CLINICAL STUDY PROTOCOL

An Open Label, Non-Randomized Multisite Phase II Trial Combining Bevacizumab, Atezolizumab and Rucaparib for the Treatment of Previously Treated Recurrent and Progressive Endometrial Carcinoma

Short Title
The EndoBARR Trial
(Endometrial Bevacizumab, Atezolizumab, Rucaparib)

William H. Bradley, MD

Version 5.0; November 22, 2022

Protocol Signature Page

Protocol No.: 5.0 **Version Date:** 11/22/2022/2020

- I agree to follow this protocol version as approved by the MCW Scientific Review Committee (SRC), Institutional Review Board (IRB) and Data Safety Monitoring Committee(DSMC).
- I will conduct the study in accordance with applicable IRB requirements, federal regulations, and state and local laws to maintain the protection of the rights and welfare of study participants.
- I certify that I, and the study staff, have received the requisite training to conduct this research protocol.
- I agree to maintain adequate and accurate records in accordance with IRB policies, Federal, state and local laws and regulations.

MCW Principal Investigator / Study Chair

WILLIAM H. BRADLEY, MD
Printed Name

Signature **Date**

Title: An Open Label, Non-Randomized Multisite Phase II Trial Combining Bevacizumab, Atezolizumab and Rucaparib for the Treatment of Previously Treated Recurrent and Progressive Endometrial Carcinoma

MCW Protocol No.: PRO 34127

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Bevacizumab – Supplied by Genentech

REVISION HISTORY

Revision history is presented in reverse order so that the information pertaining to the most current version of the protocol is presented first in this section.

Version 5.0, Version Date 11/22/2022

Version 4.0, Version Date 02/03/2020

Version 3.0, Version Date 12/02/2019

Version 2.1, Version Date 06/24/2019

Version 2, Version Date 03/05/2019

Version 1, Version Date 10/08/2018

Initial submission of the protocol.

PROTOCOL SUMMARY

Title	An Open Label, Non-Randomized Multisite Phase II Trial Combining Bevacizumab, Atezolizumab and Rucaparib for the Treatment of Previously Treated Recurrent and Progressive Endometrial Carcinoma
Protocol Number	EndoBARR
Principal Investigator	William H. Bradley, MD
Study Sites	Froedtert Hospital & the Medical College of Wisconsin
Clinical Trial Phase	Phase II
Study Disease	Recurrent Endometrial Carcinoma
Main Eligibility Criteria	Women with recurrent endometrial carcinoma, having progressed after or on primary or secondary anti-neoplastic therapy.
Study Rationale	To demonstrate the efficacy and safety of the combination of rucaparib, bevacizumab and atezolizumab in recurrent, progressive endometrial carcinoma.
Primary Objectives	To estimate the overall response of patients with progressive/persistent or recurrent endometrial cancer on study- directed therapy using RECIST 1.1.
Secondary Objectives	To estimate the progression free and overall survival and duration of response of patients with progressive/persistent or recurrent endometrial cancer, when treated with the combination of rucaparib, bevacizumab and atezolizumab. To determine the nature and degree of toxicity of treatment with this combination in this cohort of patients.
Exploratory Objectives	To explore best overall response and progression-free survival by patient and tumor factors: 1. Microsatellite instability — both genetic and epigenetic. 2. Homologous recombination deficiency. 3. TIL population and PD-L1 expression in the tumor. 4. Tumor mutational burden. 5. Loss of heterozygosity 6. Circulating tumor DNA 7. Stool Microbiome

	8. Cardiac toxicity by echo derived measurements of cardiac strain and assess the ability of this technique to predict development of toxicity for subjects under treatment
Study Design	Non-blinded, open-label, single-arm phase II protocol with safety lead- in.
Study Agent/ Intervention Description	Rucaparib, bevacizumab and atezolizumab in recurrent, progressive endometrial carcinoma.
Number of Subjects	30
Subject Participation Duration	Patients may continue on study directed treatment until disease progression, beyond progression with clinical benefit, removal for toxicity, or death from disease from the time of study entry. Subjects may continue on trial after progression if, in the opinion of the treating physician, the subject is obtaining clinical benefit from study directed treatment.
Duration of Follow-up	Until death.
Estimated Time to Complete Enrollment:	Two years.
Statistical Methodology:	The primary outcome is overall response rate (ORR). If the ORR is 27% (Castonguay et al., 2014) the one sided lower 95% CI bound is 14%. If the ORR is 23% the one sided lower 95% CI bound is 11%.
Safety Assessments	All information on AEs and SAEs will be listed by patient, and will be summarized. The SAE report will include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE v.5 as a guideline whenever possible. Frequencies will be presented for the categorical variables (e.g., race) and descriptive statistics will be presented for continuous variables (e.g., weight, age).
Efficacy Assessments	Cross-sectional imaging with either CT scan or MRI (consistent modality for each subject). Imaging to be obtained every six weeks for the first 6 months on study, and then every 9 weeks while on study directed treatment.
Unique Aspects of this Study	This is the first trial to test the combination of a PARPi (rucaparib), PD- L1 blockade (atezolizumab) and anti-VEGF therapy (bevacizumab) in this population.

SCHEMA

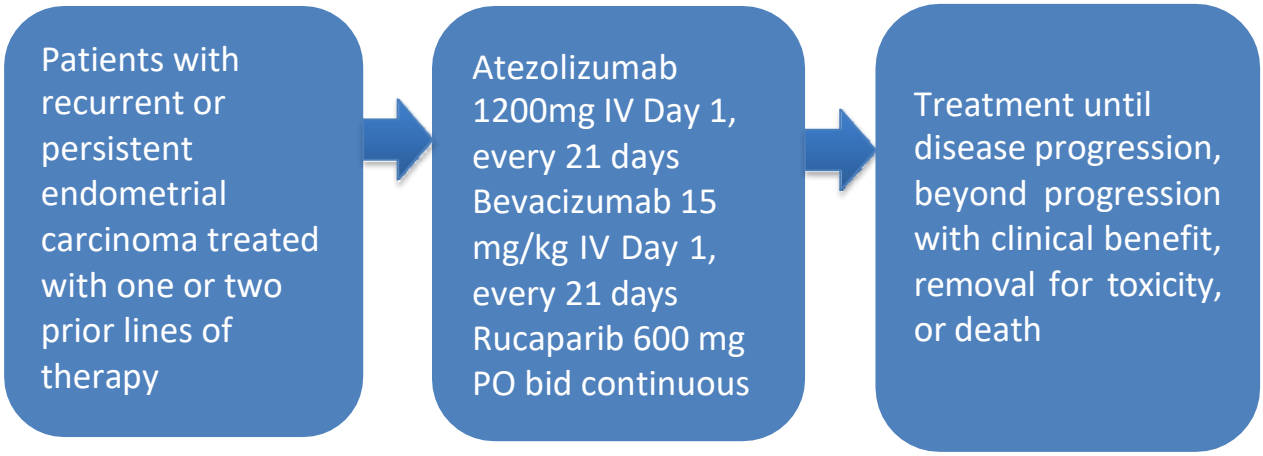
Patients with recurrent or persistent endometrial carcinoma treated with one or two prior lines of therapy
Atezolizumab 1200mg IV Day 1, every 21 days
Bevacizumab 15 mg/kg IV Day 1, every 21 days
Rucaparib 600 mg PO bid continuous
Treatment until disease progression, beyond progression with clinical benefit, removal for toxicity, or death

Table 1. Study Calendar

Period/ Procedure	Within 0-28 days prior to treatment	Cycle 1 & 2 (+/-3 days)	Cycle 1 & 2, Days 8 & 15 (+/-1 day)	Cycle 3 and beyond (+/-3 days)	End of treatment[16] Visit	Follow-up (30 and 90[14] days +/- 7 after end of treatment visit)
Informed consent	X					
Inclusion and Exclusion Criteria	X[1]					
AE assessment	X	X	X[7]	X	X	X
Demographics and Medical History	X	X[2]	X[2]	X[2]	X[2]	X[2]
Prior and Concomitant Medication Review	X	X	X[7]	X	X	X
Archival or Newly Obtained Tissue Collection	X				X[18]	
Survival Status					X	X[3]
Treatment/Drug Administration						
Atezolizumab		Every 21 Days		Every 21 Days		
Bevacizumab		Every 21 Days		Every 21 Days		
Rucaparib		Twice daily[4]		Twice daily[4]		
Clinical procedures						
Physical exam	X	X		X	X	
Vital signs, height[5] and weight	X	X	X[7]	X	X	
ECOG Performance status	X	X		X	X	
Laboratory procedures						
Study Day/Visit Day						
CBC w/ Differentials[6]	X	X[7]	X[7]	X	X	
Blood chemistry: CMP, Mg+, Phos[6]	X	X[7]	X[7]	X	X	
Non-fasting cholesterol[6]	X	X		X	X	
Thyroid Function Tests: TSH, T3 Total, Free T4[6]	X	X			X	
Blood for Correlative Studies[6/8]		X		X	X	
Urinalysis[6]	X	X[9]		X[9]		
Urine Protein/Creatinine (UPC) ratio[6]	X	X[9]		X[9]		
Prothrombin time/PTT/INR[6]	X	X[10]		X[10]		
Pregnancy test (urine or serum hCG)[11]	X	X		X		
Amylase, Lipase[6]	X	X		X		
Stool sample[12]		X		X		X

Table 1. Study Calendar

Period/ Procedure	Within 0-28 days prior to treatment	Cycle 1 & 2 (+/-3 days)	Cycle 1 & 2, Days 8 & 15 (+/-1 day)	Cycle 3 and beyond (+/-3 days)	End of Treatment Visit[16]	Follow-up (30 and 90[14] days +/- 7 after End of Treatment Visit)
Imaging procedures						
Imaging: CT Chest, abdomen, pelvis preferred	X	X[13]				X[15]
2-D Echocardiography[17]	X	X		X	X	
ECG/EKG[17]	X	X		X	X	

1. Signed by the treating physician and confirmed by sponsor site prior to study entry (please see appendix 3 for enrollment worksheet)
2. If any changes from screening.
3. Survival to be re-assessed every three months (i.e. 90 days) +/- 7 days after end of treatment visit.
4. Compliance to be assessed by pill count.
5. Height should be recorded at screening and then once every 12 months from Cycle 1 Day 1 (i.e. 360 days +/- 7 days).
6. If CBC with differential and Blood Chemistry labs are collected within 14 days before Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1. If Cholesterol, Thyroid Function Tests, PT/INR/PTT, Urine protein creatine (UPC) Ratio, Amylase, Lipase, and Urinalysis are collected within 28 days before Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.
7. CBC, CMP will be drawn weekly along with vital signs, AE and concomitant medication assessment (+/- 1 day) for the first two cycles.
8. Correlative blood draws collected only if consented and while on treatment per study directed therapy. Cycle 1 Day 1 correlative blood can be drawn any time within 0 to 28 days prior to treatment (blood should be collected before first cycle dose). Correlative draw will be collected pre-dose for the first 8 cycles, then stopped. One draw will be collected at end of treatment visit.
9. Urine protein creatine (UPC) Ratio to be collected within 28 days of Cycle 1 Day 1 and then on the first day of every odd cycle while on study (i.e. cycles 3, 5, 7, 9 and so on while subject is on study directed therapy). Urine protein via dipstick or urinalysis (either method is acceptable) to be collected within 28 days of Cycle 1 Day 1 and then on the first day of every even cycle while on study (i.e. cycles 2, 4, 6, 8 and so on while subject is on study directed therapy).
10. PTT/PT/INR will be drawn with each cycle if the subject is on anticoagulation therapy and PTT/PT/INR is the method indicated to monitor therapy.
11. If subject has child bearing capacity.
12. First stool sample to be collected by patient within 7 days before Cycle 1 Day 1. Second stool sample to be collected by patient within 7 days before Cycle 4 Day 1, if on study directed therapy. Third stool sample to be collected by patient within 7 days before 30-day follow up visit, after treatment has ended.
13. CT Chest/Abdomen/ Pelvis will be done every 6 weeks +/- 7 days from Cycle 1 Day 1 for the first 24 weeks, then every 9 weeks +/- 7 days while on treatment. If subject has chest CT negative for disease on screening, Chest X-ray may be substituted in subsequent imaging per investigator's discretion.
14. 90 day follow up may be done via phone to assess Adverse Events. Resolution or continuation of AE's will be documented.
15. Subjects removed from active treatment for reasons other than progression should be imaged every 3 months

(i.e. 90 days) +/- 7 days or as indicated until consent is withdrawn.

16. End of treatment visit should occur up to but no more than +7 days after last exposure to rucaparib or, if rucaparib is discontinued, no more than +21 days after last exposure to bevacizumab and/or atezolizumab.
17. ECG/ Echocardiogram should be completed every 3 months (i.e. 90 days) +/- 7 days from Cycle 1 Day 1 while on treatment. End of treatment ECG/ Echocardiogram should be completed within +/- 7 days of the end of treatment visit.
18. Newly-obtained tissue at end of treatment to be provided if consented and available. Tissue can be collected at any time after discontinuation of study treatment prior to the start of any new treatment regimens.

Table of Contents

List of Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BUN	blood urea nitrogen
CBC	complete blood cell (count)
CR	complete response
CRC	clinical research coordinator
CRF	case report form
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DC	dendritic cell
DFS	disease-free survival
DLT	dose-limiting toxicity
DSMB	Data and Safety Monitoring Board
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
FCBP	female of childbearing potential
FDA	Food and Drug Administration
FFPE	Formalin Fixed, Paraffin Embedded

GCP	Good Clinical Practice
HBeAg	hepatitis B “e” antigen
HBV	hepatitis B virus
HCT	hematocrit
HCV	hepatitis C virus
HGB	hemoglobin
HIV	human immunodeficiency virus
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IND	investigational new drug application
IP	investigational product
IRB	Institutional Review Board
IRR	Infusion Related Reactions
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IV	intravenous
LDH	lactate dehydrogenase
LFT	liver function test
LOH	loss of heterozygosity
MCWCC	Medical College of Wisconsin Cancer Center
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
ORR	overall response rate

PARP	poly (ADP-ribose) polymerase
PD	disease progression
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (by mouth, orally)
PR	partial response
QOL	Quality of Life
RBC	red blood cell (count)
SAE	serious adverse event
SD	stable disease
SD	standard deviation
SRC	Scientific Review Committee
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
ULN	upper limit of normal
UP	unanticipated problem
UPIRSO	unanticipated problems involving risks to subjects or others
VEGF	vascular endothelial growth factor
WBC	white blood cell (count)

1 BACKGROUND

1.1 Endometrial Carcinoma

Endometrial cancer is diagnosed in more than 50,000 women annually in the United States and is the cause of more than 10,000 deaths, making it the sixth most common cause of female cancer death (Siegel et al., 2017). Although the majority of cases are cured with surgical interventions, chemotherapy regimens of carboplatin and paclitaxel are often used for advanced or metastatic disease. Endometrial cancer that recurs or progresses after initial chemotherapy has no standard of care treatment agent(s), with median overall survival under two years (Fleming et al., 2004).
Multiple second line agents are utilized, but response rates are limited, with single-agent chemotherapy response rarely greater than 10% (Fleming, 2015). Hormonal therapies have been used with limited response duration (typically <12 months). Furthermore, this approach relies on an estrogen or progesterone receptor positive tumor, which may not be the case in non- endometrioid sub-types (Carlson et al., 2014). Newer approaches, including anti-vascular endothelial growth factor (VEGF/anti-angiogenic) and immunotherapy, are being utilized.
Approximately 25–35% of the cases of endometrial cancer will have microsatellite instability (MSI) (Goodfellow et al., 2015; McMeekin et al., 2016), supporting the use of immunotherapy.

1.1.1 Rationale for Antiangiogenic Therapy

Antiangiogenic agents have shown activity in treating endometrial cancer progression after treatment with chemotherapy. When used as a single agent, bevacizumab demonstrated a response rate of 13.5% with a 40% progression-free survival (PFS) at six months (Aghajanian et al., 2011). Other antiangiogenic agents, including aflibercept, brivanib and sunitinib, have all shown similar progression-free survival (PFS) at six months (Castonguay et al., 2014; Coleman et al., 2012; Powell et al., 2014). When combined with carboplatin and paclitaxel, the addition of bevacizumab improved overall survival in a chemotherapy naïve population and increased overall survival when compared with combination therapy with temsirolimus (Aghajanian et al., 2015).

1.1.2 Rationale for Anti-PD-L1 Therapy and PARPi

The use of immunotherapy in solid tumors offers a number of salient points in this disease site. In the Keynote Trial, treatment of endometrial cancer using pembrolizumab showed a response rate of 13% in a cohort of 24 patients. The median PFS for stable disease was 25 weeks. A hypermutated patient with a POLE mutation (without MSI) was noted to have strong response (Ott et al., 2017). Patients with colon cancer that demonstrates microsatellite instability have shown increased rates of response to PD-L1 blockade, with response rates of up to 40% and PFS of 78% (median not reached) (Le et al., 2015).

