NRG ONCOLOGY

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SUMMARY OF CHANGES

For Protocol Amendment #2 to: NRG-GY021
NCI Protocol #: NRG-GY021
Local Protocol #: NRG-GY021
NCI Version Date: 08/27/2021

This amendment for NRG-GY021 is being submitted in response to an RRA from Dr. Percy Ivy (ivyp@ctep.nci.nih.gov).

Section	Comments
Title Page(s)	• NCI Version Date is now August 27, 2021. • Protocol Administrator changed to Kathryn Miller, contact info updated.
1.3	Note now reads: "*The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens."*
2.6	Note now reads: "*The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens."*
7.3	Revised Olaparib CAEPR (Version 2.5, July 1, 2021) inserted into protocol: •The SPEER grades have been updated. •Added New Risk: o Rare but Serious: Allergic reaction; Febrile neutropenia; Skin and subcutaneous tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders - Other (erythema nodosum) o Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Arterial thromboembolism; Atrial fibrillation; Death NOS; Dermatitis radiation; Enterocolitis; Erythema multiforme; Esophageal stenosis; Hypoxia; Muscle weakness upper limb; Obstruction gastric; Peripheral ischemia; Reversible posterior leukoencephalopathy

Section	Comments
	syndrome; Sinus bradycardia; Soft tissue necrosis lower limb; Treatment related secondary malignancy • Increase in Risk Attribution: o Changed to Likely from Less Likely: Abdominal pain o Changed to Less Likely from Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Mucositis oral; Muscle cramp; Myalgia; Pain in extremity; Rash maculo-papular •Decrease in Risk Attribution: o Changed to Rare but Serious from Less Likely: Platelet count decreased o Changed to Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution from Less Likely: Fever; Lymphocyte count decreased •Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements: o Added to SPEER: Back pain; Neutrophil count decreased •Provided Further Clarification: o Infection listed under Less Likely is now captured as "Upper respiratory infection" and "Urinary tract infection" under Less Likely.
10.0	Note now reads: "*The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens."*
10.5	Note now reads: "*The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens."*
Appendix VI	• Note now reads: "*The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens."* • NRG Oncology Biospecimen Bank-Columbus Kit Management URL has been updated throughout Appendix VI to "https://kits.bpc-apps.nchri.org/".
ICDs	Please see the ICDs for additional changes made.

NRG ONCOLOGY
NRG-GY021
(ClinicalTrials.gov NCT # 04034927)

A PHASE II RANDOMIZED TRIAL OF OLAPARIB VERSUS OLAPARIB PLUS TREMELIMUMAB IN PLATINUM-SENSITIVE RECURRENT OVARIAN CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

Coordinating Center:
NRG Oncology
Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

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Protocol Agents

Agent	**Supply**	**NSC #**	**IND #**	**IND Sponsor**
Olaparib	CTEP	747856		DCTD, NCI
Tremelimumab	CTEP	744483		DCTD, NCI

Participating Sites

☒ U.S.
☐ Canada
☐ Approved International Member Sites

Document History	
Amendment 2	**August 27, 2021**
Amendment 1	April 24, 2020

Initial	10/02/2019

This protocol was designed and developed by NRG Oncology. It is intended to be used only in conjunction with institution-specific IRB approval for study entry. No other use or reproduction is authorized by NRG Oncology nor does NRG Oncology assume any responsibility for unauthorized use of this protocol.

CONTACT INFORMATION (24-APR-2020)		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

NRG Oncology Participating Institutions for Safety Lead-ins	
AZ151	Arizona Cancer Center
CA088	University of California Medical Center at Irvine-Orange Campus
CO070	University of Colorado Cancer Center
CT009	Hartford Hospital
GA020	Georgia Regents University
IA018	University of Iowa Hospitals and Clinics
IL057	University of Chicago
MD017	Johns Hopkins University/Sidney Kimmel Cancer Center
MO011	Washington University School of Medicine
NM004	University of New Mexico Cancer Center
NY016	Memorial Sloan Kettering Cancer Center
NY158	Roswell Park Cancer Institute
OH007	Ohio State University
OH027	Cleveland Clinic Foundation
OH029	Case Western Reserve University
OH274	UHHS – Chagrin Highlands Medical Center
OK003	Oklahoma University
PA015	University of Pittsburgh Cancer Center
PA075	Abramson Cancer Center at the University of Pennsylvania
PA086	Fox Chase Cancer Center
PA121	Thomas Jefferson University
RI012	Women's and Infants Hospital
TX035	M.D. Anderson Cancer Center
VA009	University of Virginia Health Systems
VA010	Virginia Commonwealth University
WI013	Froedtert and the Medical College of Wisconsin

TABLE OF CONTENTS

NRG-GY021
SCHEMA

This study consists of three components, which will be conducted in sequence:

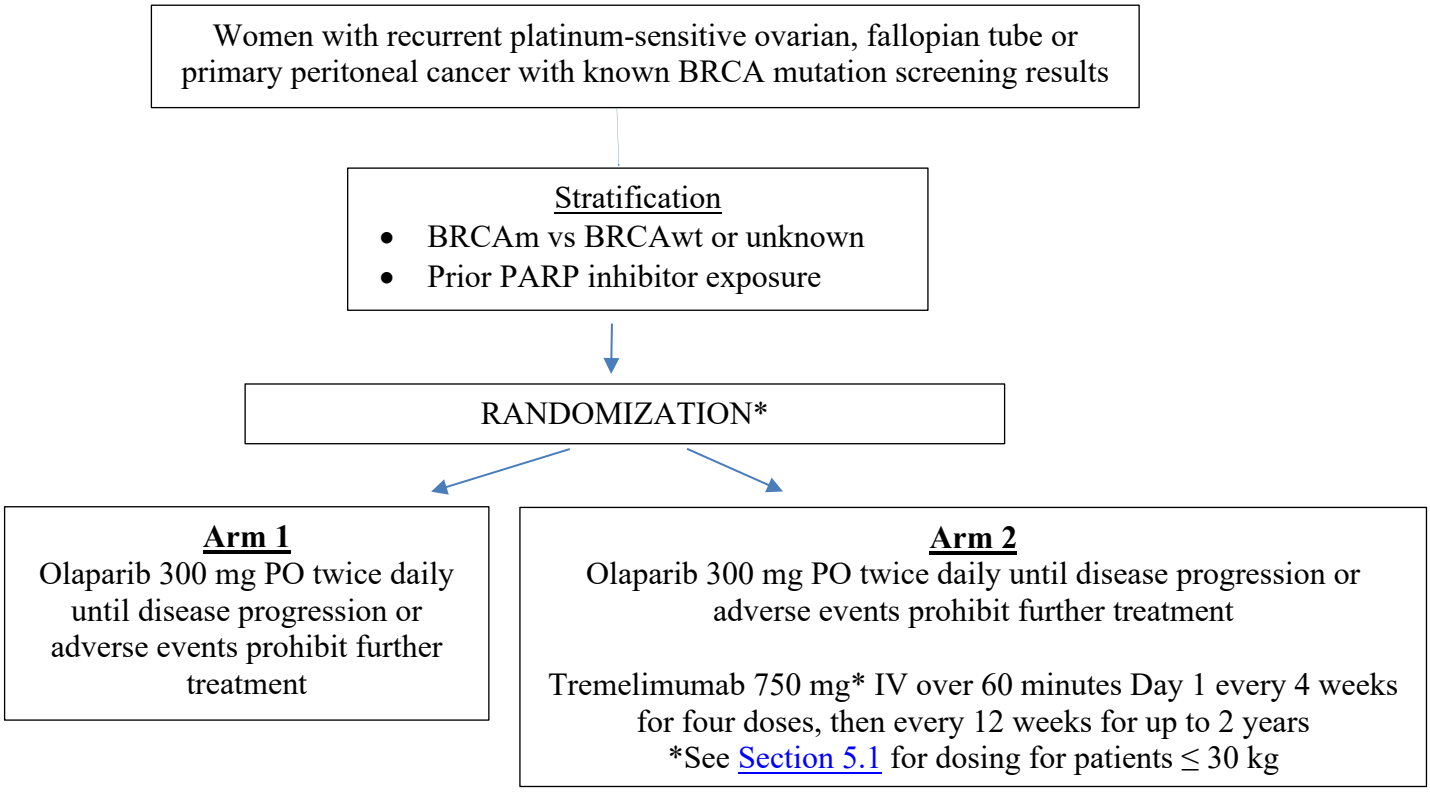
1. **Initial safety lead-in (Open to NRG Oncology Safety Lead-in Sites ONLY—see list in title pages)**
2. **Second safety lead-in (Open to all NRG sites)**
3. **Primary Phase II study (Open to all NCTN participants)**

Initial safety lead-in

During the initial safety lead-in, treatment assignment will be randomized. At least 6 and as many as 25 patients receiving olaparib and tremelimumab will be assessed for DLT through cycle 3. If the olaparib and tremelimumab regimen is deemed sufficiently safe following this review, then the second stage of the safety lead-in will be initiated.

