is defined as time from registration (or randomization) to the earlier of immune-related progression of disease (irPD) or death due to any cause. Participants alive without immune-related disease progression are censored at date of last disease evaluation.

11.1.8 Response Review

All films will be reviewed and response evaluated by the DF/HCC Tumor Imaging Metrics Core (TIMC).

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 Responsibility for Data Submission

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the DF/HCC Overall Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements. All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

12.4 Multicenter Guidelines

N/A

12.5 Collaborative Agreements Language

N/A

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The first two cohorts of this study are phase II designs with two sequentially enrolled cohorts, each including a safety assessment lead-in, in which the dose limiting toxicities (DLTs) of the study agents will be assessed over a 28-day period (two treatment cycles) in the first six evaluable patients enrolled. A safety review will occur after these six patients have completed two treatment cycles. Further accrual will be held until the regimen is deemed safe.

Within the safety lead-in, patients who do not have a DLT and who do not complete cycle 1 will be replaced. All patients that received any treatment will be considered evaluable for a DLT, unless they withdraw from the trial for reasons other than toxicity. If one or fewer patient out of the first six patients experience DLTs within the first two treatment cycles then the regimen will be deemed safe for administration in the phase II study. In cohort 1, if two or more patients out of the first six patients experience DLTs then the combination of nivolumab and bevacizumab will be declared unsafe and the study will be terminated.

In cohort 2, if two or more patients out of the first six patient experience DLTs while receiving the combination of nivolumab, bevacizumab, and rucaparib, a second safety lead-in of six patients will be performed with the combination using the next lower dose level of rucaparib. If one or fewer patients out of the six patients in the second safety lead-in experience DLTs within the first two treatment cycles, then the combination of nivolumab, bevacizumab, and rucaparib will be deemed safe for administration at this dose level in the phase II study. If two or more patients in the second safety lead-in in cohort 2 experience DLTs, then the combination of nivolumab, bevacizumab, and rucaparib will be declared unsafe and no further enrollment will occur for this cohort.

True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of declaring MTD	89%	66%	42%	23%	11%	4%	1%	0.2%	<0.01%

A DLT is defined as any of the following occurring during the first 28 days of treatment, assessed in accordance with the current version of NCI Common Terminology Criteria (CTCAE):

<u>Non-Hematologic Toxicity</u>

Any Grade 3 or 4 treatment-related event, excluding the following toxicities:

- Grade 3 fatigue, recovering within 7 days
- Grade 3 hypertension controlled with anti-hypertensive therapy
- Grade 3 electrolyte disturbances (e.g., hypophosphatemia, hyponatremia, hypokalemia) that are asymptomatic and correctable with electrolyte repletion.
- Grade 3 or 4 amylase or lipase elevation that is not associated with any signs or symptoms of pancreatitis
- Grade 3 rash that resolves to grade 2 or grade 1 within < 5 days.
- For patients in cohort 2 or cohort 3:
    - Asymptomatic grade 3 ALT/AST elevation that resolves spontaneously to grade 2 or better and does not recur after resumption of triplet combination

treatment
- Asymptomatic grade 3 elevation in cholesterol

Hematologic Toxicity

a) Grade 4 neutropenia of ≥ 7 days' duration
b) Grade 4 neutropenia of any duration with fever or documented infection
c) All other Grade 4 hematologic toxicities

In Cohort 3, we will implement sequential boundaries to monitor for DLTs. The accrual to Cohort 3 will be halted if excessive numbers of DLTs are seen (see table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 17.8% when the rate of DLTs is equal to the acceptable rate 20% and greater than 45.6% when DLT rate is 30% or higher.

Number of patients	1	2	3-6	7-9	10-13	14-15
Halt enrollment if these number of patients or more experience a DLT	-	2	3	4	5	6

The primary endpoint for the phase II part of the first two cohorts is objective response (CR + PR) using standard RECIST 1.1 criteria.