The Cancer Genome Atlas (TCGA) Research Network classified endometrial cancers into four subgroups based on genomic characteristics. The tumor groups are classified as 1) tumors with mutations in the DNA polymerase epsilon catalytic subunit (POLE), 2) endometrioid carcinomas with microsatellite instability (MSI), 3) endometrioid carcinomas with low copy number and 4) serous-like tumors with TP53 mutations. The POLE and MSI groups carry a higher mutationa burden and have an upregulation of immune checkpoint proteins, including PD-1 and PD-L1, and thus, contribute to the adaptive immune resistance of such tumors (Cancer Genome Atlas Research et al., 2013).

PTEN mutations are common in endometrioid endometrial cancers, leading to an increase in DNA damage and genomic instability. Heeke et al reported high rates of homologous recombination (HR) deficiency in endometrial cancers with 38% (1956/5137) showing HR mutations (ASCO, 2017. Abstract #1502). These findings suggest susceptibility of these tumors to both immunotherapy and PARPi, such as Rucaparib.

Jiao et al measured PD-L1 expression in breast cancer cell lines before and after PARPi therapy. Inactivation of GSK2β by PARPi lead to enhanced expression of PD-L1. Subsequent blockade by PD-L1 therapy led to T-cell mediated cell death. There was a significant increase in response *in vivo* to combination therapy compared to single-agent treatment (Jiao et al., 2017). Higuchi et al demonstrated CTLA-4 blockade could synergize with PARPi in a BRCA1-deficient mouse model, supporting an enhanced immune effect in combination therapy (Higuchi et al., 2015).

1.1.3 Rationale for Combination of Anti-PD-L1 and Antiangiogenic Therapy

Increasing evidence has described a link between (pro)angiogenesis and immunosuppression (Ott et al., 2015). Preclinical work by Shrimalia et al revealed that antiangiogenic therapy, in combination with adoptive T-cell transfer, yielded enhanced anti-tumor activity of T-cells compared with little tumor response to treatment when antiangiogenic was utilized alone. Initial work in understanding the angiogenic impact on dendritic cells (DCs) revealed that the normal DC population shifts to more immature precursors in the presence of antiangiogenic treatment (Gabrilovich et al., 1996). The significance of DCs on tumor immunity and prognosis has also been described. Almand et al noted that in 44 cancer patients with head and neck cancer, NSC lung cancer and breast cancer, the majority of DCs identified were immature and that the blood samples demonstrated decreased T-cell stimulation. Saito et al noted that DC infiltration and density correlated with an improved prognosis and that DC density is inversely correlated with angiogenic expression in gastric carcinoma. The combination of angiogenic inhibition with checkpoint inhibition offers a synergistic technique to enhance immune therapy. Early clinical studies have demonstrated the safety of this combination as well. Dudek et al presented their preliminary data with a combination of pembrolizumab (200 mg IV every three weeks) and bevacizumab (both 10 mg and 15 mg IV every three weeks). They reported that the combination therapy produced a greater reduction in circulating tumor cells and that in this cohort of 20 patients combination therapy was well tolerated with no dose-limiting toxicities, serious adverse events or Grade 3 or 4 drug-related toxicities.

1.1.4 Rationale for Combination of PARPi and Antiangiogenic Therapy

The combination of angiogenic inhibition and PARP inhibition is being used in serous ovarian carcinoma, with combination activity showing improvements over single-agent treatment (Liu et al., 2014). The combination of cediranib and olaparib appears to reduce invasion and microvascular formation to a greater degree than either alone. This potentially offers both a direct cytotoxic effect, as well as potentially enhances the effect of immunotherapy. The molecular make up of serous ovarian cancer mimics serous endometrial cancer in a number of important fashions, including frequent P53 mutations. The likelihood of cross-response in the endometrial disease site is supported by this commonality.

1.1.5 Rationale for Combination of PARPi, Anti-PD-L1 and Antiangiogenic Therapy.

The combination of the three proposed agents offers the opportunity to explore synergistic relationships between antiangiogenic and immunotherapy and antiangiogenic and PARPi. Increasing genetic instability by PARPi and double-strand breaks may lead to a proinflammatory state that would enhance the activity of immunotherapy, leading to synergistic response in a category of solid tumors that lack active therapy. It is expected that increased double-strand breaks may lead to increased expression of immunogenic antigens, increasing the effect of anti- PD-L1 therapy. Phase I data combining the PD-L1 inhibitor durvalumab with either olaparib or cediranib showed good tolerability and evidence of response (Lee et al., 2017). Although there is not PK data for the combination of these agents, there is no clear rationale to suspect significant interaction, or cross-toxicities.

1.2 Cardiac Assessment

Newer findings in cancer immunotherapy have included cardiotoxicity, with cardiomyopathy, symptomatic heart failure, myocarditis and fibrosis being noted (Heinzerling et al., 2016; Varricchi et al., 2017). Bevacizumab is also associated with arterial thromboembolic events in roughly 2% of patients (Totzeck et al., 2017), hypertension (5-18% incidence of Grade 3 or 4 hypertension) (FDA package insert, accessed February 24, 2018), and CHF (1.7-3%)(Choueiri et al., 2011). Given that cardiotoxicity may be an adverse event of this combination, routine monitoring with echocardiography will be undertaken. Technology, such as strain monitoring, will be used to predict and identify those at higher risk for development of these complications (Herrmann et al., 2014).

1.3 Correlative/Exploratory studies

1. Microsatellite instability (MSI) — both genetic and epigenetic
2. Homologous recombination deficiency gene alterations
3. PD-L1 expression in the tumor
4. Tumor mutational burden
5. Circulating tumor DNA
6. Stool microbiome

1.3.1 MSI

The identification of microsatellite instability in endometrial carcinoma has become a routine assessment in standard of care. The use of either immunohistochemistry or qtPCR or both on either a biopsy specimen or final specimen has been shown to demonstrate MSI in up to 30% of cases (Goodfellow et al., 2015). These changes in tumor mismatch repair have been shown to affect tumor type as well as response to therapy (Cosgrove et al., 2017; Makker et al., 2017).

1.3.2 Homologous recombination deficiency

The rate of homologous recombination deficiency (HRD) in endometrial cancers has recently been demonstrated to be high among solid tumors (Arielle Lutterman Heeke, 2017). The effect of PARPi is modulated by synthetic lethality and alterations in HRD genes may associate with increased response.

1.3.3 PD-L1 Expression

Tumor samples (from initial diagnosis) will have PD-L1 assessed by IHC. Although the association between response to PD-1/PD-L1 blockade is not directly associated with expression, the correlation between PD-L1 and the monocyte population in the tumor is exploratory in this solid tumor.

1.3.4 Tumor Mutational Burden

Tumor response to immune checkpoint blockade has been associated with higher levels of mutational burden (Rizvi et al., 2015). This level will be assessed in primary patient specimens using formalin fixed, paraffin-embedded samples.

1.3.5 Circulating Tumor DNA

One of the challenges of immunotherapy-based solid tumor treatments is the timing of response to therapy. Solid tumors may enlarge and then later respond to treatment. The use of circulating DNA from

the tumor may provide a biomarker offering an earlier assessment of the likelihood of response (Goldberg et al., 2018).

1.3.6 Stool Microbiome

The microbiome is increasingly being noted to affect the response of malignancies to immunotherapy (Gopalakrishnan et al., 2018; Matson et al., 2018). Samples collected prior to therapy, after the third cycle, and after conclusion will allow longitudinal assessments of variations of the microbiome from patient to patient, and changes within a single patient.

2 HYPOTHESIS AND OBJECTIVES

2.1 Primary Objectives

2.1.1 To estimate the overall response rate (ORR) of patients with progressive/persistent or recurrent endometrial cancer on study-directed therapy, using the combination of rucaparib, bevacizumab and atezolizumab.

2.2 Secondary Objectives

2.2.1 To estimate the progression free survival (PFS) and overall survival (OS) of patients with progressive/persistent or recurrent endometrial cancer when treated with the combination of rucaparib, bevacizumab and atezolizumab.

2.2.2 To determine the nature and degree of toxicity of treatment with this combination in this cohort of patients.

2.3 Exploratory Objectives

2.3.1 To explore best overall response and progression-free survival stratified by patient and tumor factors:

1. Microsatellite instability (MSI) — both genetic and epigenetic
2. Homologous recombination deficiency gene alterations
3. PD-L1 expression in the tumor
4. Tumor mutational burden
5. Loss of Heterozygosity
6. Circulating tumor DNA
7. Stool Microbiome
8. To evaluate cardiac toxicity by echo derived measurements of cardiac strain and assess the ability of this technique to predict development of toxicity for subjects under treatment

3 STUDY DESIGN

3.1 General Description

This is a phase II, open-label trial estimating primarily the ORR, secondarily PFS and OS of patients with persistent/progressive or recurrent endometrial cancer on bevacizumab, atezolizumab, and rucaparib. A safety lead-in of six-plus patients for toxicity will confirm tolerability. Patients will have recurrent or persistent/progressive endometrial carcinoma and have undergone one to two lines of prior therapy. Patients who have undergone two prior lines must have an ECOG performance status of 0 or 1. Patients will be treated with an every three- week cycle of atezolizumab and bevacizumab. Rucaparib will be provided daily. Cross-sectional imaging will be undertaken every six weeks to assess disease status during the first six months on therapy, then imaging will be taken every nine weeks unless clinically indicated.

As stated above, there will be a planned six-subject safety lead in. After the first six subjects are enrolled and have received one cycle of study directed treatment, the DSMB/sponsors/PI will assess for associated DLTs attributed to the study medications. If there are three DLTs attributable to the study medication (in a cohort of either six or nine) the study enrollment will be stopped and dosing and schedule re-considered. The trial may be continued with lower doses of the agent(s) considered to be the attributed source or sources of the DLT. The decision to continue the trial will be addressed at this point. If the trial is continued after the safety lead-in, the subjects enrolled during the lead-in will be considered assessable for primary, secondary and translational outcomes, regardless of whether one had had a DLT.

3.1.1 Number of Subjects

Thirty subjects will be enrolled. The planned enrollment is two years.

3.2 Randomization

This is a nonrandomized, open label, single-arm trial.

3.3 Primary Completion

The study will reach primary completion 30 months from the time the study opens to accrual. This is based on an expected enrollment time of two years to accrue 30 patients, and follow-up of approximately six months to complete treatment of subjects.

Patients who progress on study-directed therapy may remain on study if, in the opinion of the treating physician, the subject is receiving clinical benefit.

3.4 Study Completion

The study will follow patients until death or close out of study. This is anticipated to be less than five years from enrollment at recurrent disease.

4 PATIENT SELECTION

4.1 Inclusion Criteria

1. Patients must have recurrent or persistent/progressive endometrial carcinoma, which is refractory to curative therapy or established treatments. Histologic confirmation of the original primary tumor is required. Stained slides of either the primary or recurrent tumor are required. If primary FFPE samples are not available, a biopsy demonstrating recurrent disease must be obtained. Pathologic Slides/Blocks will be reviewed at the primary site for confirmation.

2. Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.), mucinous adenocarcinoma, squamous cell carcinoma, transitional cell carcinoma and uterine carcinosarcoma (MMT).

3. Patients must have had one prior chemotherapeutic regimen for management of endometrial carcinoma. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer **WILL** be counted as a chemotherapy regimen. Patients may have had, but are not required to have received, a second chemotherapeutic regimen for recurrent disease.

4. All patients must have either measurable disease or non-measurable but evaluable disease, as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). For disease to be measurable, each target lesion should be ≥ 10 mm when measured by CT or MRI and lymph nodes must be > 15 mm in short axis when measured by CT or MRI.

5. Patients may be enrolled if they do not have a target lesion (i.e. ≥ 10 mm lesion or ≥15 mm lymph node), if they have evaluable disease. This is defined by RECIST 1.1 as a suspicious lesion <10 mm or a lymph node ≥10 mm but <15 mm.

6. Patients must have an EGOG Performance Status of 0, 1.

7. Recovery from effects of recent surgery, radiotherapy, or chemotherapy.

8. Patients should be free of active infection requiring antibiotics (with the exception of uncomplicated UTI).

9. Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration.

10. Any other prior therapy directed at the malignant tumor, including chemotherapy and immunologic agents, must be discontinued at least three weeks prior to first cycle of treatment.

11. Any prior radiation therapy must be completed at least four weeks prior to first cycle of treatment.

12. Prior hormonal therapy is allowed. There is no limit on the number of prior hormonal therapies allowed. Hormonal therapy will not be counted as a line of therapy for purposes of this trial.

13. Patients must have a urine protein of ≤ 2+ on dipstick and urine protein creatinine ratio < 3.5. If urine protein dipstick is >2+, 24-hour urine protein must be obtained and should be < 1g for patient to be eligible.

14. Patients must have signed an approved informed consent and authorization permitting release of personal health information for study purposes.

15. Patients must meet pre-entry requirements, as specified in section 5.

16. Patients of childbearing potential must agree to use an accepted and effective nonhormonal method of contraception i.e., double-barrier method (e.g., condom plus diaphragm) from the time of signing the informed consent through six months after last dose of study drug.

17. Patients 18 years of age or greater.

18. Be willing to provide tissue from the primary surgical resection or recurrent disease (paraffin block or slides).

19. Must have laboratory values in the below ranges:

System	Laboratory Value
Endocrine	
Thyroid function testing (TSH)	0.350 – 5.500 ulU/mL (Or within institutional laboratory range).
Free T4/Total T3	If TSH is outside of laboratory range and subject is clinically euthyroid, enrollment may occur if Free T4/Total T3 are in normal range by local lab values
Hematological	
System	**Laboratory Value**
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** **≤ 5 X ULN for subjects with liver metastases**
Albumin	>2.5 mg/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

4.2 Exclusion Criteria

1. Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of the other malignancy being present within the last two years. Patients with Ductal Carcinoma in situ (DCIS) of the breast in the prior two years may be enrolled on study if the treatment required no chemotherapy or radiation. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

2. Patients must not have had exposure to Bevacizumab, PARPi, or immunotherapy. Patients may have had exposure to anti-angiogenic therapy provided it was not Bevacizumab.

3. Patients who have received prior radiotherapy to any portion of the abdominal cavity or pelvis OTHER THAN for the treatment of endometrial cancer within the last three years are excluded. Prior radiation for localized cancer of the breast, head and neck or skin is permitted, provided that it was completed more than three years prior to registration, and the patient remains free of recurrent or metastatic disease.

4. Patients who have received prior chemotherapy for any abdominal or pelvic tumor OTHER THAN for the treatment of endometrial cancer within the last three years are excluded. Patients may have received prior adjuvant chemotherapy for localized breast cancer, provided that it was completed more than two years prior to registration, and that the patient remains free of recurrent or metastatic disease.

5. Inability to tolerate an oral medication or keep pills down.

6. Patients who are pregnant or nursing.

7. Patients with a complete bowel obstruction; recent (within six months) history of fistula, intraabdominal abscess or bowel perforation; subjects requiring total parenteral nutrition or parenteral hydration.

8. Has a current diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within seven days prior to the first dose of trial treatment.

9. Patients with history or evidence upon physical examination of CNS disease, including brain tumor, seizures not controlled with standard medical therapy or any brain metastases.

10. Patients with clinically significant cardiovascular disease. This includes:

    - Myocardial infarction or unstable angina within 12 months of the first date of study treatment.

    - New York Heart Association (NYHA) Class II or greater congestive heart failure (Appendix I).

    - History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or cardiac arrhythmias requiring antiarrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication).

    - Grade 2 or greater peripheral vascular disease.

    - Cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage within six months of the first date of study treatment.

    - History of arterial ischemia or thrombus.

11. Patients with uncontrolled hypertension defined as systolic > 150 mm Hg or diastolic > 90 mm Hg. The use of antihypertensive medications to control hypertension is permitted.

12. Patients who have undergone major surgical procedure, open biopsy or significant traumatic injury within 28 days prior to the first date of study treatment or who have a major surgical procedure anticipated during the course of the study. Laparoscopic biopsy is acceptable and

will not require a delay in study treatment.

13. Patients with serious nonhealing wound, ulcer (including gastrointestinal) or bone fracture.

14. Patients with any condition, which in the investigator's opinion, makes the patient unsuitable for study participation.

15. Patients not available for follow-up assessments.

16. Patients with known sensitivity to any of the products to be administered during dosing.

5 STUDY ENTRY AND WITHDRAWAL: STUDY PROCEDURES

5.1 Study Entry Procedures

The study-specific assessments are detailed in this section and outlined in the study calendar. Screening assessments must be performed within 28 days prior to enrollment. Any results falling outside of the reference ranges may be repeated at the investigator's discretion. Contact the medical monitor regarding screening/rescreening concerns. Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation but should be properly documented.

A written, signed informed consent form (ICF) and a Health Insurance Portability and Accountability Act (HIPAA) authorization must be obtained before any study-specific assessments are initiated. A signed ICF copy will be given to the subject and a copy will be filed in the medical record. The original will be kept on file with the study records.

All patients who are consented will be registered in OnCore®, the MCW Cancer Center Clinical Trial Management System. The system is password protected and meets HIPAA requirements.

5.1.1 Registration Process

Once a subject is identified by the investigator, the option of participation in the trial should be presented to the subject. Patients will be consented by either the treating oncologist or his/her authorized agent. Patients may enroll on trial without consenting for acquisition of de novo tissue or blood/serum samples. The only exception would be if there is no slides or blocks left from the primary diagnosis. These subjects will need a new biopsy to prove disease.

Registration of both aspects — study-directed treatment and blood/tissue donation for exploratory analyses — will be noted at registration.