Second safety lead-in

Treatment assignment will be randomized. 20 patients receiving olaparib and tremelimumab will be assessed for DLT through cycle 3. If the olaparib and tremelimumab regimen is deemed sufficiently safe following this review, then the primary Phase II component of this study will be initiated.



*Randomization is 1:1

1. OBJECTIVES

1.1 Primary Objective

1.1.1 Safety Lead-in Trial Components:
To determine whether olaparib plus tremelimumab has adequate safety in the study population.

1.1.2 Phase II Trial Component:
To compare the progression-free survival (PFS) duration of olaparib monotherapy versus olaparib plus tremelimumab in women with recurrent, platinum sensitive ovarian, primary peritoneal, or fallopian tube cancer.

1.2 Secondary Objectives

1.2.1 To compare the overall response rate (ORR) by RECIST 1.1 in women with recurrent, platinum sensitive ovarian, primary peritoneal or fallopian tube cancer treated with either olaparib monotherapy or olaparib plus tremelimumab.

1.2.2 To compare the overall survival (OS) of women with recurrent, platinum sensitive ovarian, primary peritoneal or fallopian tube cancer treated with either olaparib monotherapy or olaparib plus tremelimumab.

1.3 Exploratory Objectives (27-AUG-2021)

Note: The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens.

1.3.1 To explore whether conditions in the tumor microenvironment (as measured by gene expression signature in archived tumor samples) identify patients that benefit from combined olaparib and tremelimumab immunotherapy.

1.3.2 To explore whether mutations in BRCA1/2 genes or other evidence of homologous repair deficiency (HRD+) is prognostic and/or predictive of response to combined olaparib and tremelimumab immunotherapy.

1.3.3 To explore associations between PD1 expression in the tumor microenvironment and (1) outcome and (2) changes in circulating leukocyte populations.

1.3.4 To explore the correlation between tumor mutational burden and response to olaparib and tremelimumab immunotherapy.

1.3.5 To explore the impact of olaparib and tremelimumab versus olaparib monotherapy on circulating leukocyte subsets via exploration of the immunomodulatory effects of PARP inhibition and the added impact of CTLA4 blockade in this patient population.

1.3.6 To explore cytokine/chemokine levels using a multiplex immunoassay (Olink) and correlate these levels with clinical endpoints.

1.3.7 To use cell-free DNA to assess BRCA mutation status as a mechanism of acquired resistance to prior PARP inhibition and to compare with treatment efficacy.

2. BACKGROUND

2.1 Platinum-sensitive ovarian cancer

In the United States, ovarian cancer has the highest mortality rate of any gynecologic malignancy (Coleman, 2013). Although platinum-based frontline chemotherapy is effective, a majority of patients experience disease recurrence. Platinum-sensitive recurrence is defined as disease recurring at least 6 months after the last receipt of platinum-based chemotherapy. For these patients, additional platinum-based therapy is recommended, however repeated courses of platinum-based regimens result in cumulative toxicity and increased risks of allergic reaction to platinum. There is a need for alternatives to platinum-based chemotherapy for women with recurrent platinum-sensitive ovarian cancer.

2.2 PARP inhibitors in ovarian cancer

PARP inhibitors are a class of drugs that have demonstrated significant activity in the treatment of recurrent ovarian cancer in recent clinical trials (Ledermann, 2012; Liu, 2014; Swisher, 2017). While initial studies focused on women with germline mutations in BRCA1 or BRCA2 genes, emerging evidence indicates that PARP inhibitors have therapeutic benefit beyond this cohort of patients with hereditary cancer syndromes (Fong, 2010). When olaparib was evaluated for the treatment of recurrent ovarian cancer in a phase II trial that was not limited to women with germline BRCA mutations, objective responses were seen in 41% with a germline BRCA mutation and 24% without an identified mutation (Gemon, 2011). Recent studies of other PARP inhibitors have also demonstrated benefit in women without germline BRCA mutations. In a phase II trial of rucaparib in women with relapsed, platinum-sensitive high grade ovarian cancer, median progression-free survival among patients with wild type BRCA was 5.7 months (Swisher, 2017). Similar survival rates were demonstrated in a phase II study of olaparib versus the combination of olaparib and cediranib in a BRCAwt subset of women (Liu, 2014). Notably, the benefit of combined olaparib and cediranib was most pronounced among women with BRCAwt tumors, indicating that combinatorial regimens may enhance the efficacy of PARP-inhibitors particularly among BRCAwt patients (Liu, 2014).

Olaparib has also been evaluated as a maintenance regimen in women with platinum-sensitive recurrent high grade serous ovarian cancer (Ledermann, 2012; Mirza, 2016; Lheureux, 2017). Results were not stratified by BRCA status and demonstrated a longer disease-free interval in the treatment group (8.4 vs 4.8 months; HR = 0.35, P<0.001) (Ledermann, 2012). With a recent phase III trial demonstrating a marked increase in progression-free survival with the addition of olaparib maintenance to frontline platinum-based chemotherapy among women with BRCA-deficient ovarian cancer, PARP inhibition has been incorporated into the standard of care for this patient cohort (Moore, 2018). Importantly, the use of olaparib does not appear to limit the efficacy of subsequent chemotherapeutic regimens (Ang, 2013).

<u>Olaparib</u>

Olaparib (AZD2281, KU-0059436) is a potent inhibitor of polyadenosine 5'diphosphoribose polymerase (PARP) developed as a monotherapy as well as for combination with chemotherapy, ionizing radiation and other anti-cancer agents including novel agents and immunotherapy. The capsule formulation of olaparib was approved in December 2014 by the United States (US) Food and Drug Administration

(FDA) as monotherapy in patients with deleterious or suspected deleterious germline *BRCA* mutated (as detected by an FDA-approved test) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Recently, this approval was extended to maintenance therapy following front-line chemotherapy based on the results of the SOLO-1 trial (Moore, 2018).

Clinical PK
The recommended tablet monotherapy dose is 300 mg twice daily (bd). Following a single 300 mg po tablet dose the mean apparent oral plasma clearance was approximately 7.4 L/h (Sd 3.9 L/h). Olaparib exhibited a mean volume of distribution of 158 L (Sd 136 L), indicating distribution into the tissues. The plasma protein binding in vitro was moderate and showed evidence of concentration dependence (% unbound was 81.9% at 10 μg/ml).

Clinical Safety Summary
As of 15 December 2016, approximately 6558 patients are estimated to have received olaparib in the clinical program including AstraZeneca-sponsored studies (3923 patients), a Managed Access Program (MAP; 676 patients), investigator-sponsored studies and collaborative group studies (1959 patients). Toxicities considered to be associated with administration of olaparib include hematological effects (anemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, mean corpuscular volume [MCV] elevation), decreased appetite, nausea and vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash and dermatitis. In a small number of patients, pneumonitis, myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) and new primary malignancies have been reported.