A key secondary endpoint is modified objective response that allows immune related objective response subsequent to initial PD per RECIST criteria. Subjects with initial PD per RECIST who continue treatment in their initially assigned treatment arm beyond progression (Section 5.8) and subsequently reach confirmed immune related CR or PR (relative to initial tumor assessment and evaluated by including the measurement of longest diameter of any new measurable lesions in the sum of the measurements of the original target lesions, Section 10.1.7) will be considered as having an objective response for the purposes of meeting criteria for moving from Stage 1 to Stage 2. Although not standard objective response per RECIST, these immune related response criteria using unidimensional measurements account for the unusual immune related tumor response patterns reported with various immunotherapies, including nivolumab.

The response rate for bevacizumab monotherapy in relapsed ovarian cancer is approximately 15%. In order to detect a doubling from this comparison to a target response rate to 30%, an admissible two-stage design indicates that 38 total patients will provide statistical power of 80% when controlling alpha at 10%. (Simon *et al.,* 1989; Jung *et al.,* 2004) The first stage (including patients from the safety lead-in) comprises 16 patients and if two or fewer responses (including immune related responses subsequent to initial PD) are seen in this group then the trial will stop early for futility. After completion of the second stage, 9 or more responses (not including immune related responses subsequent to initial PD) in 38 patients are required to reject the null hypothesis and conclude there is sufficient efficacy to warrant further study.

The primary endpoint for Cohort 3 is the tolerability of the combination of nivolumab, bevacizumab, and rucaparib based upon maintenance of dosing without drug modifications

within the first 100 days of dosing. A single stage design will be used to test the null hypothesis than the probability of modification within the first 100 days of dosing is 50% or greater. With 15 patients in cohort 3, the study has 94% power to reject the null hypothesis at the 10% one-sided type I error level if the probability of modification within the first 100 days of dosing is 20% or less.

The secondary endpoints for Cohort 3 will be to assess efficacy of the combination via objective response rate by RECIST 1.1. or modified GCIG CA-125 criteria.

13.2 Sample Size, Accrual Rate and Study Duration

The planned sample size for each cohort is 38 patients. The total sample size will be adjusted to allow for replacement of participants who never began protocol therapy for reasons including ineligibility, inevaluability, and participant drop out. Cohorts will accrue sequentially, with cohort 2 starting accrual after cohort 1 accrual is complete. Cohort 3 will include 15 patients. It is anticipated that approximately 6 patients will be enrolled per month for an approximate accrual period of 14 months for the first two cohorts. In cohort 3 it is anticipated that 15 patients will be accrued over 10 months and analysis will occur 100 days after the last patient is accrued. All patients who begin protocol therapy will be included in the evaluation of objective response and toxicity.

13.3 Stratification Factors

No stratification factors are planned.

13.4 Interim Monitoring Plan

The study includes a safety assessment lead-in for cohorts 1 and 2; please see section 13.1 for details.

Patients will be enrolled following a two-stage design with continuation of enrollment to the second stage if sufficient anti-tumor activity is seen in the first stage. The first stage for each cohort comprises 16 patients and if two or fewer responses (including immune related responses) are seen in this group then the cohort will stop early for futility.

Cohort 3 will use continuous monitoring for DLTs; please see section 13.1 for details.

13.5 Analysis of Primary Endpoints

The objective response rate (CR + PR) using RECIST 1.1 criteria will be reported with a 90% standard exact binomial confidence interval that does not adjust for the two-stage design. This is chosen as a conservative estimation procedure considering the allowance of continuation to the second stage based on a secondary efficacy endpoint.

Time-to-drug discontinuation or modification of any protocol treatment will be reported using the method of Kaplan-Meier, and the probability of discontinuation within 100 days will be presented with a one-sided 90% confidence interval (upper bound). Patients that discontinue

protocol therapy due to disease progression with no discontinuation or modification of any protocol treatment for toxicity will be censored at the time of disease progression.