This is a planned multi-site trial. Patients will be screened locally at the institution where they are being treated. Registration will be local. Each site will be assigned a site number, and

subjects will be numbered chronologically per the local site enrollment. All screening data will be entered into OnCore and screening source documentation will be de-identified and uploaded in OnCore for verification by the parent site, Medical College of Wisconsin. The PI will determine eligibility of subjects and will sign off on the subject enrollment form which should be uploaded into OnCore along with screening data for confirmation of eligibility by the sponsor-PI. A delegate will be assigned if the sponsor-PI is unavailable.

5.1.2 Pretreatment Period

The screening procedures and assessments must be completed within 28 days prior to treatment

- Blood chemistry assessment, including: comprehensive metabolic panel, magnesium, phosphorus, non-fasting cholesterol, thyroid function tests (TSH, free T4, total T3)
- Complete Blood Count (CBC) with differential.
- Urine protein/creatine ratio
- Complete medical history – Medical history will include all active conditions and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator.
- Concomitant medications
- Evaluation of adverse events
- Performance status (ECOG, KPS, etc.)
- Physical examination
- Prothrombin time (PT)/ international normalized ratio (INR), partial thromboplastin time (PTT)
- Pregnancy test if subject has child bearing capacity (Urine or Serum hCG)
- Radiographic tumor assessment (CT of Chest/Abdomen/Pelvis), or MRI of Abdomen/Pelvis with Chest imaging of physician choice. Chest may be omitted in subsequent imaging if not involved in recurrent disease. CT is preferred imaging.
- Vital signs
- Urinalysis
- Blood for correlative studies if consented (only once prior to treatment, either in screening or on Cycle 1, Day 1 pre-treatment)
- Stool Sample (to be collected by patient within 7 days before Cycle 1, Day 1)
- ECG
- 2-D Echocardiography

Assessment within four weeks prior to entry and every three months while on study, with one echo after completion of study-directed treatment:

Conventional 2D Echocardiography

All enrolled patients will undergo baseline standard 2D echocardiography (GE E9 and E95,

as well as Philips EPIQ) and Doppler assessment. Parasternal long and short axis, apical 4- 3- and 2 chamber and subcostal imaging will be performed. Doppler of mitral inflow and tissue Doppler imaging of the mitral annulus will also be assessed in order to perform a diastolic function assessment (Nagueh et al., 2016). The left ventricular ejection fraction will be estimated by Simpson's biplane method, using the apical 4- and 2-chamber views. Left atrial volumes will be measured estimated, using the atrial-focused 4- and 2-chamber views. Parasternal long axis views will be employed to measure indexed LV mass using the ASE method (Lang et al., 2015). Pulmonary artery systolic pressure will be estimated using the tricuspid regurgitation velocity when the signal permits (Rudski et al., 2010). Thus, LV systolic and diastolic function, RV systolic function, atrial size, LV mass and pulmonary artery pressures will be reported for each patient. The presence of a pericardial effusion will also be reported.

Global Longitudinal Strain Analysis

Where available, GE software will be used to perform strain analysis (Thavendiranathan et al., 2014). Endocardial borders at end systole and at end diastole will be traced within the apical 4- 3- and 2-chamber views, using the aortic valve pulse wave doppler recording to guide timing of valve closure. Speckles will be tracked frame by frame throughout the cardiac cycle. The average strain per segment will be determined and reported on a polar map, using a 17-segment model.

The global longitudinal strain (GLS) will be reported as the average strain of all 17 segments. A GLS of < -18% will be reported to be abnormal.

Serial Echo Monitoring

Patients will undergo surveillance echocardiography per protocol. After the initial full study, a limited study will be performed assessing left ventricular size and function, as well as right ventricular size and function. These parameters, in addition to the global longitudinal strain, will be reported during the serial echo monitoring period.

5.1.3 Treatment Period

During the treatment period, the following procedures will be performed.

5.1.3.1 Cycles 1 and 2 Day 1

- Assessment of AEs
- Review of demographics and medical history – if any changes since screening
- Review of concomitant medications
- Physical Examination
- Vital signs and weight
- ECOG performance status
- Complete Blood Count (CBC) with differential

- Blood Chemistry -Comprehensive Metabolic Panel (CMP); Magnesium, Phosphorous, nonfasting cholesterol, thyroid function tests (TSH, free T4, total T3)
- Blood samples for correlative studies if consented (once prior to treatment on Cycle 1, Day 1 and then again prior to treatment on Cycle 2, Day 1)
- Urine protein via dipstick or urinalysis on Day 1 of every even cycle (i.e. cycles 2, 4, 6, 8 and so on while subject is on study directed therapy)
- Prothrombin time/PTT/INR (if method used to monitor subject's anticoagulation therapy)
- Pregnancy test if subject has child bearing capacity (Urine or Serum hCG)
- Administration of study drug(s)

5.1.3.2 Cycles 1 and 2 Days 8 and 15

- Complete blood count with differentials
- Comprehensive Metabolic Panel (CMP)
- Vital signs
- Assessment of AEs
- Review of concomitant medications

5.1.3.3 Cycles 3 and beyond Day 1

- Assessment of AEs
- Review of demographics and medical history if any changes from screening.
- Review of concomitant medications
- Physical Examination
- Vital signs and weight
- ECOG performance status
- Complete Blood Count (CBC) with differential
- Blood Chemistry- Comprehensive Metabolic Panel (CMP); Magnesium, Phosphorous, non-fasting cholesterol
- Blood samples for correlative studies if consented (prior to treatment on Day 1 of each cycle. The last pretreatment sample will be collected on Cycle 8, Day 1)
- Stool sample for correlative studies if consented (to be collected by patient within 7 days before Cycle 4 Day 1)
- Urine protein/Creatinine ratio on Day 1 of every other cycle (i.e. cycles 3, 5, 7, 9 and so on while subject is on study directed therapy)
- Urine protein via dipstick or urinalysis on Day 1 of every even cycle (i.e. cycles 2, 4, 6, 8 and so on while subject is on study directed therapy)
- Prothrombin time/PTT/INR (if it is the method used to monitor subject's anticoagulation therapy)

- Pregnancy test if subject has child bearing capacity (Urine or Serum hCG)
- Administration of study drug(s)
- ECG to be collected every 3 months (i.e. 90 days) +/- 7 days while on study directed treatment
- 2-D Echocardiography to be collected every 3 months (i.e. 90 days) +/- 7 days while on study directed treatment

5.2 End of Treatment

5.2.1 End-of-Treatment Procedures

End of treatment visit should occur up to but no more than +7 days after last exposure to rucaparib or, if rucaparib is discontinued, no more than +21 days after last exposure to bevacizumab and/or atezolizumab.

- Physical examination, vitals, medical history, ECOG performance status, medication review
- Complete Blood Count (CBC) with differential, Comprehensive Metabolic Panel (CMP), Magnesium, Phosphorus, thyroid function tests (TSH, free T4, total T3)
- Evaluation of adverse events
- 2-D Echocardiography, ECG (to be collected within +/- 7 days of end of treatment visit)
- Blood samples for correlative studies if consented (to be collected at end of treatment visit)
- Stool sample for correlative studies if consented (to be collected by patient within 7 days before 30-Day Follow-Up visit)

5.3 Post-treatment

5.3.1 Follow-Up Visits

There will be a 30-day and 90-day follow-up for safety assessment. The 30-day follow-up should occur 30 days +/- 7 days after the end of treatment visit, and the 90-day follow-up should occur 90 days +/- 7 days after the end of treatment visit. The 90-day follow up may be done via phone to assess Adverse Events. Resolution or continuation of AE's will be documented.

- Assessment of AEs (AEs for 90-day follow-up collected by phone)
- Review of demographics and medical history if any changes from screening.
- Review of concomitant medications

5.3.2 Survival Follow-up

Survival Follow-up should occur every three months (i.e. 90 days) +/- 7 days via medical records or best efforts to contact the patient (e.g. phone or letter) until death or lost to follow up.

5.3.2.1 Adverse Event Follow-up

If a subject is taken off-study for adverse events, adverse events should be followed to resolution through best efforts to contact the patient.

5.4 Study Withdrawal Procedures

5.4.1 Duration of Therapy

Patients are allowed to withdraw at any time should they choose. In the absence of withdrawal, patient will continue on study-directed treatment continue for or until:

- Disease progression
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the investigator's judgment.
- Inter-current illness that prevents further treatment administration
- Patient decides to withdraw from the study
- Significant patient noncompliance with protocol
- Unacceptable adverse event(s)

Patients with progression who, in the opinion of the treating physician are receiving clinical benefit on study directed therapy, may stay on study directed therapy after consultation with the sponsor-investigator.

Patients who withdraw from treatment due to progression or toxicity are asked to remain on study for follow up.

5.4.2 Patient-Initiated Withdrawal

A patient may decide to withdraw from the study at any time from either treatment, follow up, or both. Subject data will be used from the time of enrollment until death or they are lost to follow- up unless they withdraw from follow up. Patients who withdraw will not be replaced unless they have not received any study directed treatment.

5.4.3 Investigator-Initiated Withdrawal

The investigator will withdraw a patient whenever continued participation is no longer in the patient's best interests. Reasons for withdrawing a patient include, but are not limited to, disease progression, the occurrence of an adverse event or a concurrent illness, a patient's request to end participation, a patient's noncompliance or simply significant uncertainty on the part of the investigator that continued participation is prudent. If a patient is benefiting clinically, she may continue on study-directed treatment after progression and after consultation with the sponsor-investigator. There may also be administrative reasons to terminate participation.

5.4.4 Sponsor-Initiated Withdrawal

Sponsor's decision to discontinue the study.

5.4.5 Withdrawal Documentation Procedure

The reason for study withdrawal and the date the patient was removed from the study must be documented in the case report form.

6 TREATMENT PLAN

6.1 Investigational Agent Administration

Cycle length = 21 days

Atezolizumab 1,200mg IV on ay 1 Bevacizumab 15mg/kg IV on day 1
Rucaparib 600mg orally twice daily by continuous dosing

The atezolizumab infusion should be administered first, followed by the bevacizumab infusion in the following manner:

- Atezolizumab 1,200 mg administered over 60 (± 15) minutes (for the first infusion, reducing to 30 [± 10] minutes for subsequent infusions if first infusion is tolerated. Followed by
- Bevacizumab 15 mg/kg administered over 90 (± 15) minutes (for the first infusion, reducing to 60 [± 15] minutes and then 30 [± 10] minutes for subsequent infusions if prior infusion is tolerated)
- Actual body weight from baseline will be used to calculate the bevacizumab dose. If the patient's weight changes by +/- 10 % during the course of the study, the dose will be recalculated with the new weight, per institutional standards

For the first atezolizumab infusion and all subsequent infusions, the patient's vital signs (heart rate, respiratory rate, BP and temperature) should be determined the day of treatment prior to infusion. Vital signs will be recorded during and after the infusion only if clinically indicated or if the patient experienced an infusion-related reaction (IRR) during any previous infusions. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

6.2 Dose Escalation/De-escalation Schedule

There is no planned dose escalation or de-escalation. Rucaparib may be dose reduced for toxicity as described in section 8.2.2. Bevacizumab or Atezolizumab may be halted for toxicity per sections 8.1.3 and 8.1.4.

6.3 General Concomitant Medication and Supportive Care Guidelines

6.3.1 Premedication

No premedication will be allowed for the first dose of atezolizumab. Premedication with antihistamines may be administered for cycles ≥ 2 at the discretion of the treating physician if

the patient experienced IRRs during any previous infusions.

6.3.2 Usage of Concurrent/Concomitant Medications

All concomitant medication taken within 28 days prior to C1D1 and any taken during the study up to 30 days after the last dose of study treatment will be recorded in the source documents and CRF. This includes all prescription, over-the-counter (OTC) and herbal supplements. If changes occur during the trial period, documentation of drug dosage, frequency, route and date should also be included on the CRF.

6.3.3 Dietary Restrictions

Rucaparib may be taken with or without food.

6.3.4 Prohibited Medications

Subjects are prohibited from receiving the following therapies during the screening and treatment phase:

Any concomitant therapy intended for the treatment of cancer that is not specified in this protocol, whether health authority approved or experimental, is prohibited. This includes but is not limited to the following:

- Any hormonal therapy directed at the malignant tumor must be discontinued at least seven days prior to Cycle 1 Day 1 of treatment.
- Any other prior therapy directed at the malignant tumor, including chemotherapy, biological therapy and immunologic agents must be discontinued at least 21 days prior to Cycle 1 Day 1 of treatment
- Any prior radiation therapy must be completed at least 28 days prior to Cycle 1 Day 1 of treatment

The following medications are excluded while the patient is receiving study treatment:

- Receptor activator of nuclear factor kappa-B ligand−inhibitor (denosumab). Patients who are receiving denosumab prior to study start date must be willing and eligible to receive a bisphosphonate instead while in the study.
- Treatment with systemic immunostimulatory agents (including but not limited to, interferon- alpha or interleukin-2) within six weeks prior to Cycle 1 Day 1, during treatment and for 10 weeks post-treatment.
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone dose (or dose equivalent) >10 mg/day, cyclophosphamide, azathioprine, methotrexate and anti TNF agents) within two weeks prior to Cycle 1 Day 1 and during treatment.
    - Patients who have received acute, low-dose, systemic immunosuppressant medications may be allowed at prednisone dose (or dose equivalent) <=10 mg/day.
    - The use of inhaled corticosteroids and mineral corticoids (i.e., fludrocortisone)

for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

- Administration of a live, attenuated vaccine within four weeks before cycle 1, day 1 or during the study.
    - Influenza vaccination should be given during influenza season, however, patients must agree not to receive live, attenuated influenza vaccine within 28 days prior to the start of treatment, during treatment or within five months of the last atezolizumab dose.

Rucaparib, *in vitro*, was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. It is reported to be a minor substrate of CYP1A2, CYP2D6, CYP3A4 and P-glycoprotein/ABCB1. Concomitant treatment with proton pump inhibitors has no meaningful change in steady-state exposures of rucaparib. In vitro, rucaparib induced CYP1A2, and down-regulated CYP2B6 and CYP3A4. Clinically, rucaparib is a moderate inhibitor of CYP1A2, and a weak inhibitor of CYP2C9, CYP2C19, and CYP3A4. Sensitive substrates of these enzymes may be used with caution.

6.4 Monitoring Subject Compliance

Pill counts will be taken for the compliance of rucaparib. These will be reported at each visit. Patients will be provided a pill diary and educated on the use prior to study directed treatment and then at each visit after while on study directed treatment.

7 PHARMACEUTICAL INFORMATION

7.1 Bevacizumab

7.1.1 Product Description

Classification: "Monoclonal antibody" and "anti-angiogenesis" drug.

Mechanism of Action: Bevacizumab is a recombinant humanized monoclonal antibody that blocks angiogenesis by inhibiting vascular endothelial growth factor A (VEGF-A). VEGF-A is a chemical signal that stimulates angiogenesis in a variety of diseases, especially in cancer.

Metabolism: Bevacizumab is metabolized and eliminated via the reticuloendothelial system.

Contraindications: Pregnancy (category C), lactation; nephrotic syndrome; active bleeding; surgery within 28 days; dental work within 20 days.

Side Effects: (1%) Body as a Whole: Asthenia, pain, wound dehiscence. CNS: Syncope, headache, dizziness, confusion, abnormal gait. CV: DVT, hypertension, heart failure, intra-abdominal thrombosis, cerebrovascular events. GI: Abdominal pain, diarrhea, constipation, nausea, vomiting, anorexia, stomatitis, dyspepsia, weight loss, flatulence, dry mouth, colitis, gastrointestinal perforation. Hematologic: Leukopenia, neutropenia, thrombocytopenia,

thromboembolism. Metabolic: Hypokalemia, hyperbilirubinemia. Musculoskeletal: Myalgia. Respiratory: Upper respiratory infection, epistaxis, dyspnea, hemoptysis. Skin: Exfoliative dermatitis, alopecia. Special Senses: Taste disorder, increased tearing. Urogenital: Proteinuria, urinary frequency/urgency.

7.1.2 Solution Preparation

Infusion: Withdraw the desired dose of 15 mg/kg and dilute in 100 mL of NS injection per institution standards.

7.1.3 Investigational Agent Administration

IV Infusion: DO NOT administer IV push or bolus. Infuse first dose over 90 (± 15) minutes; if well tolerated, infuse second dose over 60 (± 15) minutes; if well tolerated, infuse all subsequent doses over 30 (± 10) minutes.

7.1.4 Storage Requirements

Store Bevacizumab 100mg or 400mg vials at 2°–8° C (36°–46° F) and protect from light. Do not freeze or shake.

7.1.5 Stability

Store diluted solution at 2°–8° C (36°–46° F) for up to eight hours.

7.1.6 Route of Administration

Intravenous.

7.1.7 Nursing (RN) Implications

Monitor for signs and symptoms of an infusion reaction (hypersensitivity); infusion should be interrupted in all patients with severe infusion reactions and appropriate therapy instituted. Monitor for dizziness, lightheadedness or loss of balance. Take appropriate safety measures.

7.1.8 Handling

Use institutional standards for appropriate handling and disposal.

7.1.9 Availability

Commercially available.

7.1.10 Agent Ordering

Pharmacies will obtain supplies from normal commercial supply chain or wholesaler.