2.3 CTLA4 immune checkpoint inhibition and ovarian cancer

Immunotherapy has been identified as a breakthrough in cancer treatment, leading to new treatment paradigms in multiple tumor types (Pardoll, 2012; McNutt, 2013). Despite evidence that ovarian cancer is a target for immunomodulatory regimens, there are currently no approved immune therapies for ovarian cancer (Zhang, 2003). Multiple studies have demonstrated that tumor-infiltrating T cells are associated with improved prognosis for women with ovarian cancer, however the functional capacity of tumor-specific lymphocytes is restricted in the immunosuppressive ovarian tumor microenvironment (Hwang, 2009; Lavoue, 2013). One mechanism for T cell inhibition in ovarian cancers results from signaling through co-inhibitory receptors, restricting lymphocyte activation and promoting functional exhaustion (Topalian, 2015; Flies, 2016). Antibody-mediated blockade of these signaling pathways has achieved durable treatment benefit in melanoma and other solid tumors (Ott, 2013). To date, however, ovarian tumors have been relatively resistant to immune checkpoint inhibition (Hodi, 2003).

CTLA-4 blockade is thought to maintain T cell activation and promote the establishment of tumor-specific immune responses. CTLA-4 inhibition was the first immune checkpoint blockade strategy to be approved by the FDA in 2011 based on phase III trials in melanoma (Hodi, 2010). The observed disease stabilization and durable remissions

among patients who respond to CTLA-4 antibody therapy has significantly improved outcomes for this disease and other solid tumors (Sangro, 2013; Camacho, 2009; Ralph, 2010; Millward, 2013). Women with ovarian cancer enrolled in early clinical trials of CTLA-4 antibody therapy had evidence of tumor marker reduction, but did not demonstrate the clinical benefit observed in subjects with melanoma (Hodi, 2003). Here we present a strategy to use PARP inhibitors to sensitize ovarian tumors to CTLA-4 immune checkpoint inhibition.

2.3.1 Tremelimumab

2.3.1.1 Mechanism of Action

Tremelimumab is a human IgG2 mAb that is directed against cytotoxic T lymphocyte-associated molecule (CTLA)-4 (CD152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (Tarhini and Kirkwood, 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

2.3.1.2 Clinical PK

Clinically, tremelimumab exhibits linear (dose-proportional) PK following IV infusion. The estimate of CL, volume of distribution at steady state (V_{ss}), and terminal-phase half-life is 0.132 mL/h/kg, 81.2 mL/kg and 22.1 days, respectively. These values are consistent with those of natural IgG2.

2.3.1.3 Clinical safety summary

As of July 12, 2017, approximately 1617 patients have been exposed to one or more doses of tremelimumab monotherapy across company-sponsored studies, legacy studies, and externally sponsored studies. **Identified risks of tremelimumab monotherapy** based on the DETERMINE study include diarrhea (47.1%), colitis/enterocolitis (9.2%/0.5%), intestinal perforation (0.8%), hypophysitis (1.1%), hypothyroidism (3.4%), hyperthyroidism (1.1%), adrenal insufficiency (1.3%), rash (20.8%), and pruritus (27.1%); in addition, increased amylase (2.1%) and lipase (4.7%) are identified laboratory abnormalities

2.3.1.4 AESIs and irAEs

Adverse events of special interest (AESIs) and immune-related adverse events (irAEs) associated with tremelimumab include hepatitis, including autoimmune hepatitis, and increased serum ALT and AST; pancreatitis; respiratory tract events, including pneumonitis and interstitial lung disease; nervous system events, including encephalitis, peripheral motor and sensory neuropathies, proximal muscle weakness, and Guillian-Barre; cytopenias including thrombocytopenia, anemia and neutropenia; renal failure, acute kidney injury, nephritis and nephrotic syndrome, including autoimmune nephritis,

electrolyte abnormalities; autoimmune diseases including autoimmune arthritis, Sjogren's syndrome, giant cell temporal arteritis and ulcerative colitis; and hyperglycemia, including diabetes mellitus.

The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by following current guidelines for the management of immune-mediated toxicities. A detailed summary of tremelimumab monotherapy AE data can be found in the current version of the Tremelimumab Investigator's Brochure (2017).

2.4 Rationale for combining olaparib with CTLA4 immune checkpoint inhibition

2.4.1 ***Preclinical studies****:* Evidence that PARP inhibition synergizes therapeutically with CTLA-4 blockade comes from preclinical work in our lab (Higuchi, 2015). These studies used an immune competent BRCA1m murine ovarian cancer model, which demonstrated selective sensitivity to PARP-inhibition *in vitro* and evidence of *in vivo* tumor cytotoxicity. Despite confirmed activity *in vivo*, monotherapy with the PARP-inhibitor did not improve overall survival, even at doses of 40mg/kg which is four-fold higher than the recommended treatment doses for patients (veliparib, olaparib 400mg BID). In contrast, when a PARP-inhibitor was administered together with a single dose of CTLA-4 antibody, all mice survived longer than controls and 80% demonstrated durable tumor-free survival ($p<0.001$ compared with either agent alone). In these experiments, combined therapy with the PARP-inhibitor and the CTLA-4 antibody successfully induced protective immune memory.

We attribute the observed synergy of PARP inhibition and CTLA-4 blockade in ovarian cancer to dynamic interactions with conditions in the ovarian tumor environment (Higuchi, 2015; Klemm, 2015; Swartz, 2012; Quail, 2013; Su, 2016). PARP inhibition together with CTLA-4 blockade induces a marked increase in interferon-gamma production by tumor-associated CD4 and CD8 T cells that is sustained long after completion of therapy (Higuchi, 2015). Interferon-gamma enhances the cytotoxic effects of PARP-inhibition *in vitro* and is required for a survival benefit *in vivo* (Higuchi, 2015; Warrener, 2012). This is in keeping with evidence that interferon signaling directs both cell-intrinsic and cell-extrinsic determinants of response to cytotoxic agents (Minn, 2015, 2016). We interpret these data as evidence of a positive feedback loop in which PARP inhibitor-induced tumor cell death results in the recruitment of T cells to the tumor environment. Released from CTLA4 inhibition, these T cells produce high levels of interferon-gamma, which engages additional cytotoxic effects to promote tumor clearance. These results indicate that the CTLA4 immune checkpoint may be an important therapeutic target in the ovarian tumor microenvironment.

2.4.2 ***Clinical studies***: Based on the selective therapeutic synergy of CTLA-4 blockade and PARP inhibition in our preclinical studies, we launched INST 1419: A phase I/II study of the combination of olaparib and tremelimumab in BRCA1 and BRCA2 mutation carriers with recurrent ovarian cancer (NCT02571725, S. Adams, Principal Investigator). Women with a confirmed germline BRCA1 or BRCA2 mutation and recurrent ovarian, tubal or peritoneal cancer are eligible for this trial. The study has no restrictions on the

number or type of prior treatment, including prior PARP inhibitor or immune therapy, and women with both platinum-sensitive and platinum-resistant disease are eligible. As a result, subjects enrolled to date comprise a heavily pre-treated cohort with an average of 3.2 prior chemotherapy regimens (range 1-7). Olaparib is administered at 300mg by mouth twice daily, and tremelimumab is dosed at 10mg/kg every 4 weeks for 4 to 6 cycles followed by maintenance dosing every 12 weeks.

The phase I portion of this study revealed no evidence of new toxicity in subjects receiving the combination of olaparib and tremelimumab beyond what has been reported with monotherapy regimens. The most common grade 3 adverse event has been colitis or gastroenteritis (17% of patients treated to date). Notably, grade 3 colitis or gastritis was significantly associated with a history of prior gastrointestinal surgery (Harris, 2018). Additional grade 3 toxicity observed among 36 patients receiving at least one cycle of treatment includes anemia (17%), electrolyte abnormalities (14%), fatigue (14%), hypophysitis or adrenal insufficiency (10%), rash (8%), myalgias (8%), muscle weakness (8%), headache (8%), fever (8%), leukocytosis (8%), and thrombocytopenia (8%).

The primary endpoint for the phase II portion of the trial is overall response rate based on modified world health organization immune related response criteria (mWHO irRC) (Wolchock, 2009). Among the first 13 patients who completed three cycles of treatment, clinical responses were observed in 10 (4 complete responses, 6 partial responses, ORR 77%). This compares favorably with historic response rates of 31% to olaparib monotherapy (Matulonis, 2016).