13.6 Analysis of Secondary Endpoints

Best overall response will be assessed among all patients who received at least one dose of both study drugs at the MTD. Best overall response will be estimated according to RECIST criteria as described in Section 11.1.4.4. Best overall immune related response and immune-related objective response rate will be estimated according to irRECIST criteria as described in Section 11.1.7. composite response rate will be assessed using the modified composite endpoint (CR + PR, including immune related objective responses) and using modified GCIG CA-125 criteria as a secondary analysis, and each will be reported with 90% confidence intervals that do not adjust for the two-stage design.

Time-to-event endpoints including duration of response, progression free survival and immune-related progression free survival will be described using the method of Kaplan-Meier, and presented with 90% confidence intervals. Patients that are alive without disease progression at time of analysis are censored at the date of last disease evaluation.

Treatment-related toxicities will be summarized by maximum grade and by term using CTCAE v4.0 and reported with 90% binomial exact confidence intervals.

The association of baseline PD-L1 expression with anti-tumor activity will be evaluated using a Wilcoxon rank sum test of marker levels in responders versus non-responders using a one-sided alpha = 0.05. With 20 or more patients evaluable at baseline for PD-L1 expression, there will be at least 80% power to detect a difference of 1.25 standardized units in PD-L1 expression.

Analysis of exploratory biomarkers will be estimation-only, using summary statistics (such as mean, sd, median, IQR and range) to give the empirical distribution of marker levels detected at baseline and changes in marker levels during and after treatment in the subset of patients with paired specimen.

13.7 Reporting and Exclusions

13.7.1 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13.7.2 Evaluation of the Primary Efficacy Endpoint

All of the participants who met the eligibility criteria and who receive at least one dose of study drug will be included in the main intent-to-treat analysis of the response rate.

14. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome

data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B SAFETY ALGORITHMS

Renal Adverse Event Management Algorithm

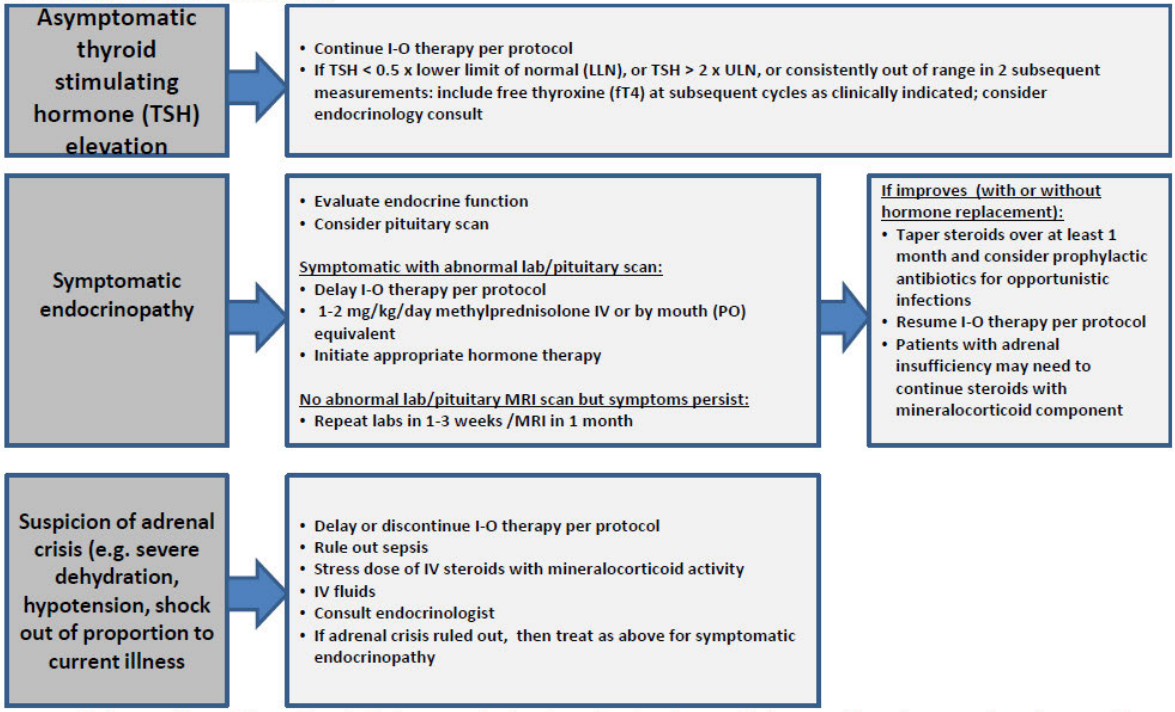
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