7.1.11 Agent Accountability

The investigational pharmacist will manage drug accountability records. Commercial supply bevacizumab will be accounted for per institutional standards

7.1.12 Agent Destruction and Return

Appropriate precautions for handling and disposal will be used per institutional standards.

7.2 Rucaparib (Rubraca®)

7.2.1 Product Description

Rubraca is available as 200 mg, 250 mg and 300 mg tablets.

Classification: Rubraca is a poly (ADP-ribose) polymerase (PARP) inhibitor.

Mechanism of Action: Rucaparib is an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair.

Metabolism: In vitro, rucaparib had a low metabolic turnover rate in human liver microsomes, and was metabolized primarily by CYP2D6 and to a lesser extent by CYP1A2 and CYP3A4. Based on population pharmacokinetic analyses, steady-state concentrations following rucaparib 600 mg twice daily did not differ significantly across CYP2D6 or CYP1A2 genotype subgroups.

Contraindications: Pregnancy (category C), lactation.

Side Effects: Most common adverse reactions (≥ 20%) were nausea, fatigue (including asthenia), vomiting, anemia, abdominal pain, dysgeusia, constipation, decreased appetite, diarrhea, thrombocytopenia, and dyspnea.

7.2.2 Solution Preparation

Not applicable.

7.2.3 Investigational Agent Administration

This is an oral agent.

7.2.4 Storage Requirements

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

7.2.5 Stability
(This section is intentionally left empty)

7.2.6 Route of Administration

Oral.

7.2.7 Nursing (RN) Implications

Advise patient that the drug may cause photosensitivity. Precautions should be taken such as applying sunscreen (sun protection factor 50+) and /or covering exposed skin with clothing and wearing a hat and sunglasses.

7.2.8 Handling

Use institutional standards for appropriate handling and disposal.

7.2.9 Availability
Rucaparib was approved (accelerated) in December 2016 for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated advanced ovarian cancer who have been treated with two or more chemotherapies.
Rucaparib is provided by Clovis Oncology. The agent is supplied as immediate release 200, 250mg and 300 mg tablets.

7.2.10 Agent Ordering

To order drug, the Clinical Trial Material form must be completed and faxed to Clovis Oncology.

7.2.11 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of receipt, dispensing, and final disposition of the investigational product.

7.2.12 Agent Destruction and Return

Investigational rucaparib patient returns should be documented and reconciled on site and destroyed on site according to the institution's standard operating procedure.

7.3 <u>Atezolizumab</u>

7.3.1 Product Description

Drug is available as 1,200 mg/20 mL (60 mg/mL) solution in a single-dose vial.

Classification: A fully humanized, engineered monoclonal antibody of IgG1 isotype against

the protein programmed cell death-ligand 1.

Mechanism of Action: Atezolizumab blocks the interaction of PD-L1 with programmed cell death protein 1 (PD-1) and CD80 receptors (B7-1Rs). PD-L1 can be highly expressed on certain tumors, which is thought to lead to reduced activation of immune cells (cytotoxic T-cells in particular) that might otherwise recognize and attack the cancer. Inhibition of PD-L1 by atezolizumab can remove this inhibitor effect and thereby engender an anti-tumor response. It is one of several ways to block inhibitory signals related to T-cell activation, a more general strategy known as "immune checkpoint inhibition."

Metabolism: Terminal half-life of atezolizumab is 27 days. Steady state is achieved after six to nine weeks of therapy (two to three cycles).

Contraindications: Pregnancy and lactation.

Side Effects: >10% All grades unless otherwise stated Fatigue (52%)**,** Decreased appetite (26%)**,** Nausea (25%)**,** Urinary tract infection (22%)**,** Constipation (21%)**,** Pyrexia (21%)**,** Diarrhea (18%)**,** Peripheral edema (18%)**,** Abdominal pain (17%)**,** Vomiting (17%)**,** Dyspnea (16%)**,** Back/neck pain (15%)**,** Rash (15%)**,** Arthralgia (14%)**,** Pruritus (13%).

7.3.2 Solution Preparation

The dose should be diluted in 250ml 0.9% NaCl and infused through a 0.2 micron in-line filter.

7.3.3 Investigational Agent Administration

Administer the initial dose over a minimum of 60 (± 15) minutes. If no adverse infusion-related reactions occur, administer the second and all subsequent doses over a minimum of 30 (± 10) minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

7.3.4 Storage Requirements

- Discard product if it contains particulate matter, is cloudy, or discolored.
- Discard unused portion. Do not store for later use.
- Do not freeze.
- Protect from light.
- Refrigerate (between 36 and 46° F).
- Store in original container.

7.3.5 Stability

The prepared solution may be stored at 2-8°C or room temperature for up to 8 hours.

7.3.6 Route of Administration

Intravenous.

7.3.7 Nursing (RN) Implications

Instruct patient that adverse events may occur and to report them. Assess baseline comfort and self-care strategies to maintain comfort and energy conservation.

7.3.8 Agent Ordering

To order drug, the Clinical Trial Material form must be completed and faxed to Genentech Oncology.

7.3.9 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of receipt, dispensing, and final disposition of the investigational product.

7.3.10 Agent Destruction and Return

Used or unused atezolizumab vials requiring destruction should be documented and reconciled on site and destroyed on site according to the institution's standard operating procedure.

8 DOSING DELAYS/DOSE MODIFICATIONS

8.1 Monitoring and Toxicity Management

The severity of adverse events will be graded according to the NCI CTCAE v5.0 grading system.

- Dose reduction of atezolizumab and bevacizumab is not permitted.
- When several toxicities with different grades of severity occur at the same time, the dose modifications should be according to the highest grade observed.
- If, in the opinion of the investigator, a toxicity is considered to be due solely to one component of the study treatment (i.e., rucaparib, atezolizumab or bevacizumab) and the dose of that component is delayed or modified in accordance with the guidelines below, the other component may be administered, if there is no contraindication.
- When treatment is temporarily interrupted because of toxicity caused by rucaparib, atezolizumab and/or bevacizumab (if applicable), the treatment cycles will be restarted such that the atezolizumab and bevacizumab infusions remain synchronized (if applicable).
- A subject that has one or two drugs stopped for toxicity may continue treatment on study with the remaining drug(s).

8.2 Rucaparib

The starting dose of rucaparib is 600 mg ingested twice a day (BID). Patients may take rucaparib with or without food. Each dose should be taken with approximately 8 ounces (240 mL) of room temperature water. Tablets should be swallowed whole without crushing or chewing.

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

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

8.2.1 Toxicity Management

Toxicity	Action
Renal Impairment Creatinine Clearance < 30[a]	Hold.
[a] Creatinine clearance should be calculated per institutional standard.	

8.2.2 Table 2. Dose Adjustments - Rucaparib

Dose level	Dose
Starting dose	600 mg twice daily (two 300 mg tablets or 3 200 mg tablets)
-1	500 mg twice daily (two 250 mg tablets)
-2	400 mg twice daily (two 200 mg tablets)
-3	300 mg twice daily

8.2.2.1 Rucaparib Dose Modification Criteria

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

- Grade 3 or 4 hematologic toxicity. Anemia should be managed as described below in section 8.2.2.2.

- Grade 3 or 4 nonhematologic toxicity (except for alopecia, nausea, vomiting, or diarrhea adequately controlled with systemic antiemetic/antidiarrheal medication administered in standard doses according to the study center routines). Grade 3 or Grade 4 ALT/AST elevations should be managed as described below in section 8.2.2.3.

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

medications and/or supportive care. If rucaparib is held, it can be re-started when toxicity is controlled per the investigator discretion.

For patients who meet treatment interruption guidelines above, treatment with rucaparib should be held until the toxicity improves to ≤ CTCAE Grade 2. Twice daily dosing may then be resumed at either the same dose or a lower dose, per investigator discretion. If treatment is resumed at the same dose and the patient experiences the same toxicity, treatment should be interrupted then resumed at a reduced dose following resolution of the event to ≤ CTCAE Grade 2. If the patient continues to experience toxicity, additional dose reduction steps are permitted;

however, the investigator should consult with the sponsor's medical monitor before reducing to 300 mg BID. If a patient continues to experience toxicity despite dose reduction steps to 300 mg BID, or if dosing with rucaparib is interrupted for > 14 consecutive days due to toxicity, treatment should be discontinued, unless otherwise agreed and documented between the investigator and the sponsor.

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

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

8.2.2.3 Management of Rucaparib Treatment-Emergent ALT/AST Elevations:

- Grade 4 ALT/AST elevations: hold rucaparib until values have improved to Grade 2 or less, then resume rucaparib with a dose reduction. Monitor liver function tests weekly for three weeks after rucaparib has been restarted.
- Grade 3 ALT/AST elevations, in the absence of other signs of liver dysfunction, should be managed as follows:
- Monitor liver function tests weekly until improvement to ≤ Grade 2.

- Continuation of rucaparib with elevation of ALT/AST up to Grade 3 is permitted provided bilirubin is < ULN and alkaline phosphatase is < 3 x ULN.
- If patient has Grade 3 ALT/AST and continues on rucaparib, and levels do not decline within two weeks or they continue to rise, treatment interruption and resolution to ≤ Grade 2 will be required before rucaparib can be resumed, either at the current dose or at a reduced dose.

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

https://www.federalregister.gov/documents/2009/07/30/E9-18135/guidance-for-industry-on- drug-induced-liver-injury-premarketing-clinical-evaluation-availability

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

ALT or AST > 3 x ULN

and

Bilirubin > 2 x ULN

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

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

8.2.2.4 Rucaparib Dose Reduction Steps

Dose reduction steps are presented in Table 2 above.

Dose reescalation upon improvement of toxicity to ≤ CTCAE Grade 1 is permitted at the discretion of the investigator. Dose modifications (interruption, reduction, and reescalation) must be recorded for each patient in the appropriate section of the eCRF.

Rucaparib Retreatment Criteria

Treatment may resume if:

- ANC ≥ 1.0 x 10^9/L
- Platelet count ≥ 50.0 x 10^9/L
- Hemoglobin ≥ 8.0 g/dL
- Creatinine Clearance: ≥ 30
- Nonhematologic toxicities have returned to baseline or ≤ CTCAE Grade 1 severity (or, at the investigator's discretion, ≤ CTCAE Grade 2 severity if not considered a safety risk for the patient).
- Grade 3 or Grade 4 ALT/AST elevations should be managed as described above in section 8.2.2.3.

8.3 Atezolizumab

Toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology.

Although most immune-related adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-related toxicities may require acute management with topical corticosteroids, systemic corticosteroids or other immunosuppressive agents.

The investigator should consider the benefit-risk balance a given subject may be experiencing prior to further administration of atezolizumab. In subjects who have met the criteria for permanent discontinuation, resumption of atezolizumab may be considered, if the subject is deriving benefit and has fully recovered from the immune-related event. Subjects can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

8.3.1 Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Subjects will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 3.

Table 3. Management Guidelines for Pulmonary Events, including Pneumonitis		
	Severity	**Management**
Pulmonary Events/Pneumonitis	**Grade 1**	• Continue atezolizumab and monitor closely. • Re-evaluate on serial imaging. • Consider patient referral to pulmonary specialist. • For recurrent pneumonitis, treat as a Grade 3 or 4 event.
	Grade 2	• Withhold atezolizumab. • Refer subject to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and contact medical monitor, if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c] • For recurrent events, treat as Grade 3 or 4 event.
	Grade 3 or 4	• Permanently discontinue atezolizumab and contact medical monitor.c • Bronchoscopy or BAL is recommended. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve after 48 hours of initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

BAL = bronchoscopic alveolar lavage; IVIG = intravenous immunoglobulin

a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

8.3.2 Hepatic Events

Immune-related hepatitis has been associated with the administration of rucaparib and atezolizumab. Eligible subjects must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment.
Management guidelines for hepatic events are provided in Table 4.

Subjects with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have LFTs performed immediately and reviewed before administration of the next dose

of study drug.

For subjects with elevated LFTs, concurrent medications, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 4. Management Guidelines for Hepatic Events		
	Severity	**Management**
Hepatic Events	**Grade 1**	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits if levels were normal at baseline. If Grade 1 at baseline, may be monitored per study calendar.
	Grade 2	**All events:** • Monitor LFTs weekly until return to baseline values. **Events of > 5 days' duration:** • Withhold atezolizumab. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent.
		• Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a,b] • Permanently discontinue atezolizumab and contact medical monitor if event does not resolve to Grade 1 or better within 12 weeks.[a,b,c]
	Grade 3 or 4	• Permanently discontinue and contact medical monitor.[c] • Consider subject referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
LFT = liver function tests a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor. c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.		

8.3.3 Gastrointestinal Events

Immune-related colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 5.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased c-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 5. Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

	Severity	Management
GI Events (Diarrhea/Colitis)	**Grade 1 Diarrhea or Colitis**	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.
		• Withhold atezolizumab. • Initiate symptomatic treatment.
	Grade 2 Diarrhea or Colitis	• Subject referral to GI specialist is recommended. • For recurrent events or events that persist > 5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and contact medical monitor, if event does not resolve to Grade 1 or better within 12 weeks. [a, b, c]
	Grade 3 Diarrhea or Colitis	• Withhold atezolizumab. • Refer subject to gastrointestinal specialist for evaluation and confirmatory biopsy. • Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab, if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and contact medical monitor if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c]

	Grade 4 Diarrhea or Colitis	• Permanently discontinue atezolizumab and contact medical monitor.[c] • Refer subject to gastrointestinal specialist for evaluation and confirmation biopsy. • Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1, taper corticosteroids over ≥ 1 month.
a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor. c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.		

8.3.4 Endocrine Events

Thyroid disorders or adrenal insufficiency has been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in table 6 below.

Subjects with unexplained symptoms, such as fatigue, myalgias, impotence, mental status changes or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. The subject should be referred to an endocrinologist, if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Table 6. Management Guidelines for Endocrine Events

	Severity	Management
	Asymptomatic Hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
	Symptomatic Hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider subject referral to an endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.

Endocrine Events	**Asymptomatic Hyperthyroidism**	**TSH ≥0.1 mU/L and < 0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** Follow guidelines for symptomatic hyperthyroidism.
	Symptomatic Hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with antithyroid drug such as methimazole or carbimazole as needed. • Consider subject referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab and contact medical monitor for life-threatening immune-related hyperthyroidism. [c]
	Symptomatic adrenal insufficiency, Grade 2 – 4	• Withhold atezolizumab. [a] • Refer subject to endocrinologist. • Perform appropriate imaging. • Initiate treatment with 1–2 mg/kg per day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab, if event resolves to Grade 1 or better and subject is stable on replacement therapy (if required) within 12 weeks. [a,b] • Permanently discontinue atezolizumab and contact medical monitor, if event does not resolve to Grade 1 or better or subject is not stable on replacement therapy within 12 weeks. [a, b, c]
	Hyperglycemia, Grade 1 or 2	• Continue atezolizumab. • Initiate treatment with insulin, if needed. • Monitor for glucose control.
	Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Resume atezolizumab when symptoms resolve and glucose levels are stable.

TSH = thyroid-stimulating hormone

a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

Table 6.1 Management Guidelines for Endocrine Events - Hypophysitis	
Event	Management
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

IV = intravenous; MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re-challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

8.3.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 7.

Table 7. Management Guidelines for Ocular Events		
	Severity	**Management**
	Grade 1	• Continue atezolizumab. • Subject referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.

Ocular Events	**Grade 2**	• Withhold atezolizumab. • Subject referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks.[a, b] • Permanently discontinue atezolizumab and contact medical monitor, if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c]
	Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor.[c] • Refer patient to ophthalmologist. • Initiate treatment with 1-2 mg/kg/day oral prednisone or equivalent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.
a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor. c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.		

8.3.6 Infusion-Related Reactions

No premedication is indicated for administration of cycle 1 of atezolizumab. However, subjects who experience an infusion-related reaction with cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions.

Guidelines for medical management of infusion-related reactions during Cycle 1 are provided in Table 8. For subsequent cycles, infusion-related reactions should be managed according to institutional guidelines.

Table 8. Management Guidelines for Infusion-Related Reactions

Infusion-Related Reactions	**Severity**	**Management**
	Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset. • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.

	Grade 2	• Interrupt atezolizumab infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. • For subsequent infusions, administer oral premedication with antihistamine and antipyretic and monitor closely for IRRs.
	Grade 3 or 4	• Stop infusion. • Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). • Permanently discontinue atezolizumab and contact medical monitor.[a]
IRR = infusion-related reactions; IV = intravenous. a Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.		

8.3.7 Pancreatic Events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 9.

Table 9. Management Guidelines for Pancreatic Events, Including Pancreatitis

	Severity	Management
	Amylase and/or Lipase Elevation, Grade 1	• Continue atezolizumab. • Monitor amylase and lipase prior to dosing.
	Amylase and/or Lipase Elevation, Grade 2	**Amylase and/or lipase > 1.5-2.0 x ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase > 2.0-5.0 x ULN:** • Treat as a Grade 3 event.