Evidence that the clinical response to olaparib and tremelimumab is not exclusively due to the sensitivity of BRCAm cancers to PARP inhibition is demonstrated by the significant reduction in tumor burden observed in a subject whose tumor was refractory to prior olaparib monotherapy. This patient previously received single-agent olaparib, but stopped treatment after 4 cycles when a CT scan demonstrated tumor progression. Following initiation of treatment on NCT02571725 with olaparib and tremelimumab in March 2016, she had a partial response by cycle 3 (63% reduction in tumor burden by mWHO). Due to immune-related toxicity, tremelimumab was discontinued after cycle 5, however she had an additional 50% reduction in tumor burden from cycle 6 to cycle 9 while receiving ongoing olaparib monotherapy on study. These results indicate that the addition of tremelimumab to olaparib had benefit beyond olaparib monotherapy in this patient.

While our current phase II single-arm study of olaparib and tremelimumab is limited to women with germline BRCA1/2 mutations, evidence that PARP inhibitors are active in the treatment of BRCAwt tumors indicates that a majority of women with ovarian cancer could benefit from the combination of PARP inhibition and CTLA4 blockade. With evidence that this regimen has significant clinical activity in heavily pre-treated women with ovarian cancer, we propose to test whether combined olaparib and tremelimumab will improve progression free survival for women with recurrent disease compared with olaparib monotherapy. This presents an opportunity to adapt the recent paradigm shift in cancer treatment to achieve lasting benefit for women with ovarian cancer by combining immune therapy with targeted cytotoxic agents.

2.5 Rationale for the control arm

Recent trials of olaparib restricted to women with platinum-sensitive recurrent disease have reported response rates of 63% among gBRCAm patients and as high as 32% in BRCAwt patients (Liu, 2014). In light of the significant activity of olaparib monotherapy and the fact that this regimen is well-tolerated, we have chosen to use olaparib as the control regimen to determine whether the addition of tremelimumab can significantly improve patient outcomes beyond what has been achieved with olaparib monotherapy.

2.6 Rationale for Exploratory Biomarker Testing in Collaboration with CIMAC (27-AUG-2021)

Note: The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens.

2.6.1 *Gene Expression Signatures*

We hypothesize that conditions in the tumor environment measured by gene expression signatures in archived tumor samples will identify patients who will benefit from combined therapy with olaparib and tremelimumab.

IFNgamma: With evidence that IFNgamma is required for the treatment response to PARP inhibition and CTLA4ab in ovarian cancer models, will predict that an interferon gene expression signature will be linked with response to olaparib + tremelimumab (Weichselbaum, 2008). This analysis will follow the guidelines outlined by Pepe, et. al. for a Phase I/II biomarker trial, with the objective of 1) identifying and prioritizing potential biomarkers that correlate with survival; and 2) estimating the true positive, and false positive rate of these biomarkers. We will compare the TSP classifier based on the IRDS gene expression score in archived tumor from these subjects to determine the sensitivity of this score in predicting treatment outcomes. We will estimate the sensitivity and specificity of the TSP classifier and the receiver operating curve for the IRDS score.

Autophagy: An autophagy-linked gene signature has been predictive of response to CTLA4ab but not PD1ab in melanoma (Shulka, 2018). With pre-clinical data demonstrating selective synergy of PARPi and CTLA4 blockade (Higuchi, 2015), we hypothesize that this autophagy-linked signature will also predict response to olaparib + tremelimumab.

VEGF: A VEGFs signature has been linked with BRCAm status and T cell recruitment to tumor sites (Yin, 2016). With evidence that BRCAm status modulates tumor angiogenesis, with downstream effects on T cell infiltration, we hypothesize that VEGFs expression will correlate with response to olaparib + tremelimumab.

NFkB pathway activation: We and others have demonstrated that PARP inhibitors suppress NFkB activation. We hypothesize that this effect modulates IFNg signaling pathways to promote immunogenic cell death in tumors, contributing to the therapeutic

synergy of PARP inhibition and CTLA4 blockade. We hypothesize that an NFkB activation signature will be predictive of response to olaparib + tremelimumab.

2.6.2 *Homologous Repair Deficiency (HRD) Status*

Based on evidence that ovarian cancers associated with mutations in BRCA1/2 genes or other evidence of homologous repair deficiency (HRD+) have a high neoantigen load, and that HRD+ tumors are more responsive to PARP-inhibition, we hypothesize that HRD status is not only prognostic, but also predictive for combined olaparib and tremelimumab treatment. Whole exome sequencing (WES) will be used to confirm BRCAm status and to identify sBRCAm tumors.

2.6.3 *Tumor Infiltrating Leukocytes*

Tumor infiltrating lymphocytes have been associated with a marked survival advantage in ovarian cancer (Zhang 2003, Hwang 2009). Subsequent work in ovarian cancer and other tumor types have provided additional evidence that leukocyte populations in the tumor microenvironment can identify patients likely to benefit from immune therapy. We hypothesize that high numbers of intraepithelial CD8 T cells, and low numbers of FoxP3+CD4 T cells will be associated with better overall survival and with clinical response to olaparib + tremelimumab. Additional exploratory assays will compare tumor infiltration by additional leukocyte subsets including tumor associated macrophages and dendritic cells. PDL1 expression on tumor cells, but not on myeloid cells in the TME, has been associated with outcomes in ovarian tumor models. We plan to compare PDL1 expression in the TME with treatment outcomes and changes in circulating leukocyte populations.

2.6.4 *Tumor Mutational Burden*

Tumor mutational burden has been associated with response to immune checkpoint inhibition and CTLA4 blockade in particular. BRCAm tumors and HRD ovarian cancers have been shown to have high TMB. We hypothesize that TMB will correlate with response to olaparib + tremelimumab. TMB in cell-free DNA will be used to assess for changes in response to treatment and an association with clinical outcome. Tumor infiltrating lymphocytes are expected to be more prevalent in tumors with high TMB scores.

2.6.5 *Circulating Leukocyte Subsets*

Response to immune checkpoint blockade has been linked with changes in circulating lymphocyte subsets. In particular, an increase in PD1+Ki67+ “reactivated” T cells is linked with response to immune therapy in patients with melanoma. In addition, multi-parameter analyses of circulating leukocytes has demonstrated that both myeloid and lymphoid subset remodeling is associated with immunotherapeutic efficacy in preclinical models (Gubin, 2018). We hypothesize that dynamic changes in circulating leukocyte subsets will predict response to olaparib + tremelimumab. We will also compare the impact of olaparib + tremelimumab with olaparib monotherapy on circulating leukocyte subsets to identify immunomodulatory effects of PARP inhibition and the added impact of CTLA4 blockade in this patient population. Multiplex IHC will be used to provide information about lymphocytes in the TME prior to treatment for comparison with

circulating subsets at baseline.

2.6.6 *Cell-Free DNA*

Mechanisms of drug resistance: Reversion of BRCA mutations has been identified as a mechanism of acquired resistance to PARP inhibitors. This can be measured in cfDNA, and has been associated with response to treatment in ovarian cancer (Lin, 2019). In our single-arm trial of olaparib + tremelimumab, we have observed a significant difference in response based on prior PARP inhibitor use. Notably, a patient with primary resistance to olaparib did have a clinical response to olaparib + tremelimumab. In contrast, patients who developed resistance following long-term treatment with a PARP inhibitor have not responded to olaparib + tremelimumab. Based on these observations, we hypothesize that specific mechanisms of resistance to prior PARP inhibitor therapy can determine a patient's response to the combination of olaparib + tremelimumab. We propose to use cfDNA to assess BRCAm status as a mechanism of acquired resistance to prior PARP inhibition, and to compare this with treatment efficacy.

Tumor mutational burden: TMB has been successfully assessed using cfDNA in other tumor types (Anagnostou, 2019). Changes in TMB are predictive of response to immune checkpoint blockade in patients with lung cancer. We propose to compare TMB during treatment as a biomarker of response. We will additionally compare baseline and on-treatment TMB with an assessment of TMB in archived tumor tissue to compare the predictive utility of these assays.

3. ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Submission of tumor tissue is required for all patients. Investigators should check with their site's pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See Section 10 for details.)

3.1.1 Patients must have platinum-sensitive, recurrent high-grade serous or high-grade endometrioid (grade 3) ovarian, primary peritoneal, or fallopian tube cancer.