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

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

Endocrinopathy Management Algorithm

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



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

GI Adverse Event Management Algorithm

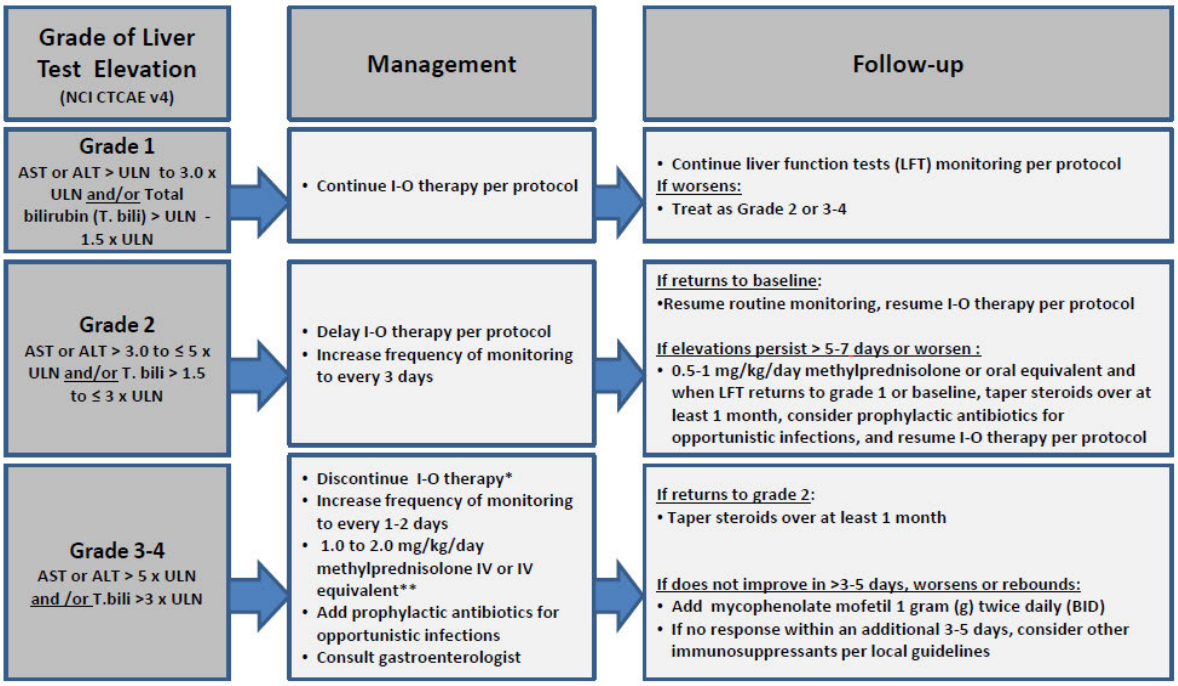
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade (G) 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hours (hrs); not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with activities of daily living (ADL) Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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