Pancreatic Events	**Amylase and/or Lipase Elevation, Grade 3 or 4**	• Withhold atezolizumab for up to 12 weeks after event onset. a
		• Refer patient to GI specialist.
		• Monitor amylase and lipase every other day.
		• If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
		  • If event resolves to Grade 1 or better, resume
		  • atezolizumab. b
		  • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. c
		  • For recurrent events, permanently discontinue atezolizumab and contact Medical Monitor. c

	Immune-related Pancreatitis, Grade 2 or 3	• Withhold atezolizumab. • Refer subject to gastrointestinal specialist. • Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Resume atezolizumab, if event resolves to Grade 1 or better within 12 weeks.[a,b] • Permanently discontinue atezolizumab and contact medical monitor, if event does not resolve to Grade 1 or better within 12 weeks.[a, b, c] • For recurrent events, permanently discontinue atezolizumab and contact medical monitor.[c]
	Immune-related Pancreatitis, Grade 4	• Permanently discontinue atezolizumab and contact medical monitor.[c] • Refer subject to gastrointestinal specialist. • Initiate treatment with 1−2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

8.3.8 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless

contraindicated. Management guidelines for dermatologic events are provided in Table 10.

Table 10. Management Guidelines for Dermatologic Events

	Severity	Management
Dermatologic Events	**Grade 1**	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
	Grade 2	• Continue atezolizumab. • Consider subject referral to dermatologist. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
	Grade 3	• Withhold atezolizumab. • Refer subject to dermatologist. • Initiate treatment with 10 mg/day oral prednisone or equivalent, increasing dose to 1–2 mg/kg/day if event does not improve within 48–72 hours. • Resume atezolizumab, if event resolves to Grade 1 or better within 12 weeks.[a,b] • Permanently discontinue atezolizumab and contact medical monitor, if event does not resolve to Grade 1 or better within 12 weeks.[a, b,c]
	Grade 4	• Permanently discontinue atezolizumab and contact medical monitor.[c]

a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

8.3.9 Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Subjects may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 11.

Table 11. Management Guidelines for Neurologic Disorders

	Severity	Management
	Grade 1	• Continue atezolizumab. • Investigate etiology.

Immune-related Neuropathy	**Grade 2**	• Withhold atezolizumab. • Investigate etiology. • Initiate treatment as per institutional guidelines. • Resume atezolizumab if event resolves to Grade 1 or better within 12 weeks. [a,b] • Permanently discontinue atezolizumab and contact medical monitor, if event does not resolve to Grade 1 or better within 12 weeks. [a, b,c]
	Grade 3 or 4	• Permanently discontinue atezolizumab and contact medical monitor.[c] • Initiate treatment, as per institutional guidelines.
Myasthenia Gravis and Guillain-Barre Syndrome	**All Grades**	• Permanently discontinue atezolizumab and contact medical monitor.[c] • Refer subject to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of 1–2 mg/kg/day oral or intravenous prednisone or equivalent.

a If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed.

b Atezolizumab may be withheld for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤ 10 mg/day oral prednisone or equivalent. The acceptable length of the extended period of time must be agreed upon by the investigator and the medical monitor.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.

8.3.10 Immune-Related Events: Immune-Related Meningoencephalitis

Immune-related meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-related meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral or fungal) or progression of malignancy or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted. Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.

Table 12. Management Guidelines for Immune-Related Meningoencephalitis

Event	Management

Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab and contact medical monitor.[a] • Refer patient to neurologist. • Initiate treatment with 1−2 mg/kg/day IV methylprednisolone or equivalent and convert to 1−2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.
IV = intravenous. a Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be rechallenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the medical monitor.	

8.3.11 Immune-Related Events: Renal Events and Immune-Related Nephritis

Immune-related nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function, and renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as nonsteroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. If no alternative cause of acute kidney injury is identified, patients with signs and symptoms of acute kidney injury, in the absence of an identified alternate etiology, should be treated according to the management guidelines for immune-related renal events in the table below.

Table 12.1. Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset.[a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab.[b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor.[c]

Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab and contact Medical Monitor. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event. Patients can be re-challenged with atezolizumab only after approval has been documented by both n appropriate delegate) and the Medical Monitor.

8.3.12 Immune-Related Events: Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 12.2.

Table 12.2 Management Guidelines for Immune-Mediated Myositis

Severity	Management
Immune-mediated myositis, Grade 1	• Continue atezolizumab. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines.

Immune-mediated myositis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c]
Immune-mediated myositis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset [a] and contact Medical Monitor. • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab and contact Medical Monitor. [c] For recurrent events, treat as a Grade 4 event.
Immune-mediated myositis, Grade 4	• Permanently discontinue atezolizumab and contact Medical Monitor. [c] • Refer patient to rheumatologist or neurologist. • Initiate treatment as per institutional guidelines. • Respiratory support may be required in more severe cases. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., > 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤ 10 mg/day oral prednisone. The acceptable length of the extended period of time must be agreed upon by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed.

[c] Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. Patients can be re--challenged with atezolizumab only after approval has been documented by both the investigator (or an appropriate delegate) and the Medical Monitor.

8.3.13 Immune-related Events: Immune-mediated Myelitis

- Patients should be monitored for clinical signs and symptoms that are suggestive of myelitis. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies.
- Refer patient to neurologist.
- For Grade 1 myelitis, continue immunotherapy unless symptoms worsen or do not improve.
- Initiate treatment as per institutional guidelines.
- Atezolizumab should be permanently withdrawn for ≥Grade 2 immune-mediated myelitis.

8.3.14 Immune-related Events: Immune-mediated Facial Paresis

- Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies.
- Refer patient to neurologist.
- Initiate treatment as per institutional guidelines.
- Atezolizumab should be withheld for patients with Grade 1 or 2 immune-mediated facial paresis and permanently withdrawn for ≥ Grade 3 immune-mediated facial paresis

8.4 Bevacizumab

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a Grade 3 or 4 nonserious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to Grade ≤ 1, bevacizumab may be restarted at the same dose. If bevacizumab is delayed due to toxicity for > 42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days respectively, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be withheld for a minimum of 28 days prior to the procedure. Reinitiation of bevacizumab following surgery should not occur for at least 28 days and until wounds have fully healed. Reinitiation of bevacizumab after surgery requires documented approval from the medical monitor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE Grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

Guidelines for management of specific adverse events are outlined in Table 13.

Table 13. Guidelines for Management of Bevacizumab-Specific Adverse Events		
Event	**CTCAE.v5.0 Grade**	**Action to Be Taken**

Allergic reactions **or** **Acute infusional reactions/ cytokine release syndrome**	Grade 1–3	• If infusion-related or allergic reactions occur, premedications should be given with the next dose and infusion time may not be reduced for the subsequent infusion. Follow the guidelines in the package insert for bevacizumab administration. • **For patients with Grade 3 reactions**, bevacizumab infusion should be stopped and not restarted on the same day. At the physicians' discretion, bevacizumab may be permanently discontinued or reinstituted with premedications and at a rate of 90 ±15 min. **If bevacizumab is reinstituted, the patient should be closely monitored during and following the administration of bevacizumab.**
	Grade 4	• Discontinue bevacizumab.
Arterial Thrombosis - Cardiac ischemia/ infraction - CNS ischemia (TIA, CVA) - any peripheral or visceral arterial ischemia/thrombosis	Grade 2 (if new or worsened since bevacizumab therapy)	• Discontinue bevacizumab.
	Grade 3–4	• Discontinue bevacizumab.

Venous Thrombosis	Grade 3	• Hold bevacizumab treatment. If the planned duration of full-dose anticoagulation is < 2 weeks, bevacizumab should be held until the full-dose anticoagulation period is over. • If the planned duration of full-dose anticoagulation is >2 weeks, bevacizumab may be resumed during the period of full-dose anticoagulation **IF** <u>all</u> of the criteria below are met: • The subject must have an in-range INR (usually 2–3) on a stable dose of warfarin or be on a stable dose of heparin prior to restarting bevacizumab. • 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. • If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.
	Grade 4	• Discontinue bevacizumab.
Hypertension*	[Treat with antihypertensive medication as needed. The goal of BP control should be consistent with general medical practice.]	
	Grade 1	• Consider increased BP monitoring.
	Grade 2 asymptomatic **and** diastolic BP < 100 mmHg	• Begin antihypertensive therapy and continue bevacizumab.
	Grade 2-3 Symptomatic **OR** Diastolic BP > 100 mmHg	• Hold bevacizumab until symptoms resolve **AND** BP < 160/90mmHg.
	Grade 4	• Discontinue bevacizumab.
Congestive Heart Failure	Grade 3	• Discontinue bevacizumab.
	Grade 4	• Discontinue bevacizumab.
Proteinuria	Proteinuria should be monitored by urine dipstick or urine protein creatinine (UPC) ratio, if dipstick is > 2 plus then a UPC ratio should be performed.	
	UPC ratio < 3.5 (<Grade 3)	• Continue bevacizumab.
	UPC ratio 3.5 and up (>=Grade 3)	• Hold bevacizumab until UPC recovers to < 3.5.
	Nephrotic syndrome	• Discontinue bevacizumab.
Hemorrhage (CNS or pulmonary)	Grade 2–4	• Discontinue bevacizumab.

Hemorrhage (non-CNS; non-pulmonary)	Grade 3	• Patients receiving full-dose anticoagulation should discontinue bevacizumab • For patients not on full-dose anticoagulation, hold bevacizumab 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 study therapy.
	Grade 4	• Discontinue bevacizumab.
RPLS (reversible posterior leukoencephalopathy syndrome **or PRES** (posterior reversible encephalopathy syndrome)		• **Hold bevacizumab in patients with symptoms / signs suggestive of RPLS**; • subsequent management should include MRI • **scans and control of HTN.** • **Discontinue bevacizumab upon diagnosis of RPLS.**
Wound dehiscence requiring medical or surgical intervention		• **Discontinue bevacizumab.**
GI perforation, GI leak or fistula		• Discontinue bevacizumab.
Bowel obstruction	Grade 2 requiring medical intervention	• Hold bevacizumab until complete resolution, with a minimum of four weeks after surgery.
	Grade 3-4	• Hold bevacizumab until complete resolution. If surgery is required, patient may restart bevacizumab after full recovery from surgery, and at investigator's discretion.
Other unspecified bevacizumab-related AEs (except controlled nausea/vomiting).	Grade 3	• Hold bevacizumab until symptoms resolve to ≤ grade 1.
	Grade 4	• Discontinue bevacizumab. • **Upon consultation with the study chair,** resumption of bevacizumab may be considered, if a patient is benefiting from therapy and the Grade 4 toxicity is transient, has recovered to ≤ Grade 1 and unlikely to recur with retreatment.

9 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Definitions of Adverse Events

An AE is defined as any untoward medical occurrence in a patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or

not related to the investigational medicinal product or other protocol-imposed intervention, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with {insert condition being studied} that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention.
- An exacerbation of preexisting conditions or events, intercurrent illnesses, drug interaction, or the significant worsening of the indication under investigation that is not recorded elsewhere on the eCRF under specific efficacy assessments. Anticipated fluctuations of preexisting conditions, including the disease under study, that do not represent a clinically significant exacerbation or worsening, are not considered AEs.

It is the responsibility of the investigator to document all AEs that occur during the study. AEs should be elicited by asking the patient a nonleading question (e.g., "Have you experienced any new or changed symptoms since we last asked/since your last visit?"). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination; or from special tests such as the ECG, laboratory assessments, or other study-specified procedure (source of AE). Symptoms reported spontaneously by the patient during the physical examination would also qualify as an AE (and hence documented on the AE eCRF, not on the physical examination eCRF, which is reserved for physical signs or findings).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the
P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

9.1.1 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that occurs at any dose (or, occurs after informed consent is given and prior to dosing if the SAE is related to a study procedure) that:

- Results in death. Any event resulting in death during the reporting period (from date of first dose of study drugs through 30 days after last dose) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing, that results in death must also be reported as an SAE.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred)
- Requires in-patient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity

- Results in a congenital anomaly or birth defect in a neonate/infant born to a mother exposed to the IMP

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home or the development of drug dependency or drug abuse.

9.1.1.1 Events or Outcomes Not Qualifying as Serious Adverse Events

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

- Preplanned or elective hospitalization including social and/ or convenience situations (e.g., respite care)
- Hospital visits of less than 24 hours duration (e.g., patient presents to the emergency room, but is not admitted to a ward)
- Overdose of either study drugs or concomitant medication unless the event meets SAE criteria (e.g., hospitalization). However, the event should still be captured as a nonserious AE on the appropriate eCRF page.
- Events of progression of the patient's underlying cancer as well as events clearly related to progression of the patient's cancer (signs and symptoms of progression) should not be reported as an AE/SAE unless the outcome is fatal within the safety reporting period. If the event has a fatal outcome within the safety reporting period, then the event of progression of disease must be recorded as an AE and as an SAE with CTCAE Grade 5 (fatal outcome) indicated.
- Events that meet the SAE criteria and occur after informed consent, but before the first dose of study directed treatment, which are considered unrelated to screening procedures.

9.1.2 Clinical Laboratory Assessments as Adverse Events and Serious Adverse Events

It is the responsibility of the investigator to assess the clinical significance of all abnormal values as defined by the list of reference ranges from the local laboratory. In some cases, significant changes in lab values within the normal range will require similar judgment. An abnormal laboratory value that is not already associated with an AE is to be recorded as an AE only if any one of the following criteria is met:

- an action on rucaparib, atezolizumab, or bevacizumab treatment is made as a result of the abnormality
- intervention for management of the abnormality is required
- at the discretion of the investigator should the abnormality be deemed clinically significant.

9.1.3 Definition of an Adverse Event of Special Interest

AESIs (serious or nonserious) are defined as AEs of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by

the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.

Details on the sponsor's currently agreed list of AESIs for study drugs can be found in the current study drug IBs. These AESIs are to be reported to the sponsor expeditiously (see below).

The Atezolizumab Events of Special Interest are:
Non-Drug Specific AESIs:
Adverse events of special interest for this study include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law:
    - Treatment-emergent ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN
    - Treatment-emergent ALT or AST > 3 × ULN in combination with clinical jaundice
- Suspected transmission of an infectious agent by Atezolizumab and/or Bevacizumab, as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected

Atezolizumab AESIs

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis

- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g. Stevens Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

Bevacizumab AESIs:

- Hypertension ≥ Grade 3
- Proteinuria ≥ Grade 3
- GI perforation, abscesses and fistulae (any Grade)
- Wound healing complications ≥ Grade 3
- Hemorrhage ≥ Grade 3 (any grade CNS bleeding; > Grade 2 hemoptysis)
- Arterial thromboembolic events (any Grade)
- Venous thromboembolic events ≥ Grade 3
- Posterior reversible encephalopathy syndrome (PRES - any grade)
- CHF ≥ Grade 3
- Non-GI fistula or abscess ≥ Grade 2

Rucaparib AESIs:
Myelodysplastic Syndrome and Acute Myeloid Leukemia

A review of all reports of MDS and AML that have occurred in the entire clinical development program up to 10 April 2017 revealed a total of 10 reports in patients exposed to rucaparib in Studies CO-338-010, CO-338-017, and CO-338-014. Reports in each study are as follows:

Rucaparib
• CO-338-010 (2 MDS),
• CO-338-017 (2 MDS, 1 AML),
• CO-338-014 (2 MDS, 2 AML, 1 MDS evolving to AML).

Placebo
• CO-338-014 (1 AML).

The rate of MDS/AML was 0.5% for patients on treatment and during the 28-day safety follow-

up, and 0.9% for all patients including during the long-term safety follow-up (rate is calculated based on overall safety population of 1077 patients exposed to at least one dose of oral rucaparib in all clinical studies).

There was one case of AML in 189 patients exposed to placebo in Study CO-338-014.

All of the patients diagnosed with MDS or AML had received multiple cycles and regimens of prior chemotherapy, including platinum- and/or taxane-containing regimens. One patient had also received prior treatment with an alkylating agent (cyclophosphamide) and 2 patients had received radiation for breast cancer (1 patient received rucaparib and 1 received placebo). One patient was discontinued from rucaparib 14 months prior to MDS diagnosis and was treated with olaparib for 13 months between rucaparib discontinuation and MDS diagnosis. One patient discontinued rucaparib 9 months prior to MDS diagnosis and was treated with cisplatin and trabectedin for an unspecified time between rucaparib discontinuation and MDS diagnosis. Exposure to DNA-damaging therapies for ovarian and breast cancer present an increased risk of developing MDS or AML.

In patients diagnosed with MDS, duration from start of primary disease treatment to diagnosis was between approximately 1 and 23 months (i.e., 35 days to approximately 693 days). In patients diagnosed with AML, duration from start of primary disease treatment to AML diagnosis was between approximately 3.5 and 28.5 months (i.e., 106 to 868 days). In the patient with MDS that evolved into AML, the duration of time from starting treatment with rucaparib to diagnosis of MDS was approximately 12.5 months (i.e., 380 days) and from start of rucaparib to diagnosis of AML was approximately 18 months (i.e., 541 days).

Nearly every patient who developed MDS/AML reported having experienced multiple/persistent cytopenias prior to the diagnosis of MDS/AML. The cytogenetic abnormalities currently available in 3 of the 4 patients diagnosed with AML were consistent with aberrations (primarily abnormalities in chromosome 5) typically observed in patients with secondary MDS/AML due to prior chemotherapy. One patient who developed both MDS and AML had chromosomal abnormality in chromosome 7. The patients who have developed MDS and AML have significant confounding risk factors, including prior cytotoxic chemotherapy, as well as a deleterious BRCA mutation presenting a higher risk of developing one or more malignancy(ies).