Patients with other histologies are also eligible, provided that the patient has a known deleterious germline or somatic BRCA1 or BRCA2 mutation identified through testing at a clinical laboratory.
Submission of pathology reports and BRCA testing reports (germline and/or somatic) is required for all patients.

3.1.1.1 Platinum-sensitive disease defined as no clinical or radiographic evidence of disease recurrence for > 6 months (or 182 days) after last receipt of platinum-based therapy. The date should be calculated from the last administered dose of platinum therapy.

3.1.1.2 Patients must have had response (complete or partial) to their prior line of platinum therapy and cannot have had progression through prior platinum-based therapy.

3.1.2 Patients must have RECIST 1.1 measurable disease. Patients with biochemical recurrence based on CA125 levels alone are not eligible.

3.1.3 Prior therapy:

- Prior chemotherapy must have included a first-line platinum-based regimen with or without consolidation chemotherapy.
- Prior bevacizumab therapy as a component of frontline or recurrent treatment is permitted.
- Patients may have received an unlimited number of platinum-based therapies in the recurrent setting.
- Patients may have received up to one non-platinum-based line of therapy in the recurrent setting. Prior hormonal therapy will not be counted as this non-platinum-based line.
- Prior treatment with a PARP inhibitor:
  - Patients may not have had a prior PARP inhibitor in the recurrent setting.
  - Prior use of a PARP inhibitor in the upfront maintenance setting is allowed for women with a confirmed BRCA1 or BRCA2 germline or somatic mutation.
  - Women who received a PARP inhibitor for maintenance therapy in the frontline setting must have received at least one other chemotherapy regimen for recurrence prior to enrolling on this trial.
  - Patients who demonstrated disease progression while on a PARP inhibitor are excluded.
- Prior hormonal therapy for ovarian, primary peritoneal, or fallopian tube cancer is acceptable.

3.1.4 Age ≥ 18.

3.1.5 Body weight >30 kg.

3.1.6 ECOG Performance Status of 0, 1 or 2 (see Appendix II).

3.1.7 Adequate hematologic function within 14 days prior to enrollment defined as follows:

- ANC ≥ 1,500/mcl
- Platelets ≥ 100,000/mcl
- Hemoglobin ≥ 10 g/dL
  - *Note: blood transfusions are not permitted within 28 days prior to enrollment (see section 3.2.17).*

3.1.8 Adequate renal function within 14 days prior to enrollment defined as follows:

- Creatinine ≤ 1.5 x institutional/laboratory upper limit of normal (ULN)

3.1.9 Adequate hepatic function within 14 days prior to enrollment defined as follows:

- Total bilirubin ≤ 1.5 x institutional ULN.
- AST and ALT ≤ 3 times institutional ULN.

3.1.10 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction and TSH within normal limits. Thyroid replacement therapy is permitted to achieve a TSH within normal limits.

3.1.11 Patients must be able to swallow and retain oral medications and not have gastrointestinal illnesses that would preclude absorption of olaparib as judged by the treating physician.

3.1.12 Evidence of post-menopausal status or negative urinary or serum pregnancy test for pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution/laboratory or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

- Administration of study drugs (olaparib, tremelimumab) may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of childbearing potential (WOCBP) must agree to use two (2) highly effective forms of contraception from up to 14 days prior to enrollment (for oral contraceptives), during treatment, and for 6 months after the last dose of study medication.

3.1.13 Life expectancy ≥12 weeks.

3.1.14 Patients with brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression. Imaging studies must have been completed no later than 14 days prior to enrollment. In addition, patients must have been successfully

weaned off steroid support. Patients should not have received steroids for the treatment of brain metastases within 14 days prior to enrollment.

3.1.15 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.16 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Active infection requiring antibiotic therapy (except for uncomplicated urinary tract infections), including tuberculosis.

3.2.2 Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; and cirrhosis. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.2.3 Hormonal therapy directed at treatment for the cancer must be discontinued at least 28 days prior to enrollment. Hormone replacement therapy for symptom management is permitted.

3.2.4 Any other therapy directed at treating the cancer including chemotherapy, biologic/targeted agents, and immunologic agents, unless discontinued at least 28 days prior to enrollment.

3.2.5 Any radiation therapy unless discontinued at least 28 days prior to enrollment.

3.2.6 Major surgical procedure within 28 days prior to enrollment.

3.2.7 Current or prior use of immunosuppressive medication within 14 days before enrollment. The following are exceptions to this criterion:

a. Intranasal, inhaled, topical steroids, or local steroid injections (i.e. intra-articular injection)
b. Systemic corticosteroids at physiologic doses not to exceed 10mg/day of prednisone or its equivalent
c. Steroids as premedication for hypersensitivity reactions (i.e. CT scan contrast allergy premedication)

3.2.8 Patients with active autoimmune disease that has required systemic treatment in the past 2 years (*i.e.*, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (*e.g.*, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

- Patients with autoimmune disease (e.g., psoriasis, extensive atopic dermatitis, severe asthma, IBD, M.S., uveitis, vasculitis) requiring concurrent use of any systemic immunosuppressants or steroids are excluded from the study. Patients with vitiligo, mild, intermittent asthma requiring only occasional beta-agonist inhaler use, or mild localized eczema are eligible.
- Any patient with an allo-transplant of any kind is excluded, including xenograft heart valve.
- Chronic use of immune-suppressive drugs (i.e. systemic corticosteroids) for the management of cancer or non-cancer related illnesses (i.e. COPD).

***Note**: ongoing steroid use for the management of brain metastases is not permitted per section 3.1.14.*

3.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib or tremelimumab.

3.2.10 Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

3.2.11 Subjects must not have evidence of bowel obstruction on imaging or symptoms consistent with a bowel obstruction. Additional workup to rule this out is not required.

3.2.12 Known potent CYP3A4 inhibitors or inducers must be discontinued prior to starting treatment. (See Section 5.2.2.)

3.2.13 Symptoms associated with toxicities (> Common Terminology Criteria for Adverse Event [CTCAE v 5.] grade 2) caused by prior cancer therapy, excluding alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Chair.

3.2.14 Patients who are receiving any other investigational agent.

3.2.15 Resting ECG with QTc>470msec on two or more time points within a 24-hour period, or a family history of long QT syndrome. If an initial ECG is within normal limits, a repeat ECG is not required.

3.2.16 Patients who have previously received anti-CTLA-4 antibody therapy.

3.2.17 Blood transfusions are not permitted within 28 days prior to study enrollment.

3.2.18 Patients must not have signs or symptoms suggestive of myelodysplastic syndrome or acute myeloid leukemia.

3.2.19 Pregnant or lactating patients (see Section 3.1.12) for information of contraception and pregnancy).

3.2.20 Receipt of live attenuated vaccines within 30 days of enrollment. Note: patients, if enrolled, should not receive live vaccines while receiving study treatment and up to 30 days after the last treatment dose. Inactivated vaccines are permitted.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 PRE-TREATMENT ASSESSMENTS

Assessments **See Section 10.4.1 for Mandatory Biospecimen Submission Information.**	**Prior to Registration (calendar days)**	**Prior to Treatment (calendar days) (Cycle 1, Day 1)**
History and Physical	≤ 14 days	≤ 14 days
Concomitant Medications	≤ 14 days	≤ 14 days
Vital Signs (weight required)	≤ 14 days	≤ 14 days
Performance Status	≤ 14 days	≤ 14 days
Toxicity Assessment	≤ 14 days	≤ 14 days
CBC/Differential/Platelets	≤ 14 days	≤ 14 days
Chemistries (BUN, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)	≤ 14 days	≤ 14 days
Thyroid stimulating hormone [TSH], with reflex T4 (T4 can be omitted if TSH normal)	≤ 28 days	
CA-125	≤ 28 days	≤ 28 days
Electrocardiogram (ECG)	≤ 28 days	≤ 28 days
Pregnancy test (for women of childbearing potential) Urine or serum testing is permitted	≤ 14 days	≤ 72 hours
Germline and/or somatic BRCA mutation testing	X	
Radiographic Tumor Measurement*	≤ 28 days	≤ 28 days

*Radiographic tumor measurements should be obtained via imaging of the chest, abdomen and pelvis to establish the location and extent of disease. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline (and subsequent assessments). Contrast CT is the preferred modality.