Hepatic Adverse Event Management Algorithm

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



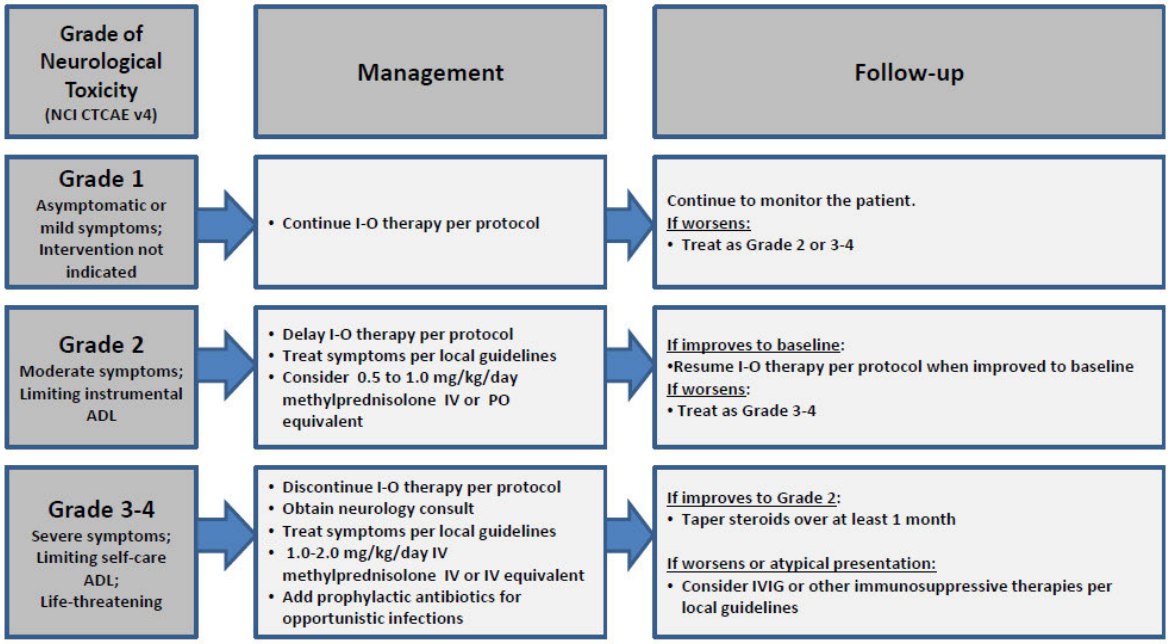
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

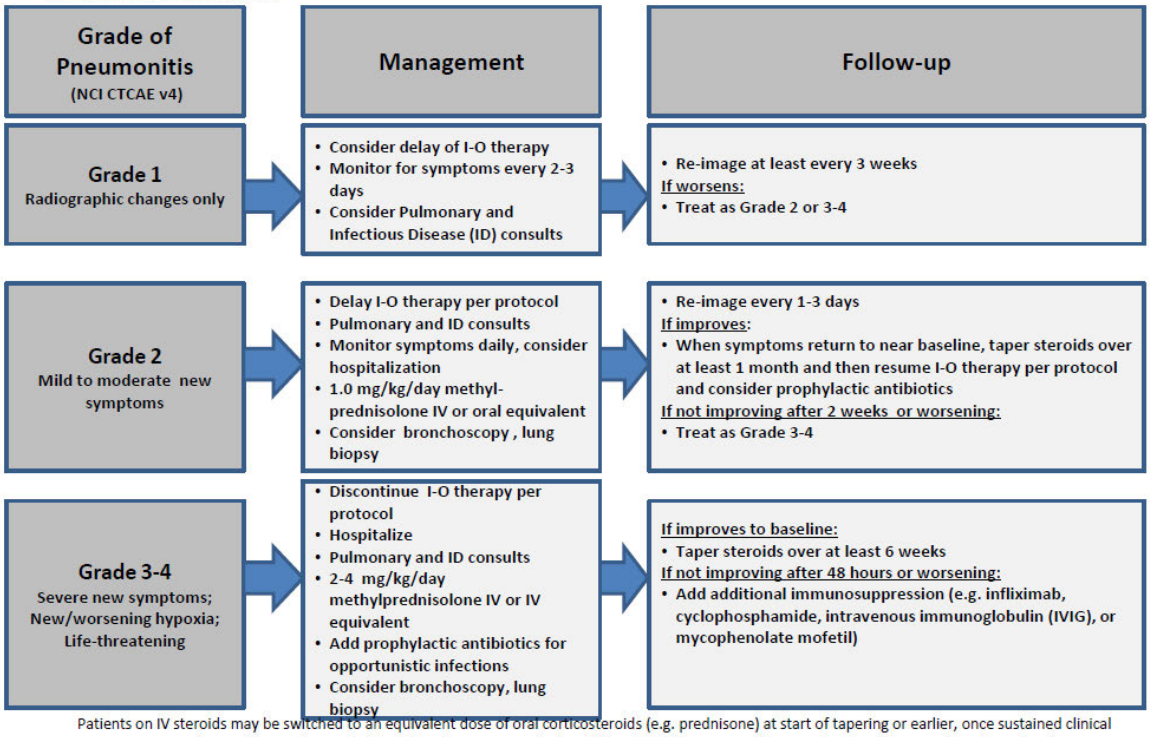
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Pulmonary Adverse Event Management Algorithm