Based upon the above confounding factors, there is insufficient scientific evidence to conclude that MDS and AML are causally related to rucaparib.

Events of MDS and AML have also been reported with other PARP inhibitors. While the etiology of these events is confounded by prior treatments and the relationship to rucaparib is not clear, Clovis has added these potential risks to all Informed Consent Forms (ICFs) / Patient Information Sheets (PISs). AESI's (both serious and non-serious) will be reported to Clovis within 24 hours of awareness and will continue to be reported to Clovis under SAE reporting requirements.

9.1.4 Pregnancy or Drug Exposure during Pregnancy

If a patient becomes pregnant during the course of the study, study drug dosing should be held immediately.

Pregnancy is not considered to be an AE or SAE; however, all pregnancies occurring during study participation or within six months of last dose of study drug, must be reported expeditiously to the sponsor using the Clinical Pregnancy Report Form within the same timelines as for an SAE.

All pregnancies should be followed through to outcome whenever possible. Once the outcome of a pregnancy is known, the Clinical Pregnancy Outcome Report Form should be completed and submitted to the sponsor. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE.

AEs, SAEs, or AESIs that occur during pregnancy will be assessed and processed according to the AE or SAE/ AESI processes using the appropriate AE or SAE/ AESI forms.

9.2 Recording of Events

Events that occur after signing of informed consent, but prior to initiation of rucaparib, atezolizumab, or bevacizumab, unless serious and due to a protocol-mandated procedure, should be recorded on the Medical History eCRF. Any serious event related to a protocol-mandated procedure should be reported as an SAE during the screening period. Any AE that occurs after first dose of rucaparib, atezolizumab, or bevacizumab through 30 days after receiving the last dose of rucaparib atezolizumab, or bevacizumab will be recorded on the AE eCRF.

In order to avoid vague, ambiguous, or colloquial expressions, the AE should be recorded in standard medical terminology rather than the patient's own words. Whenever possible, the investigator should combine signs and symptoms that constitute a single disease entity or syndrome into a final diagnosis, if appropriate. For example, fever, cough, and shortness of breath may be reported as pneumonia, if that is a reasonable diagnosis.

Each AE is to be evaluated for duration, severity, seriousness, and causal relationship to the investigational drug. The action taken and the outcome must also be recorded.

SAEs and AESIs that occur during the study or within 30 days after receiving the last dose of rucaparib, atezolizumab, or bevacizumab, whether or not related to rucaparib, atezolizumab, or bevacizumab, must be reported immediately (i.e., within 24 hours of knowledge of the event) to the sponsor. The contact information for reporting of SAEs/AESIs can be found on the SAE/AESI Reporting Form. After the 30-day reporting window after discontinuation of rucaparib, atezolizumab, or bevacizumab treatment, only SAEs assessed as related to rucaparib, atezolizumab, or bevacizumab, and all AESIs, irrespective of causality, need to be

reported.
Information on the follow-up of AEs, SAEs, and AESIs is provided below.

9.2.1 Intensity of Adverse Events

The severity of each AE will be graded using the NCI CTCAE, Version 5.0 or later grading scale: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

Severity is not the same as serious.

For AEs not covered by NCI CTCAE, the severity will be characterized as mild, moderate, severe, life-threatening, or fatal according to the following definitions:

- Mild events are usually transient and do not interfere with the patient's daily activities
- Moderate events introduce a low level of inconvenience or concern to the patient and may interfere with daily activities
- Severe events interrupt the patient's usual daily activities and hospitalization (or prolongation of hospitalization) may be required
- Life-threatening events require urgent intervention to prevent death
- Fatal events are those events that led to the patient's death

9.2.2 Causal Relationship of Adverse Events to Rucaparib, Atezolizumab, or Bevacizumab

Medical judgment should be used to determine the cause of the AE considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study medication, and de-challenge or re-challenge with rucaparib, atezolizumab, or bevacizumab.

Table 14. Causal Relationship of Adverse Events to Rucaparib, Atezolizumab, or Bevacizumab

Causality	Description
Not Related to rucaparib, atezolizumab, or bevacizumab	• An AE that is clearly due to extraneous causes (e.g., concurrent disease, concomitant medications, disease under study, etc.) • It does not follow a reasonable temporal sequence from administration of rucaparib, atezolizumab, or bevacizumab • It does not follow a known pattern of response to rucaparib, atezolizumab, or bevacizumab, • It does not reappear or worsen when rucaparib, atezolizumab, or bevacizumab is restarted • An alternative explanation is likely, but not clearly identifiable

Related to rucaparib, atezolizumab, or bevacizumab	• An AE that is difficult to assign to alternative causes • It follows a strong or reasonable temporal sequence from administration of rucaparib, atezolizumab, or bevacizumab • It could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient • It follows a known response pattern to rucaparib, atezolizumab, or bevacizumab • It is confirmed with a positive re-challenge or supporting laboratory data

Outcome and Action Taken

The investigator will record the action taken and outcome for each AE according to the following criteria:

Action Taken with Study Drug (note all that apply)

- None
- Dose reduced/delayed
- Study drug temporarily interrupted
- Study drug permanently discontinued
- Other (specify)

Outcome

- Recovered
- Recovered with sequelae
- Recovering/ Resolving/ Improving
- Ongoing
- Death
- Lost to follow-up

9.2.3 Follow-up of Adverse Events, Serious Adverse Events

All AEs (including SAEs and AESIs) occurring during the study are to be followed up in accordance with good medical practice until resolved; judged no longer clinically significant; or, if a chronic condition, until fully characterized through 30 days after the last dose of rucaparib, atezolizumab, or bevacizumab for statistical considerations. Any SAEs, AESIs, and treatment-related Grade 3/4 AEs must be followed until resolution or stabilization, death, or until lost to follow-up. After the 30-day window, treatment-related SAEs and all AESIs, irrespective of causality, need to be reported.

9.2.4 Regulatory Aspects of Serious Adverse Event and Adverse Events of Special Interest Reporting

All SAEs and AESIs, regardless of relationship to rucaparib, atezolizumab, or bevacizumab, must be reported to the sponsor/SAE designee within 24 hours of knowledge of the event, during the

study through 30 days after receiving the last dose of study treatment, according to the procedures below. After the 30-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. The 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 Report Form and Pregnancy Report Form.

The sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to the US FDA, according to 21 Code of Federal Regulations (CFR) 312.32; to the European regulatory authorities according to the European Commission Clinical Trials Directive (2001/20/EC); and to other applicable regulatory authorities, according to national law and/or local regulations. All investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their IRB or IEC. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

The sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

9.2.5 Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re- assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

Adverse Event Reporting

The Medical College of Wisconsin will track all protocol-defined AE and pregnancy reports originating from the Study for the Product.

Each participating site will be responsible for adverse event assessment and reporting to the respective site IRBs per institutional guidelines. Each serious unexpected event must be reported to the Sponsor-Investigator within 24 hours as specified in the protocol. The Sponsor-Investigator will further evaluate the event and report to regulatory agencies.

A member of the study staff from each site should complete the SAE eCRF within 24 hours of learning of the event and fax (414-805-6622) the completed form signed by the site investigator to the Medical College of Wisconsin.

Investigators must report all Adverse events (AEs), Serious Adverse events (SAEs), AEs of Special Interest (AESIs), pregnancy reports and special situation reports (if applicable) adequately to the sponsor within the stated timelines. The completed MedWatch/case report should be faxed immediately upon completion to IIT EndoBARR at:

Fax: +1-414-805-6622
Email: BradleyIITEndoBARR@mcw.edu

Relevant follow-up information should be submitted to the sponsor as soon as it becomes available and/or upon request.

10 REPORTING AND DOCUMENTING RESULTS (MEASUREMENT OF EFFECT)

10.1 Evaluation of Efficacy (or Activity)

10.2 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version1.1). 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

10.2.1 Definitions

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment on study.

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

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

10.2.2 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, as >10 mm with CT scan, or >10 mm with 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 will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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, and abdominal masses (not followed by CT or MRI), are considered as 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 patient, 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.

10.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using annotation on the source image (CT or MRI). 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 diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

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. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, 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.

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.

10.2.4 Response Criteria

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.

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.

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

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

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

Progression-Free Survival:

Progression-Free Survival (PFS) is defined as the duration of time from date of study entry to time of progression or death, whichever occurs first.

Survival:

Survival is defined as the duration of time from date of study entry to time of death or the date of last contact.

11 CORRELATIVE STUDIES/SPECIAL STUDIES

Correlative studies are planned using the primary tumor specimens and subject blood and serum if consent is provided. Associations between markers identified and between the markers (e.g. MSI, HRD mutations, Immuno-environment) and histological subtypes (e.g., endometrioid, clear cell, serous, carcinosarcoma) and disease status at entry will be evaluated. Additionally, the association between each marker and clinical endpoints will be assessed for each agent.

The aim is to prioritize likely candidates for prediction of outcome worthy of future confirmatory study.

Tissue samples will be batch shipped to Foundation Medicine for FoundationOneCDX testing as well as PD-L1IHC, utilizing Ventana SP142 stain slides. Plasma and stool samples will be batch shipped to the Medical College of Wisconsin, PI office via FedEx (label will be provided).

Kits with specimen containers and instructions for stool collection will be provided.

Planned correlatives include:
1. Measurement of tumor Microsatellite Instability (MSI) via IHC. This will be done at the local sites from the primary tumor as standard of care.

2. Evaluation of genes leading to homologous recombination deficiency including but not limited to:

a. ATM

b. AATRX

c. BARD1

d. BLM

e. BRCA1

f. BRCA2

g. NBN

h. PALB2

i. PTEN

j. WRN

k. FANCA

l. FANCC

m. FANCD2

n. FANC3

o. FANCF

p. FANCG

q. FANCL

r. MRE11A

s. RAD50

t. RAD51

u. PMS2

v. MLH1

w. MSH2

x. MSH6

y. POLE

z. P53

These will be read out from Foundation Medicine.

3. Measure of PD-1/PD-L1 in the tumor and immune environment. This will be read out from Foundation Medicine.

4. Tumor mutational burden by number of mutations per megabase to be divided into low (≤5), intermediate (6-19), and high (≥20). This will be run at Foundation Medicine.

5. Measurement of circulating tumor/cell free DNA both before and during treatment. This will be measured at Medical College of Wisconsin.

Table 15. Lab protocol

Time of Samples	**Blood collection before study directed therapy**	**Blood collection pre-dose of study directed therapy Cycles 1 through 8.**	**Blood collection at the time of Radiographic progression or End of treatment visit**
Cohort:	10 ml peripheral blood into an EDTA tube (purple top) and Streck Cell-Free DNA BCT	10 ml peripheral blood into an EDTA tube (purple top) and Streck Cell-Free DNA BCT	10 ml peripheral blood into an EDTA tube (purple top) and Streck Cell-Free DNA BCT

In this study, it is requested that blood sample (before initiation of study directed therapy, three months after initiation of study directed therapy, and at the time of progression, 10 ml each time point) be submitted for translational research.

Blood specimens will be prepared in the lab by a qualified technician.

- Specimens are collected in purple-top tube (10 mL tube).
- The tubes may be kept refrigerated (4-8° C) until processing (tubes may be on ice up to two hours.). Whole blood specimens will be centrifuged at approximately 2500 RPM in a standard clinical centrifuge for 10 minutes.
- Using sterile techniques to avoid contamination, aliquot 0.5-1 mL plasma into cryovials and Freeze at -80° C. Care will be taken to collect only plasma and avoid collecting any white blood cell (white layer) before transferring plasma into the cryovials.
- Each aliquot will be labelled with study protocol, study-specific case numbers, the data collection time point (i.e. A, B, C, or D), and specimen type (i.e., plasma).
- One cryovial of white blood cells (white layer) is also aliquoted and stored at -80°C. The remaining portion will be thrown away.
- The specimen can be transported frozen by MCW study staff. A specimen tracking log will provide documentation and accountability for specimen processing and transport to MCW. To better preserve the biospecimens, we will guarantee the following in sample transport:
    - sample identification and traceability, handling and transport conditions required for the blood and plasma, and proper training for the personnel handling and preparing the samples. Placement of this cooler in the transport vehicle will be in accordance with IATA rules to ensure both sample and occupant safety.
    - Immediately after arrival at Dr. Wang's laboratory, these biospecimen will be put in -80°C for
      longer storage. Sample transportation will comply with applicable IRB protocol, including appropriate training for all study staff involved in specimen transport.
    - Blood samples will be processed by MCW staff via standard DNA analysis pipeline. Once
      this test is completed, the leftover plasma will be destroyed with bleach (1:10).

6. Microbiome of the stool

Shipping Instructions for Microbiome

1. Provide patient with stool collection kit several days prior to the treatment visit. Note: Label the SAMPLE and OUTER stool collection containers with the patient name, date of birth, and date and time of sample collection (as specified in the stool collection kit instructions) prior to providing the kit to the patient. The SAMPLE and OUTER stool collection containers must be relabeled as described below before sending to the MCW.
2. Review the EasySampler stool collection instructions (provided with the stool collection kit) with patient and instruct the patient to collect the sample within 24 hours of the treatment visit, as close to the visit as possible. Note: The patient must refrigerate the stool sample within one hour of collection (as specified in the patient collection

instructions) and keep the sample refrigerated until it is returned to the clinic. The patient should note the collection time and the time the sample was refrigerated (as specified in the patient collection instructions).

3. Upon receipt in the clinic, record the collection date on the label provided and adhere it to the sealing bag.
4. Place the frozen stool in a -70^{O}C to -80^{O}C freezer until ready to batch ship. If a -70^{O}C to -80^{O}C freezer is not available for storage, store and ship on dry ice within 24 hours of collection.
5. When completing Form TR, the collection time noted by the patient should be recorded as "Collection Time." The "Estimated Processing Time" should be recorded as the amount of time elapsed between sample collection and sample freeze (as noted by the patient).

Labeling Stool Biospecimens

A waterproof permanent marker or printed label should be used to label each translational science biospecimen with:

Biospecimen code (# #)

Collection date (mm/dd/yyyy)*

*Collection date should be recorded on the label provided and adhered to the sealing bag after the patient returns the sample at the treatment visit.

12 STATISTICAL CONSIDERATIONS

12.1 Study Endpoints

Primary Efficacy Variables

The primary efficacy variables are the overall response rate (ORR) of patients with persistent or recurrent endometrial cancer when treated with the combination of rucaparib, bevacizumab and atezolizumab.

ORR will be measured beginning on the date of initiation of study-directed therapy to the date of the first clinical, biochemical or radiological evidence of response, progression or death due to any cause or to date of last assessment. Response will be measured by RECIST 1.1. ORR will be censored at the last assessment of disease progression for patients who have not progressed or died.

Secondary Efficacy Variables

Progression free survival (PFS) of patients with persistent or recurrent endometrial cancer, when treated with the combination of rucaparib, bevacizumab and atezolizumab.
Overall survival (OS) of patients with persistent or recurrent endometrial cancer, when treated

with the combination of rucaparib, bevacizumab and atezolizumab.

Biomarker Variables

The relationship of ORR, PFS, and OS to

- Microsatellite instability — both genetic and epigenetic
- Homologous recombination deficiency
- PD-L1 expression in the tumor
- Tumor mutational burden
- Loss of heterozygosity
- Circulating tumor DNA
- Stool microbiome

12.2 Study Design

This is an open-label, non-blinded, phase II protocol with safety lead-in, anticipated to accrue for two years. Subjects will be followed until progression, death, or until withdrawal of consent.

Safety population

The safety population will consist of all patients who have received at least one dose of study medication, whether withdrawn prematurely or not.

Analysis Population

The observed cases (OC)

This will include all patients who have undergone tumor assessment at baseline, received at least the first cycle of the combination of rucaparib-, bevacizumab- and atezolizumab-based chemotherapy, and have had at least one post-dose tumor assessment.

The OC will be used to describe the population from which the sample is taken.

This will be the primary population for all analyses of primary and secondary efficacy variables of the observed cases (i.e., the actual assessments at each visit). All other populations will be exploratory

The modified observed cases (OC)

The modified OC cases will be the OC for which there is at least one post enrollment evaluable assessment.

The per-protocol population will be defined as the subset of the OC who completed all treatments and who did not have any major protocol violations (such as lack of compliance to the study medication schedule). The definitions of these protocol violations will be finalized

before the database closure and will be documented in the analysis plan. The analysis of this group will be exploratory.

12.3 Randomization

There is no randomization. For documentation purposes in OnCore, date of randomization is considered to be the same as date of verification of enrollment when signed by sponsor-investigator at MCW.

12.4 Exploratory Analysis

ORR will be summarized by

- Microsatellite instability — both genetic and epigenetic
- Homologous recombination deficiency
- PD-L1 expression in the tumor
- Tumor mutational burden
- Loss of heterozygosity
- Stool microbiome

12.5 Determination of Sample Size and Accrual Rate

The sample size will be 30 with accrual up to the end of the two-year period. Patients will be followed until progression, death, or until withdrawal of consent.

12.6 Sample Size Justification and Futility Analysis

The primary outcome is ORR. If the ORR is 27% (Castonguay) the one sided lower 95% CI bound is 14%. If the ORR is 23% the one sided lower 95% CI bound is 11%.