4.2 ASSESSMENTS DURING TREATMENT

Assessments	Prior to Each Cycle, Day 1 (after Cycle 1, Day 1)	Timed (Treatment Cycle Independent)
History and Physical	≤ 3 days	
Concomitant Medications	X	
Vital Signs, weight required. (See Sec 5.1.2 for additional monitoring *during* tremelimumab infusions)	X	
Performance Status	X	
Toxicity Assessment	X	
Pregnancy test (for women of childbearing potential) Urine or serum testing is permitted	≤ 7 days	As clinically indicated
CBC/Differential/Platelets	≤ 3 days	
Chemistries (BUN, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)	≤ 3 days	
Thyroid stimulating hormone [TSH]), with reflex T4 (T4 can be omitted if TSH normal) **(24-APR-2020)** NOTE: FOR PATIENTS ENROLLED IN ARM 2	≤ 3 days	
CA125	≤ 3 days	
Radiographic Tumor Measurement		X[1]
Review of pill diary to assess treatment compliance	X	

[1] First assessment scan at 12 weeks (+/- 7 days), followed by every 8 weeks (+/- 7 days) for the first 12 months; then every 12 weeks (+/- 7 days) thereafter. All scan dates calculated from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule). Radiographic tumor measurements are obtained until disease progression is confirmed; at the investigator's discretion, they can be repeated any other time if clinically indicated based on symptoms or physical signs suggestive of new or progressive disease. A tool is provided to calculate dates of re-imaging. Utilize **same** imaging modality of abdomen, pelvis and chest (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. PET CT should not be used.

4.3 ASSESSMENTS IN FOLLOW UP

Assessments	**Timed**
Vital Status	1
Physical exam and labs, including CBC, Chemistries with LFTs and TSH (for patients on Arm 2)	**2**
Toxicity Assessment	3
Radiographic tumor measurement	4

1 Every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected for the 5-year follow-up period or until study termination, whichever occurs first.

2 **Monthly for 3 months after discontinuation of tremelimumab**.

3 Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For reporting of delayed toxicity, see Section 7.

4 In the case that protocol-directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under Assessments During Treatment (until disease progression documented by RECIST 1.1 or until patient initiates a subsequent cancer therapy).

Definition of Disease Assessments

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

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Treatment Plan

Protocol treatment should begin within 7 days of registration.

ARM 1
Olaparib 300 mg (2 x 150 mg tablets) PO twice daily until disease progression or adverse events prohibit further treatment

ARM 2
Olaparib 300 mg (2 x 150 mg tablets) PO twice daily until disease progression or adverse events prohibit further treatment

Tremelimumab 750 mg* IV over 60 minutes on Day 1 every 4 weeks for 4 cycles, then every 12 weeks for up to 2 years total.

***If a patient's weight falls to ≤ 30 kg,** the patient should receive weight-based dosing equivalent to 10 mg/kg of tremelimumab every 4 weeks. These adjustments apply to all cycles until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of tremelimumab, 750 mg every 4 weeks. **(24-APR-2020)**

ONE CYCLE = 4 weeks

Safety Lead-In Components: Two safety lead-in components are included in this study as detailed in section 13.6.2. If the study is deemed safe after each component following review by the Data Safety Monitoring Board, it will continue to accrue patients for assessment of the primary endpoints of the phase II trial. Importantly, all patients enrolled in the safety-lead in portions of the study will be included in the assessment of primary endpoints for this trial.

5.1.1 Administration of Olaparib

- For Arm 2, Olaparib will be started concomitantly with the first dose of Tremelimumab.
- Treatment will be administered on an outpatient basis.
- No premedications are required, however standard of care anti-emetics are permitted if clinically indicated.
- Pills should not be chewed, dissolved or crushed. Pills may be taken with food.
- Olaparib should be taken twice daily, with 12 hours between doses. Missed doses should be made up within 2 hours; otherwise they should be skipped.

5.1.2 Administration of Tremelimumab

Patients will have their blood pressure and pulse measured before, during, and after every infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 60 minute observation period post-infusion for cycle 1: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.

Tremelimumab is administered intravenously. Possible risks associated with IV administration of tremelimumab are infection, redness, swelling, pain, and induration at the administration site as well as infusion related reactions such as cytokine release syndrome, cytokine storm, anaphylactic and anaphylactoid reactions, and drug hypersensitivity. Management of infusion reactions will include the following:

- In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.

- If the infusion-related reaction is ≥Grade 3 in severity, study drug will be discontinued and managed as follows:
  - Immediate interruption of the infusion.
  - Immediate IV administration of diphenhydramine, ranitidine or famotidine, and corticosteroids for the treatment of cytokine release syndrome.
  - In patients suspected of demonstrating anaphylaxis or those with infusion reactions which do not respond to the above measures the use of IV/IM epinephrine should be considered.
  - If epinephrine is required for anaphylaxis or to control an infusion-related reaction, discontinue the infusion permanently. Patients experiencing ≥ Grade 3 infusion reaction should not receive any additional tremelimumab. If tremelimumab is discontinued due to toxicity, patients may continue treatment with olaparib monotherapy.

NOTE: As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if

necessary.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All standard of care anti-emetics, anti-diarrheals, and antibiotics are permitted if clinically indicated.

5.2.1.1 Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (e.g., acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed in Section 5.2.2.	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy to non-target lesions, etc])	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

5.2.2 Prohibited Therapies

Based on in vitro data and clinical exposure data olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of CYP enzyme activity. *In vitro* data have shown that the principal enzyme responsible for the formation of the 3 main metabolites of olaparib is CYP3A and *in vivo* data have shown that metabolism is an important route of clearance in humans. Consequently, to ensure patient safety the following potent inhibitors of CYP3A must not be used by any patient receiving olaparib. While this is not an exhaustive list, it covers the known potent inhibitors that have most often previously been reported to be associated with clinically significant drug interactions: ketoconazole, itraconazole, ritonavir, indinavir, saquinavir, telithromycin, clarithromycin and nelfinavir (wash-out period 1 week).

In addition, to avoid potential reductions in exposure due to drug interactions and, therefore, a potential reduction in efficacy, the following CYP3A4 inducers should be discontinued prior to starting study treatment: phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil and St John's Wort (Hypericum perforatum).

5.2.2.1 Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
Any concurrent anticancer drugs other than those under investigation in this study	Should not be given concomitantly while the patient is on study treatment.
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding *[10 mg/day]* of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	*Should not be given concomitantly, or used for premedication prior to tremelimumab infusions. The following are allowed exceptions:* • *Use of immunosuppressive medications for the management of IP-related AEs,* • *Use in patients with contrast allergies.* • *In addition, use of inhaled, topical, and intranasal corticosteroids is permitted.* *A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of* non-immunotherapy related events experienced by *the patient (e.g., chronic obstructive pulmonary disease, nausea, etc.).*
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Live attenuated vaccines	Should not be given through 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless approved by the Study Chair

5.2.3 Participation in Other Trials

Patients are not to participate in other therapeutic trials. However, trials that do not add experimental agents are allowed (e.g., imaging trials, quality of life).

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in Section 5.1 or until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment,
- Grade ≥3 infusion reaction.
- Unacceptable adverse event(s), as described in Section 6.
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patient non-compliance.
- Initiation of alternative anticancer therapy including another investigational agent
- Pregnancy or intent to become pregnant in women of child-bearing potential.

- All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study (See section 7.5.4).

- Termination of the study by the sponsor.
- The drug manufacturer can no longer provide the study agent.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6. TREATMENT MODIFICATIONS/MANAGEMENT

NCI Common Terminology Criteria for Adverse Events (CTCAE) v.5 is used for this study. Any toxicity observed during the course of the study should be managed by interruption of the dose of study treatment if deemed appropriate by the investigator. Repeat dose interruptions are allowed as required, for a maximum of 14 days on each occasion. If the interruption is any longer, the study team must be informed. Study treatment must be interrupted until the patient recovers completely or the toxicity reverts to the National Cancer Institute (NCI) CTCAE v.5 Grade 1 or less.