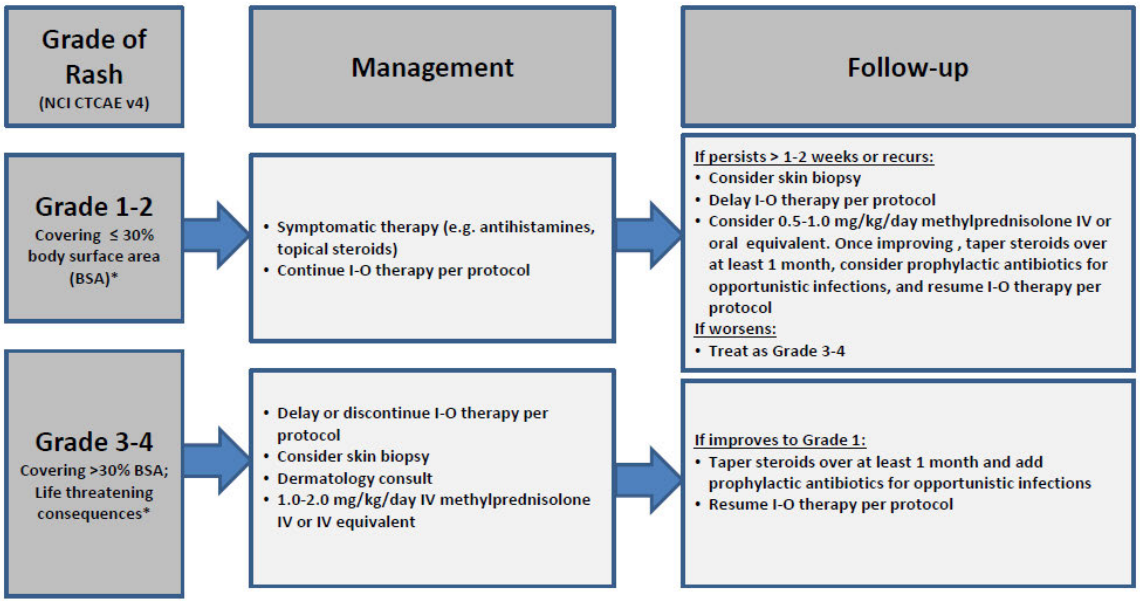
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