Futility analysis

Our plan is to stop if, in the first 12 subjects, at most 1 has a response to be considered in the ORR. Suppose we want a lower bound of 15% for a CI; then for 27 we would have a 94% CI and for 23 we would have an 84% CI. A Simon 2 stage approach at an alpha of 0.05 with 80% power requires more than 30 patients. The null hypothesis is 15% and the alternative is 30% with 30 patients. We will stop if there is 1 or less patients in 12 but continue if there are 2 or more. If we have 7 or 8 patients with ORR, the probability of an early stop is 44%. If we see 9 patients with ORR, the probability of an early stop is 9%. If the true ORR is 30%, the probability of seeing 23% or better is 84% and of seeing 8/30 is 72%.

12.7 Replacement Policy

Subjects who are removed from study prior to receiving therapy will be replaced.

12.8 Accrual Estimates

We expect to accrue one to two patients each month.

12.9 Interim Analyses and Stopping Rules

12.9.1 Toxicity/Futility Monitoring

Because this is a first-time trial combining these three agents, a safety lead in will be undertaken. The first six patients will be assessed for DLTs after completing one cycle of therapy. If there are zero to one DLTs related to study treatment, the cohort will be expanded to the planned 30. If two of the first six patients suffers a DLT thought to be associated with treatment, the safety cohort will be expanded to nine. If three subjects experience a DLT in the first cycle (either in the cohort of six or nine), the trial will be halted and assessed by the DSMC, PI, and sponsors.

12.9.2 Definition of a Dose-Limiting Toxicity (DLT) – Must be related to study directed therapy

For the safety lead-in of this study a DLT is defined as:

- Any Grade 4 immune related adverse event
- Any ≥ grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis (irrespective of duration)
- Any Grade 2 noninfectious pneumonitis that does not resolve to ≤ grade 1 within 7 days of the initiation of maximal supportive care
- Liver transaminase elevation > 8 x ULN or total bilirubin > 5 x ULN
- Any grade 4 non immune related adverse event except for the exclusion list below
- Delay of initiation of cycle 2 of greater than 3 weeks due to failure to recover AE/failure to meet protocol directed treatment parameters for restart after management of AE
- Any treatment related death

A DLT does not include:

- Grade 3 fatigue, anorexia or constipation lasting less than one week
- Grade 3 endocrine disorders (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replace therapy and the subject is asymptomatic
- Grade 3 infusion related reaction
- Grade 3 or 4 neutropenia (that is not associated with fever or infection) lasting ≤7 days
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding
- Isolated grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention
- Grade 3 hypertension

12.9.3 Anticipated toxicities from therapy include: Bevacizumab

- Febrile Grade 4 neutropenia and/or Grade 4 thrombocytopenia, regardless of the relationship to treatment
- Grade ≥ 2 fistula
- GI perforation
- Major surgery or wound healing complications
- Medically significant hypertension not controlled with antihypertensive therapy, hypertensive crisis or hypertensive encephalopathy
- Grade ≥ 3 left ventricular dysfunction (CHF)
- Nephrotic syndrome
- Arterial thrombosis/embolism (any grade)
- Grade ≥ 3 venous thrombosis/embolism
- CNS bleeding (any Grade) or ≥ Grade 3 bleeding of any kind
- Grade ≥ 2 hemoptysis
- Hypersensitivity/allergic reactions related to bevacizumab
- PRES (or RPLS)

Atezolizumab

- Grade 4 pneumonitis
- AST or ALT > 5×ULN or total bilirubin >3×ULN
- Grade 4 diarrhea or colitis
- Grade 4 hypophysitis
- Any grade myasthenic syndrome/myasthenia gravis, Guillain-Barré or meningoencephalitis
- Grade 4 ocular inflammatory toxicity
- Grade 4 pancreatitis or any grade of recurrent pancreatitis
- Grade 4 rash
- Any grade myocarditis
- Grade 3 pneumonitis
- Grade 3 Ocular inflammatory toxicity
- Grade 3 infusion related reactions

Rucaparib

- Grade 4 ALT/AST elevations

12.10 Analyses Plans

All efficacy data will be analyzed. For all efficacy variables, the baseline value will be defined as the last value taken prior to the start of the first study medication.

12.10.1 Primary Analysis (or Analysis of Primary Endpoints)

ORR will be summarized with a one sided lower 95% CI.

Best objective response (percentage of tumor reduction per RECIST 1.1): The percentage will be summarized as mean and 95% confidence interval (CI) or median and 95% CI (using a bootstrap method). The proportion receiving at least 20% reduction of target lesions will be obtained. The proportion will be compared between the stratification groups using a Fisher exact test.

12.10.2 Secondary Analysis (or Analysis of Secondary Endpoints)

PFS and OS: PFS, and OS will be summarized using Kaplan Meier curves. As an explorative analysis, strata such as 1) Microsatellite instability — both genetic and epigenetic, (2) homologous recombination deficiency, (3) PD-L1 expression in the tumor (4) Loss of heterozygosity and (5) tumor mutational burden will be shown and compared using a Wilcoxon rank sum test. A Cox proportional hazards model will be also fitted using at most 6 variables as covariates (due to sample size).

The percentage reduction will be compared using a general or generalized linear model with stratification groups and demographic and clinical variables. The number of covariates considered will be limited due to sample size.

Percent Survival at Six Months: This will be reported with 95% exact confidence intervals (CI). Survival at six months between groups will be compared using a Fisher's exact test.

12.10.3 Other Analyses/Assessments

Patient Demographics and Characteristics Data: To evaluate generalizability of results, patient characteristics at baseline, demographic and disease characteristics will be summarized, using descriptive statistics. In addition, previous and concomitant diseases and medications will be summarized. Further results will be presented stratified by groups defined by (1) Microsatellite instability — both genetic and epigenetic, (2) homologous recombination deficiency, (3) PD-L1 expression in the tumor and (4) tumor mutational burden. All information will be listed by group and by patient and will be summarized. Frequencies will be presented for the categorical variables (e.g. race) and descriptive statistics will be presented for continuous variables (e.g. weight, age).

Missing Data Handling: The dropout pattern will be plotted and summarized. To assess effects of dropouts, the dropout cohort analysis will be performed by summarizing the change of primary and secondary efficacy variables by using different dropout cohorts. Dropout cohorts will be formed by patients that had their last primary efficacy measurement in the same assessment interval. Patients who drop out or are removed from the study due to an adverse symptom profile will be reported as a safety outcome. In particular, the OC and the modified OC cohorts will be compared to check if the modified OC group appears biased.

To allow for bias due to varying assessment times, symptomatic/non-radiologic events and missing data due to lack of follow-up, sensitivity analyses, as per Bhattacharya (Bhattacharya et al., 2009) will be performed. Briefly, simulation studies with varying hypothetical ORR

and/or progression times simulated by a uniform distribution within the assessment times will be used and times backdated to the last progression-free assessment. In another analysis, we will restrict the definition of the lack of PFS to only include those who have radiologic evidence. Finally, we will make conservative assumptions for the treatment arm and not for the historical controls in a comparison.

12.11 Evaluation of Safety

All information on AEs and SAEs will be listed by patient and will be summarized. The SAE report will include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE as a guideline whenever possible.

Frequencies will be presented for the categorical variables (e.g., race) and descriptive statistics will be presented for continuous variables (e.g., weight, age).

Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:
    - Treatment-emergent ALT or AST $> 3 \times$ ULN (or $> 3 \times$ baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin $> 2 \times$ ULN (of which $\geq 35\%$ is direct bilirubin)
    - Treatment-emergent ALT or AST $> 3 \times$ ULN (or $>3 \times$ baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice
- Suspected transmission of an infectious agent by the study treatment, as defined below:
    - Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis

- Hepatitis, including AST or ALT >10 × ULN
- Systemic lupus erythematosus
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome, and systemic immune activation
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)

13 DATA AND SAFETY MONITORING PLAN (DSMP)

Please refer to the MCWCC DSMC Charter.

Data and Safety Management Overview

The Medical College of Wisconsin (MCW) Data Safety Monitoring Committee (DSMC) and the MCW Institutional Review Board (IRB) will approve protocol-specific DSM plans. A local, investigator-initiated trial will be required to be continuously monitored by the principal investigator of the study with biannual safety and progress reports submitted to the DSMC.

13.1 Study Team

The study team minimally consists of the principal investigator, the clinical research coordinator, regulatory specialist and the study biostatistician. While subjects are on treatment, the principal investigator will meet regularly with the research coordinator and the study biostatistician to review study status. This review will include but not be limited to reportable SAEs and UPIRSOs and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further subject enrollment and the specific intervention for a next subject enrollment is addressed. All meetings including attendance are documented.

13.2 Quality Assurance

Study Monitoring will be conducted by the CTSI's Clinical Trial office, which will be

responsible for ongoing oversight, monitoring, source documentation confirmation, protocol compliance, adverse events, etc.

- The study will be reviewed annually by MCW.
- 10% of subject files will be selected randomly for review (max 10 subjects at each monitoring timepoint).
- Consent/eligibility and objective based data will be reviewed for those files selected
- 1 file will be selected randomly for a comprehensive review at each monitoring timepoint.

After each QA review, a letter/report will be provided to the study staff and the DSMC. Necessary corrective action or training will be provided to the staff as needed throughout and following each QA review. Directed audits may be requested at any time by the CCCTO QA Staff, DSMC, Research Manager, study staff member, or administrative staff.

The MCW Principal Investigator will have access to the study data for all of the patients entered onto this study. Data storage is carried out according to MCW Institutional Policy.

13.3 Clinical Trials Office

The MCWCC Clinical Trials Office [CTO] provides administrative assistance and support to the DSMC.

13.4 DSMC

The Medical College of Wisconsin Cancer Center places the highest priority on ensuring the safety of patients participating in clinical trials. Every cancer interventional trial conducted at MCW includes a plan for safety and data monitoring.

More information can be found related to the MCWCC Data and Safety Monitoring Plan at the MCWCC website.

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:

- Review the clinical trial for data integrity and safety
- Review all unexpected Grade 3, and all Grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 and 5 events must be reported to the DSMC within five calendar days of study staff's knowledge.)
- Review all DSM reports
- Submit a summary of any recommendations related to study conduct
- Terminate the study if deemed unsafe for patients

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

14 REGULATORY COMPLIANCE, ETHICS AND STUDY MANAGEMENT

14.1 Ethical Standard

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

14.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards) and §312 (Investigational New Drug Application; and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

14.3 Prestudy Documentation

Prior to implementing this protocol at MCWCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MCW IRB.

The clinical investigation will not begin until either FDA has determined that the study under the Investigational Drug Application (IND) is allowed to proceed or the Investigator has received a letter from FDA stating that the study is exempt from IND requirements.

14.4 Institutional Review Board

The protocol, the proposed informed consent form and all forms of participant information related to the study (e.g. advertisements used to recruit participants) will be reviewed and approved by the MCW Institutional Review Board. Prior to obtaining MCW approval, the

protocol must be approved by the Medical College of Wisconsin Cancer Center Scientific Review Committee. The initial protocol and all protocol amendments must be approved by the IRB prior to implementation.

Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the subjects and their families. Consent forms describing in detail the study interventions/products, study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting intervention/administering study product.

Consent forms will be IRB-approved and the subject (and Legally Authorized Representative, if necessary) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the subject and answer any questions that may arise. In accordance with 46 CR 46.111, the subject will sign and date the informed consent document prior to any procedures being done specifically for the study.

A witness should only sign when required, per FH/MCW IRB policy. If a witness signs the document when not required, the study staff should document in the legal medical record (or note to file) the relationship to the patient and why a witness signed. (i.e., "Although not required, the subject's spouse was present during the consenting process and signed as the witness." Or "Although not required, hospital staff was present for consenting process and signed as a witness.")

The subjects will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial.

A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. If there are changes to the consent form, all revisions will be reviewed with study subject at the next appropriate opportunity. Patients that require reconsenting will be defined in the IRB approved amendment submission. The process for obtaining informed consent will again be performed. Study subjects will not be reconsented for continuing reviews. The MCWCC CTO will follow the MCW/FH IRB's policy for subjects who demonstrate limited English proficiency or limited literacy.

After the subject's visit in which the consent is signed, it is documented in the clinic chart that the consent has been signed and that all questions have been answered to the subject's satisfaction after adequate time for review of the consent. It is also documented that a copy of the consent is given to the subject. The original consent is kept with the subject's study file, and a copy of the consent is sent to the OCRICC office, which will then submit to HIM a copy of the signed consent to be scanned into EPIC, the legal medical record.

14.5 Subject Confidentiality and Access to Source Documents/Data

Subject confidentiality is strictly held in trust by the sponsor-investigator, participating investigators, and any staff, [and the sponsor(s) and their agents]. This confidentiality includes the clinical information relating to participating subjects, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator.

The conditions for maintaining confidentiality of the subjects' records are required for the life of the data. These rules apply equally to any and all MCWCC projects.

One risk of taking part in a research study is that more people will handle the personal health information collected for this study. The study team will make every effort to protect the information and keep it confidential, but it is possible that an unauthorized person might see it. Depending on the kind of information being collected, it might be used in a way that could embarrass the subject or affect his/her ability to get insurance.

While data are being collected and after all data have been collected but are still in the process of being analyzed, the subject's data/PHI are stored in the locked Clinical Research office in the Clinical Trials Office. Databases in which the study subject information is stored and accessed are

password protected, allowing for limited access by authorized personnel only. Data/PHI kept in the Case Report Forms contain the study identifiers, subject initials, date of birth and date of service.

The sponsor-investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor or other authorized representatives of the sponsor-investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

14.6 Protection of Human Subjects

14.6.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all subjects involved in human experimentation. This is accomplished through the IRB mechanism and the informed consent process. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed

consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

14.6.2 Protection of Privacy

As noted, patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the signed document.

14.7 Changes in the Protocol

Once the protocol has been approved by the MCW IRB, any changes to the protocol must be documented in the form of an amendment. The amendment must be signed by the investigator and approved by IRB prior to implementation.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB approval. In this circumstance, however, the Investigator must then notify the IRB in writing within five working days after implementation.

The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to the sponsor and the regulatory authority(ies) in accordance with the governing regulations.

Changes to the protocol may require approval from the sponsor.

Any departures from the protocol must be fully documented in the source documents.

14.8 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies).

Onsite Audits

Auditing is essential to ensure that research conducted at the Medical College of Wisconsin (MCW) Cancer Center is of the highest quality and meets MCW and regulatory agency standards.

Regulatory authorities, the IRB and/or sponsor may request access to all source documents, data capture records and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14.9 Product Complaints

What is a product complaint?

A product complaint is any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness or performance of a product after it has been released and distributed to the commercial market or clinical trial.

How do I file a product complaint?

For all Investigator Initiated Studies (interventional and non-interventional):

- Product Complaints **with** an AE (adverse event) should be reported via email/fax to: usds_aereporting-d@gene.com OR 650-238-6067
- Product Complaints **without** an AE (adverse event) should be reported via email to: kaiseraugst.global_impcomplaint_management@roche.com

All complaints must be filed within 1 business day for pre-approved products and 15 calendar days for approved products. Complaints can be reported using a Medwatch, CIOMS or any Genentech-approved reporting form (same as SAEs, AESI etc.).

15 DATA HANDLING AND RECORD KEEPING

15.1 Overview

Every effort is made to uphold the integrity of the project, the research, the institution, and the researchers involved. Data collection guidelines and methodologies are carefully developed before the research begins. Investigators focus on the following to ensure data integrity: well-trained data collectors/recorders to ensure consistency and quality, well-designed data collection protocols and ongoing monitoring. In this way, study rigor and validity are maintained. Data is protected from physical damage as well as from tampering, loss or theft. This project's data management is a multidisciplinary activity that includes investigators, research coordinators and nurses, data mangers, support personnel, biostatisticians and database programmers. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

15.2 Data Management Responsibilities

15.2.1 Principal Investigator

The principal investigator oversees the management of patient records/case report forms and ensures that a) complete and accurate data will be obtained and provided to the sponsor; b) patient records are maintained to include history, prescribed medication and investigational product(s), measurements,

exams, evaluations and adverse events; c) corrections are applied to clinical research data according to principles of good research practice (i.e., single-line delete, date and initial). He or she will ensure that there is correlation between the case report forms and the source documents**.**

15.2.2 Research Coordinator

A research coordinator creates, collects and organizes clinical trial documentation. He or she ensures that source documentation and data abstraction and entry are being done at protocol specified time points.

15.2.3 Research Nurse/Medical Staff

The research nurse and medical staff documents protocol-required care or assessment of the subject's outcomes, adverse events and compliance to study procedures.

15.2.4 Biostatistician

The biostatistician may assist in CRF development (content and design), dataset specifications (annotation of CRFs and record layout) and validation.

15.3 Handling and Documentation of Clinical Supplies

The MCWCC Principal Investigator will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included. The sponsor-investigator will maintain written records of any disposition of the study drug.

The principal investigator shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the principal investigator will not allow the investigational drug to be used in any manner other than that specified in this protocol.

15.4 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file. Source documents for the correlative studies are maintained in the laboratory conducting the study.

The source documents for this protocol are as follows:

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X- rays, subject files and records kept at the pharmacy, at the laboratories and

at medico-technical departments involved in the clinical trial).