Dose Re-escalation is Not permitted.

6.1 Olaparib Dose Modifications

Olaparib starting dose	Dose reduction 1	Dose reduction 2
300 mg BID (2 x 150 mg tablets)	200 mg BID (2 x 100 mg tablets)	150 mg BID (1 150mg tablet)

6.1.1 Management of anemia (see table below):

- Adverse events of anemia CTCAE Grade 1 or 2 (Hb ≥8 g/dl) should be investigated taking into account previous history of anemia. Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be excluded.

- The first occurrence of anemia with Hb < 10 and > 8g/dl will be managed based on the investigator's judgement. Patients may receive transfusion or olaparib may be held for a maximum of 14 days.

- Repeat occurrence of anemia with Hb < 10 and > 8 requires a **1-level dose reduction to 200mg twice daily**.

- An additional **dose reduction to 150mg twice daily** may be required if anemia persists (see table below).

- If a patient has been treated for anemia with multiple blood transfusions without study treatment interruptions and becomes blood transfusion dependent as judged by investigator, study treatment should be interrupted for up to a maximum of 14 days to allow for bone marrow recovery. Study treatment should be restarted at a reduced dose.

Hemoglobin	**Action to be taken**
Hb < 10 *but* **≥ 8 g/dl (CTCAE Grade 2)**	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (e.g. transfusion) *or* interrupt dose for a maximum of 14 days. If repeat Hb**< 10** *but* **≥ 8 g/dl**, dose interrupt (for max of 14 days) until Hb ≥ 10 g/dl. Upon recovery, treatment may resume at the full dose. Alternately, a dose reduction to **200 mg twice daily** as a first step and to **150 mg twice daily** as a second step may be considered based on the assessment of the treating physician.
Hb < 8 g/dl (CTCAE Grade 3)	Give appropriate supportive treatment (e.g. transfusion) and investigate causality. Interrupt Olaparib for a maximum of 14 days until improved to Hb ≥ 10 g/dl. Upon recovery, dose reduce to **200 mg twice daily** is required. Additional dose reduction to **150 mg twice daily** is required in the case of repeat Hb decrease <10g/dl.

6.1.2 Management of neutropenia and leukopenia: (see table below)

- Study treatment can be restarted at the same dose if an AE of neutropenia or leukopenia has resolved to CTCAE Grade ≤ 1 (ANC ≥1,500 mcl). Growth factor support is *not* recommended for routine use with olaparib. If administered, it should be stopped at least 24h before restarting study drug (7 days for pegylated G-CSF). Any subsequent interruptions will require study treatment dose reductions.
- If toxicity reoccurs following re-challenge with olaparib, and if further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

- Treatment must be interrupted if any NCI-CTCAE Grade 3 or 4 AE occurs which the investigator considers to be related to administration of study treatment

Hematological Toxicity Dose Reductions for Olaparib		
ANC [1]	**Platelets**	**Action**
≥ 1,500/mcl	100,000/ mcl	None.
1000-1499/mcl	75,000-99,000/mcl	-*1st Occurrence:* Hold current dose until ANC ≥ 1,500/mcl and platelets ≥ 100,000/mcl. Do not replace missed doses. Restart next treatment at the full dose. -*2nd Occurrence*: Hold current dose until ANC ≥ 1,500/mcl and platelets ≥ 100,000/mcl. Do not replace missed doses. Restart next treatment at 200mg PO BID. -*3rd Occurrence:* Hold current dose until ANC ≥ 1,500/mcl and platelets ≥ 100,000/mcl. Do not replace missed doses. Restart next treatment at 150mg PO BID. -*4th Occurrence or a delay in treatment > 28 days*: **Discontinue olaparib**
500-999/mcl	50,000-74,000/mcl	-*1st Occurrence*: Hold current dose until ANC ≥ 1,500/mcl and platelets ≥ 100,000/mcl. Do not replace missed doses. Restart next treatment at 200mg PO BID. -*2nd Occurrence*: Hold current dose until ANC ≥ 1,500/mcl and platelets ≥ 100,000/mcl. Do not replace missed doses. Restart next treatment at 150 mg PO BID. -*3rd Occurrence or delay in treatment >14 days*: **Discontinue olaparib**
<500/mcl	<50,000/mcl	-*1st Occurrence*: Hold current dose until ANC ≥ 1,500/mcl and platelets ≥ 100,000/mcl. Restart next treatment at 200mg PO BID.

		-2nd Occurrence or delay in treatment >14 days: **Discontinue olaparib**
Note: G-CSF (Filgrastim) or other growth factors are *not* recommended for routine use with olaparib. If administered at the treating physician's discretion in the event of febrile neutropenia, G-CSF should be stopped at least 24h before restarting study drug.		

6.1.3 Management of prolonged hematological toxicities while on study treatment

If a patient develops prolonged hematological toxicity such as:

- ≥14 day interruption/delay in study treatment due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥14 day interruption/delay in study treatment due to CTCAE Grade 3 or worse neutropenia (ANC <1,000/mcl)
- ≥14 day interruption/delay in study treatment due to CTCAE Grade 3 or worse thrombocytopenia (Platelets <50,000/mcl)

Then weekly differential blood counts including reticulocytes, reticulocyte index and peripheral blood smear should be performed. If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice.

Development of a confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator. Olaparib treatment should be permanently discontinued if patient's diagnosis of MDS and or AML is confirmed.

6.1.4 Management of non-hematologic toxicities

Olaparib	
Non-hematological Toxicity Dose Reductions	
Event	**Action**
Nausea	
Grade 1	Administer anti-emetics
Grade 2	Administer anti-emetics. Hold treatment until toxicity resolves to ≤ Grade 1. No change from original starting dose

Grade 3	Administer anti-emetics. Hold treatment until toxicity resolves to ≤ Grade 1, then reduce to **200mg BID.** If patients experience ≥ Grade 2 nausea at the 200mg BID dose, further reduce dose to **150mg BID.**
Grade 4	**Discontinue therapy**
Fatigue	
Grade 1-2	None
Grade 3	Hold until resolved to ≤ Grade 2, then reduce **to 200mg BID.** If patients experience ≥ Grade 2 fatigue at the 200mg BID dose, further reduce dose to **150mg BID.**

6.1.5 Criteria to Resume Treatment with Olaparib

- Treatment may resume when the AE(s) resolve(s) to Grade 1 or baseline value.
- Olaparib may be restarted or continued even if a patient has experienced a SAE that requires permanent discontinuation of Tremelimumab (see Section 6.2 for guidelines regarding tremelimumab treatment).

6.1.6 Rules for Permanent Discontinuation of Olaparib:

- Any Grade 4 toxicity or Grade 3 toxicity attributed to olaparib that does not resolve to ≤ Grade 1 within 14 days after dose reduction.
- No patient should be re-started on olaparib if, in the judgment of the treating investigator, this would be clinically contraindicated (e.g., due to the severity of the antecedent toxicity, or to the patient's medical condition)
- Patients in Arm 2 who discontinue treatment with olaparib and who recover from olaparib-induced toxicity within 4 weeks of discontinuing treatment may be considered for ongoing treatment with Tremelimumab monotherapy after consultation with the Study PI.

6.2 Tremelimumab Dose Modifications

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of suspected immune related adverse events (irAE, see Section 6.2.1). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. Based on the mechanism of action of tremelimumab, no dose reductions will be permitted. Emergent immune-related toxicity will be managed with dose delays based on the severity of the event.

If new or worsening pulmonary symptoms (*e.g.*, dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 6.2.1) will be applied. The results of the full diagnostic workup (including high-

resolution computed tomography (HRCT), blood and sputum culture, hematological parameters, etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.

- SpO2
  - Saturation of peripheral oxygen (SpO2)

- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - ILD Markers (KL-6, SP-D) and β-D-glucan
    - Tumor markers: Particular tumor markers which are related to disease progression.

  - Additional Clinical chemistry: CRP, LDH

See Section 6.2.1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

Tremelimumab dose reductions are not permitted. Dose may be delayed or permanently discontinued as directed by Dosing Modification Table below. In case of doubt, the Investigator should consult with the Study PI.