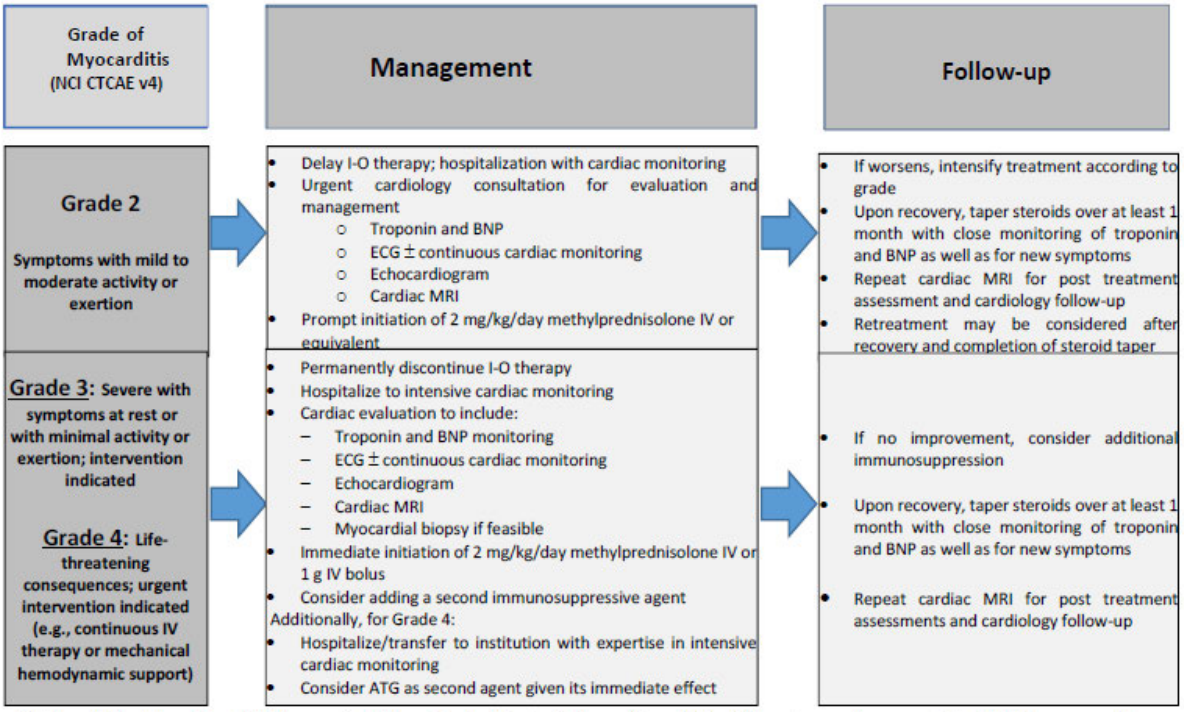
Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

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

APPENDIX C WHOLE BLOOD GENOTYPING SNP COLLECTION INSTRUCTIONS

SUPPLIES

6 mL K2 EDTA Vacutainer tube

1. Collect blood via direct venipuncture in a pre-labeled 6mL K2EDTA tube.

2. Invert gently 8 times.

3. **DO NOT CENTRIFUGE SAMPLE**.

4. Store samples in an upright position preferably in a-70ºC freezer (-20ºC is acceptable for short term storage).

   A step down freezing process is recommended, if possible. First, refrigerate the whole blood samples at 4°C for at least one day, but no longer than four days. Then the samples should be placed upright in a -70°C freezer.

   Holding samples longer than four days at 4°C may result in decreased recovery of high molecular weight DNA.

5. Complete the requisition and record the date and time of sample collection on the appropriate source document.

6. Batch ship samples on dry ice for processing per the shipment schedule.

APPENDIX D SERUM SOLUBLE BIOMARKERS COLLECTION INSTRUCTIONS

SUPPLIES

- 8.5mL SST Vacutainer
- 4 polypropylene tubes

1. Blood samples will be collected by direct venipuncture or through an indwelling catheter. If a catheter is used for blood collection, then approximately 1 mL of blood should be withdrawn initially and discarded. Only saline is permitted to keep catheters patent, unless discussed and agreed upon by the Sponsor. If samples are obtained through a heparin lock, sufficient blood (~1 mL) must be withdrawn to remove the heparin solution.

2. To ensure sufficient sample volume for the required test is obtained, fill tube until vacuum is exhausted and blood ceases to flow.

3. Immediately after collection, gently invert each blood sample 5 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).

4. Centrifuge samples at room temperature for 10 minutes (swing out) or 15 minutes (fixed) at 1100-1300 x g until clot and serum are well separated.

5. Transfer serum equally from the 8.5mL SST into four appropriately labeled screw-capped polypropylene tubes.

6. Store the serum samples immediately (within 2 hours of collection) at approximately -70°C to ensure stability of the samples until they are shipped on dry ice per the shipment schedule.

If -70 freezer is not available, store at -20 and ship monthly on dry ice.

If a sample was not collected, do not send empty tube.