Table 16. All source documents will be written following ALCOA standards:

ALCOA Attribute	Definition
Attributable	Clear who has documented the data.
Legible	Readable and signatures identifiable.
Contemporaneous	Documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
Original	Original, if not original should be exact copy; the first record made by the appropriate person. The investigator should have the original source document.
Accurate	Accurate, consistent and real representation of facts.
Enduring	Long-lasting and durable.
Available and accessible	Easily available for review by treating physicians and during audits/inspections. The documents should be retrievable in reasonable time.
Complete	Complete until that point in time.
Consistent	Demonstrate the required attributes consistently.
Credible	Based on real and reliable facts.
Corroborated	Data should be backed up by evidence.

15.5 Case Report Forms

The principal investigator and/or his/her designee will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study-specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into OnCore® via standardized CRFs, in accordance with the study calendar, using single data entry with a secure access account. The Clinical Research Coordinator will complete the CRFs as soon as possible upon completion of the study visit; the investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by MCWCC personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The principal investigator will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the MCWCC

DSMC and regulatory agencies.

15.6 Study Record Retention

The principal investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity and use by subjects, as well as written records of the disposition of the drug when the study ends.

The principal investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

Study documentation includes all CRFs, data correction forms or queries, source documents, sponsor-investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

In accordance with FDA regulations, the investigator shall retain records for a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and FDA is notified.

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APPENDIX 1. *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 2. *PREGNANCY FORM*

Pregnancy occurring in participant in a Clinical Trial of Investigational Medicinal Product, while not considered an adverse event or serious adverse event, requires monitoring and follow up.

The investigator must collect pregnancy information for female trial subjects or female partners of male trial subjects. This includes subjects who become pregnant while participating in a clinical trial or during a stage where the fetus could have been exposed to the investigational medicinal product (e.g., if the active substance or one of its metabolites has a long half-life).

Any pregnancy should be reported by the PI to the sponsor using either a study specific or generic pregnancy reporting form (see below).

The pregnancy should be followed up by the investigator until delivery. It may be necessary to monitor the development of the newborn for an appropriate period post delivery. Any occurrences that result in a Serious Adverse Event should be reported as per the SAE reporting procedure.

The below form will be used.

Study Drug: Study/Protocol Nº: Investigator's name:	PATIENT ID Patient's Initials ☐☐ 1. ☐☐☐ 2. fam. ☐☐☐ If applicable Centre No. Patient No	REPORT TYPE **Initial** **Follow-Up**

STUDY PREGNANCY FORM **Page 1 of**

1. Country:	2. LOCAL CASE ID:

I. MATERNAL INFORMATION

3. DATE OF BIRTH day month year	4. AGE yrs./mo.	5. RACE Caucasian Oriental Black Other	6. HEIGHT cm	7. WEIGHT kg

8. Date of Last Menstrual Period day month year	9. Expected Date of Delivery day month year

10. Method of Contraception	***11. Contraception used as instructed*** **yes** **no** **uncertain**

II. HISTORY

12. **PATIENT'S PAST MEDICAL HISTORY** (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy e.g. alcohol, smoking, other substance consumption, hypertension, eclampsia, diabetes including gestational, infections during pregnancy, environmental or occupationa exposure that may pose a risk factor).

13. PREVIOUS OBSTETRIC HISTORY – provide details on all previous pregnancies below, including abortion or stillbirth (use page 3 if needed)

	Gestation week	Outcome including any abnormalities
1		
2		
3		
4		
5		

14. DRUG INFORMATION – please list the Novartis drug(s) first and all other therapies taken prior to or during pregnancy

Drug Names	Daily Dose	Route	Treatment Dates Start	Treatment Dates Stop	Indication	(specify week of pregnancy) Start	(specify week of pregnancy) Stop

2. LOCAL CASE ID:

III. PREGNANCY INFORMATION

15. Date of Pregnancy Confirmation:_____/_____/_____

16. Method of Pregnancy Confirmation (Serum, Urine, Ultrasound, etc):

17. PRENATAL
Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?
No **Yes** **Not known**
If yes, please specify test date and results:

18. PREGNANCY OUTCOME
Delivery
Normal **Forceps/Ventouse** **Caesarean section**
Maternal complications or problems related to birth:_____

Abortion
Therapeutic **Planned** **Spontaneous** **Please, specify reason and any abnormalities (if known)**
_____

Unspecified
Date of abortion/delivery day month year
at week _____

19. **MATERNAL PREGNANCY ASSOCIATED EVENTS:**

If the mother experiences a serious adverse drug reaction (ADR) during a pregnancy, please complete a SAE form and submit as requested.

IV. CHILD INFORMATION

20. **Neonate**
Normal **Abnormal** **Stillbirth** **please specify any abnormalities:** _____

Sex	Height	Weight	Apgar Scores	Head circumference
Male **Female**	**inches**	**pounds**	**1 min.** **5 mins.** **10 mins.**	**inches**

For additional information, please use page 3 (please provide copies of relevant documentation)

V. ASSESSMENT OF PREGNANCY OUTCOME

24. SERIOUSNESS CRITERIA
Non Serious
day month year
Mother died | | |
☐ **Stillbirth** / Neonate Died day month year | | |
Involved or prolonged inpatient hospitalization
Life-threatening
Results in persistent or significant disability/incapacity
Other Seriousness Criteria: Congenital anomaly/birth defect Other significant medical events

25. ASSESSMENT OF CAUSALITY
Please indicate the relationship between pregnancy outcome and Novartis study drug
Not suspected ☐ Suspected

INFORMATION SOURCE

26. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR	27. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT day month year

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2. LOCAL CASE ID:

FOR ADDITIONAL INFORMATION:

INFORMATION SOURCE	
29. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR **Signature:**	**30. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING** **day** **month** **year**

PLEASE SEND FORM TO: iitendobarr@mcw.edu or fax to +1.414.805.6622

APPENDIX 3. *ENROLLMENT WORKSHEET*

PI Name:	Site No:

The EndoBARR Trial (Endometrial Bevacizumab, Atezolizumab, Rucaparib): An Open Label, Non-Randomized Multisite Phase II Trial Combining Bevacizumab, Atezolizumab and Rucaparib for the Treatment of Previously Treated Recurrent and Progressive Endometrial Carcinoma.

Enrollment Worksheet

Subject Initials:_____/
_____/_____ Subject D.O.B:_____/_____/_____ Subject ID#:
_____

Rucaparib 600mg BID + Bevacizumab 15mg/kg and Atezolizumab 1,200mg every 21days. Expected start date:

Did the patient meet all inclusion criteria and none of the exclusion criteria? ☐ Yes ☐ No

If No, Which inclusion criteria are not met and/or exclusion criteria are met?

_____

_____

(Please attach a copy of the signed Informed consent, Inclusion/exclusion and all relevant screening source documents to this enrollment form for sponsor approval.)

_____

Name of Principal Investigator or Authorized Representative (Please Print)

_____ _____

Signature of Principal Investigator or Authorized Representative. Date.

*For Sponsor Use only

Is subject approved to go on study? □Yes ☐NO	
Medical Monitor (or designee) Name:	
Signature:	Date:

APPENDIX 4. *SAE REPORTING*

METHODS AND TIMING FOR ASSESSING AND RECORDING SAFETY VARIABLES

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the Sponsor-Investigator, appropriate IRB(s), Clovis Oncology, and Genentech, Inc. in accordance with CFR 312.32 (Safety Reports). MCW (PI as sponsor) will obtain reporting on AEs and SAEs from co-investigatory sites and report as required. MCW as lead site will report to FDA as indicated. OnCore is used by all sites to collect data and events. MedWatch 3500 will be used for all SAEs and reported to sponsor within 24 hours of becoming aware. Sponsor will report AE/SAEs and SAEs of special interest to Genentech and Clovis Oncology as described below.

Assessment of Adverse Events
All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the Atezolizumab and/or Bevacizumab and/or Rucaparib (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of Atezolizumab and/or Bevacizumab and/or Rucaparib, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to Atezolizumab and/or Bevacizumab and/or Rucaparib; and/or the AE abates or resolves upon discontinuation of Atezolizumab and/or Bevacizumab and/or Rucaparib or dose reduction and, if applicable, reappears upon re- challenge.

No

Evidence exists that the AE has an etiology other than the Atezolizumab and/or Bevacizumab and/or Rucaparib (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to Atezolizumab and/or Bevacizumab and/or Rucaparib administration (e.g., cancer diagnosed 2 days after first dose of Atezolizumab and/or Bevacizumab and/or Rucaparib).

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:
• "How have you felt since your last clinical visit?"
• "Have you had any new or changed health problems since you were last here?"

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

- Hospitalizations for the following reasons do not require reporting:
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study

Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The below table should be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated d
5	Death related to adverse event [d]

NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performedby patients who are not bedridden.

c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event

d. Grade 4 and 5 events must be reported as serious adverse events

Post-Study Adverse Events

The investigator after the end of the adverse event reporting period (defined as 30 days after the last dose of study drugs) should report all deaths, (regardless of cause), and any serious adverse event including development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject or pregnancy occurring in the partner of a male study subject who participated in the study that is believed to be related to prior exposure to study drugs.

Case Transmission Verification will be performed by both parties during this period to ensure successful transmission of Single case reports

Case Transmission Verification of Single Case Reports

The Sponsor agrees to conduct the Case Transmission verification to ensure that all single case reports have been adequately received by Genentech via the Medical College of Wisconsin emailing Genentech a Quarterly line-listing documenting single case reports sent by the Medical College of Wisconsin to Genentech in the preceding time period. The periodic line-listing will be exchanged within seven (7) calendar days of the end of the agreed time period. Confirmation of receipt should be received within the time period mutually agreed upon.

If discrepancies are identified, the sponsor and investigator will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-by-case basis until satisfactory resolution. The investigator and sponsor shall receive reconciliation guidance documents within the 'Activation Package'.

Following Case Transmission Verification, single case reports which have not been received by Genentech/Roche as well as Clovis shall be forwarded by The Medical College of Wisconsin to Genentech/Roche and/or Clovis within five (5) calendar days from request by Genentech/Roche or Clovis Oncology.

At the end of the study, a final cumulative Case Transmission Verification report will be sent to Genentech/Roche and Clovis Oncology.

AEs of Special Interest (AESIs)

AEs of Special Interest are defined as a potential safety problem, identified as a result of safety monitoring of the product.

SADRs (Drug-related SAEs)
Serious AE reports that are related to the Product shall be transmitted to Genentech/ Roche and/or Clovis Oncology within one (1) calendar days of the awareness date.

Other SAEs
Serious AE reports that are unrelated to the Product shall be transmitted to Genentech / Roche and/or Clovis Oncology within one (1) calendar days of the awareness date.

AESIs
AESIs shall be forwarded to Genentech/ Roche and/or Clovis Oncology within one (1) calendar days of the awareness date.

Pregnancy reports

While such reports are not serious AEs or ADRs per se, as defined herein, any reports of pregnancy (including pregnancy occurring in the partner of a male study subject), where the fetus may have been exposed to the Product, shall be transmitted to Genentech/Roche and/or Clovis Oncology within two (2) calendar days of the awareness date. Pregnancies will be followed up until the outcome of the pregnancy is known, whenever possible, based

upon due diligence taken to obtain the follow-up information

Special situation reports

In addition to all AEs, pregnancy reports and AESIs, the following Special Situations Reports should be collected even in the absence of an Adverse Event and transmitted to Genentech/Roche and/or Clovis Oncology within thirty (30) calendar days:

- Data related to the Product usage during pregnancy or breastfeeding
- Data related to overdose, abuse, off-label use, misuse, inadvertent/erroneous administration, medication error (including potentially exposed in case of medication errors or intercepted medication errors) or occupational exposure, with or without association with an AE/SAE unless otherwise specified in the protocol
- Lack of therapeutic efficacy
- Drug Interaction: No specific interactions are suspected.
- Use of a Medicinal Product in a Pediatric and Elderly population (in addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population)

Occasionally Genentech and/or Clovis Oncology may contact the reporter for additional information, clarification, or current status of the patient for whom an adverse event was reported.

MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-Up Information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- summarizing new information and faxing it with a cover letter including patient identifiers (i.e. D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the

new information is added to the correct initial report)

MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Reporting to the Data and Safety Monitoring Committee
The investigator will use email to report SAEs to the DSMC. The SAE report must include event term(s), serious criteria, and the sponsor-investigator's or sub-investigator's determination of both the intensity of the event(s) and the relationship of the event(s) to study drug administration. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE as a guideline whenever possible.

Reporting to MCW Committee Institutional Review Board

The principal investigator must report events to the MCW IRB within five business days of his/her awareness of the event.

[Guidance on Adverse Event Reporting to the IRB is available online at MCW IRB Policies and Procedures.]

The Medical College of Wisconsin, as the Sponsor of the Study, will be responsible for the expedited reporting of safety reports originating from the Study to the Regulatory Authorities (FDA) where it has filed a clinical trial approval, in compliance with local regulations

Genentech and/or Clovis Oncology will be responsible for the expedited reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM).

The Medical College of Wisconsin will be responsible for the distribution of safety information to its own investigators, where relevant.

Additional Reporting Requirements for Holders (if applicable): For Investigator-Initiated Studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR
§600.80.

Events meeting the following criteria need to be submitted to the Food and Drug Administration (FDA) as expedited Safety Reports according to the following guidance and timelines:

Seven Calendar Day Telephone or Fax Report:

The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of Atezolizumab, rucaparib, and bevacizumab. An unexpected adverse event is one that is not

already described in the Atezolizumab and/or Bevacizumab and/or Rucaparib Investigator Brochure. Such reports are to be telephoned or faxed to the FDA and Genentech/Roche and/or Clovis Oncology within seven calendar days of first learning of the event.

Fifteen Calendar Day Written Report

The investigator is also required to notify the FDA and all participating investigators, in a written Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of Atezolizumab, rucaparib, or bevacizumab. An unexpected adverse event is one that is not already described in the Atezolizumab, rucaparib, or bevacizumab Investigator Brochure.

Written Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR
§ 312.32. All safety reports previously filed by the investigator with the concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech/Roche and/or Clovis Oncology, in addition to all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

FDA fax number for Safety Reports:

Fax: 1 (800) FDA 0178

All written Safety Reports submitted to the FDA by the Investigator must also be faxed to Genentech/Roche Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

Clovis Drug Safety:
Fax: +1.303.261.8319
Email: DrugSafety@clovisoncology.com

And to the Site IRB:
The Medical College of Wisconsin Human Research Protection Program 8701 Watertown Plank Rd Milwaukee, WI 53226

For questions related to safety reporting, please contact Genentech/Roche Drug Safety:

Tel: (888) 835-2555
Fax: (650) 225-4682 or (650) 225-4630

Clovis Drug Safety:
Email: DrugSafety@clovisoncology.com

ANNUAL REPORTS

Copies to Genentech/Roche:

All annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche and Clovis Oncology. Copies of such reports should be faxed to Genentech/Roche Drug Safety:

Fax: (650) 225-4682 or (650) 225-4630

Clovis Drug Safety:
Fax: +1.303.261.8319
Email: DrugSafety@clovisoncology.com

AGGREGATE REPORTS; Either Annual Report or DSUR ANNUAL REPORTS
All annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche and Clovis Oncology.
Copies of such reports should be emailed to Genentech Drug Safety at: Genentech Drug Safety CTV mail box:ctvist_drugsafety@gene.com
And

Clovis Drug Safety:
Fax: +1.303.261.8319
Email: DrugSafety@clovisoncology.com

Note: Investigators should also report events to their IRB as required

STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech/Roche and Clovis Oncology. This includes all annual reports and the Clinical Study Report (final study report).
Additionally, any literature articles that are a result of the study should be sent to Genentech/Roche and Clovis Oncology. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study:

Atezolizumab IIS Clinical Operations
Email: anti-pdl-1-mpd3280a-gsur@gene.com
And to Genentech Drug Safety CTV oversight mailbox at: ctvist_drugsafety@gene.com

Clovis Drug Safety:
Email: DrugSafety@clovisoncology.com

QUERIES

Queries related to the Study will be answered by MCW. However, responses to all safety queries from regulatory authorities or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech/Roche and Clovis Oncology shall have the final say and control over safety queries relating to the Product. MCW agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech/Roche and Clovis Oncology.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests for information or review of data are met. The Parties will clearly indicate on the request the reason for urgency and the date by which a response is required.

SAFETY CRISIS MANAGEMENT

In case of a safety crisis, e.g., where safety issues have a potential impact on the indication(s), on the conduct of the Study, may lead to labeling changes or regulatory actions that limit or restrict the way in which the Product is used, or where there is media involvement, the Party where the crisis originates will contact the other Party as soon as possible.

The Parties agree that Genentech/Roche and Clovis Oncology shall have the final say and control over safety crisis management issues relating to the Product. Medical College of Wisconsin agrees that it shall not answer such queries from media and other sources relating to the Product but shall redirect such queries to Genentech/Roche and Clovis Oncology.

US Department of Health and Human Services, Food and Drug Administration, CDER, CBER. Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation 2009 [Available from: http://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf.]

National Cancer Institute. Common Terminology Criteria for Adverse Events, Version 5.0[Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x 11.pdf