6.2.1 Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune-Mediated Reactions

General Considerations
General guidelines for treatment modifications: Treatment modifications will be made to manage potential immune-related AEs (irAEs) based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drugs as described in the table below, **permanent discontinuation of tremelimumab is also required for the following conditions**:

General Considerations

- Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/study regimen
- Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing

AE Grade:

Grade 1 No dose modification

Grade 2 Hold tremelimumab dose until Grade 2 resolution to Grade ≤1.
If toxicity worsens, then treat as Grade 3 or Grade 4.
Tremelimumab can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper.
Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with tremelimumab on the following conditions:

1. The event stabilizes and is controlled.
2. The patient is clinically stable as per investigator or treating physician's clinical judgement.
3. Doses of prednisone of ≤10 mg/day or equivalent.

Grade 3 Depending on the individual toxicity, tremelimumab may be permanently discontinued. Please refer to guidelines below.

Grade 4 Permanently discontinue tremelimumab.

Note: There are some exceptions to permanent discontinuation of tremelimumab for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).

Note: tremelimumab should be permanently discontinued in Grade 2 or grade 3 events with high likelihood for morbidity or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines.

Note: subjects who discontinue tremelimumab due to irAE are eligible to continue treatment with olaparib monotherapy.

Toxicity Management – general guidelines

It is recommended that management of irAEs follows the guidelines presented in this table:

- Adverse events with an inflammatory or immune mediated mechanism could occur in all organs, not all of which are noted specifically in these guidelines.
- Patients should be thoroughly evaluated to rule out alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, **all such events should be managed as if they were immune related. General recommendations follow.**
    - Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.
    - For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
    - **Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if not currently noted in the guidelines** - Initiate high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2 when clinical suspicion is high or there has been clinical

General Considerations
confirmation. Consider, as necessary, discussing with the study chairs and promptly pursue specialist consultation. o **Steroid tapering should be gradual over at least 4 weeks**. If symptoms recur or worsen during tapering, increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). o If no improvement after steroids, consider more potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive). Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity or mortality – e.g., myocarditis, or other similar events even if not currently noted in the guidelines. o **With long-term steroid and other immunosuppressive use**, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])[a] − Discontinuation of tremelimumab is not mandated for Grade 3/4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of tremelimumab in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; irAE Immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Dose Delay Treatment modifications for Specific Immune-Mediated Reactions			
Adverse Events	**Grade of the Event** (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Pneumonitis/ Interstitial Lung Disease (ILD)	General Guidance: − Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. − Initial workup may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory workup, and high- resolution CT scan.		
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding tremelimumab as clinically appropriate pending workup for other etiologies.	**For Grade 1 (radiographic changes only):** − Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory workup and then as clinically indicated. − Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold tremelimumab until resolution to Grade ≤1. • If toxicity worsens, treat as Grade 3/4 • If toxicity improves to Grade ≤1, then the decision to retreat will be based upon treating physician's discretion and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** − Monitor symptoms daily and consider hospitalization. − Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). − Reimage as clinically indicated. − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day − If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start additional immunosuppressive agent such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment Consider pulmonary and infectious disease consult. − Consider, as necessary, discussing with study physician.
	Grade 3 or 4	Permanently discontinue	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):**

	(Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	tremelimumab.	− Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. − Hospitalize the patient and Supportive care − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days − Refer to General Guidelines for PCP prophylactics for prolonged use of steroids or immunesuppressant[a]
Diarrhea/ Colitis	**For Any Grade:** − Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. − Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. − Use analgesics carefully; they can mask symptoms of perforation and peritonitis.		
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** − Monitor closely for worsening symptoms. − Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool	Hold tremelimumab until resolution to Grade ≤1	**For Grade 2:** − Consider symptomatic treatment, including hydration, electrolyte replacement, dietary

	frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	• If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then tremelimumab can be resumed after completion of steroid taper.	changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3 to 5 days or worsens, obtain GI consult for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. Promptly start IV methylprednisolone 2 to 4 mg/kg/day. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. − Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. − Once the patient is improving, gradually taper steroids over ≥28 days and − Refer to General Guidelines for PCP prophylactics for prolonged use of steroids or immunesuppressant[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated,	<u>Grade 3</u> Permanently discontinue tremelimumab for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; tremelimumab can be resumed after completion of steroid taper. <u>Grade 4</u> Permanently discontinue tremelimumab	**For Grade 3 or 4:** − Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. − Monitor stool frequency and volume and maintain hydration. − Urgent GI consult and imaging and/or colonoscopy as appropriate. − If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days − Refer to General Guidelines for infection and PCP prophylactics for prolonged use of steroids or immunesuppressant[a]

	peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)		
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis.	General Guidance **For Any Grade:** − Monitor and evaluate liver function test: AST, ALT, ALP, and TB. − Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).		
	Grade 1 (Based on ULN regardless of baseline LFT) (AST or ALT >ULN and ≤3.0×ULN and/or TB > ULN and ≤1.5×ULN)	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** − Continue LFT monitoring per protocol.
	Grade 2 (Based on ULN regardless of baseline LFT) (AST or ALT >3.0×ULN and ≤5.0×ULN and/or TB >1.5×ULN and ≤3.0×ULN)	• Hold tremelimumab dose until resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline, resume tremelimumab after completion of steroid taper.	**For Grade 2:** − Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until improvement or resolution. − If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study physician. − If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start further immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** − Once the patient is improving, gradually taper steroids over ≥28 days

			and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Based on ULN regardless of baseline LFT) (Grade 3: AST or ALT >5.0×ULN and ≤20.0×ULN and/or TB >3.0×ULN and ≤10.0×ULN) (Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)	**For Grade 3:** For transaminases elevations ≤8 × ULN, or bilirubin elevations ≤5 × ULN: • Hold tremelimumab until resolution to Grade ≤1 or baseline • Resume tremelimumab if LFT elevations resolve to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • **Permanently discontinue** tremelimumab if no resolution within 14 days **Permanently discontinue** tremelimumab for: • Transaminases elevation >8 × ULN or bilirubin >5 × ULN. • Any case meeting Hy's law criteria (AST or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b] **For Grade 4:** Permanently discontinue tremelimumab.	**For Grade 3 or 4:** − Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. − If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** − Perform hepatology consult, abdominal workup, and imaging as appropriate. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

<table>
<tr><td rowspan="4">Nephritis or renal dysfunction (elevated serum creatinine)</td><td colspan="3">Any Grade:
− Consult with nephrologist.
− Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria).
− Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections).
− Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.</td></tr>
<tr><td>Grade 1 (Serum creatinine > 1 to 1.5 × baseline; > ULN to 1.5 × ULN)</td><td>No dose modifications.</td><td>For Grade 1:
− Monitor serum creatinine weekly and any accompanying symptoms.
• If creatinine returns to baseline, resume its regular monitoring per study protocol.
• If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4.
− Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.</td></tr>
<tr><td>Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)</td><td>Hold tremelimumab until resolution to Grade ≤1 or baseline.
• If toxicity worsens, then treat as Grade 3 or 4.
• If improvement to Grade ≤1 or baseline, resume tremelimumab after completion of steroid taper.</td><td>For Grade 2:
− Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
− Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted.
− Consult nephrologist and consider renal biopsy if clinically indicated.
− If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
− If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO/IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started.
− Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
–</td></tr>
<tr><td>Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to</td><td>Permanently discontinue tremelimumab.</td><td>For Grade 3 or 4:
− Carefully monitor serum creatinine on daily basis.
− Consult nephrologist and consider renal biopsy if clinically indicated.
− Promptly start prednisone 1 to 2 mg/kg/day</td></tr>
</table>

	6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)		PO or IV equivalent. − If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO/IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
Rash (excluding bullous skin formations)	**Any Grade** (refer to NCI CTCAE v5.0 for definition of severity/grade depending on type of skin rash) General Guidance **For Any Grade:** − Monitor for signs and symptoms of dermatitis (rash and pruritus). − IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND TREMELIMUMAB DISCONTINUED.**		
	Grade 1	No dose modifications.	**For Grade 1:** − Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold tremelimumab until resolution to Grade ≤1 or baseline. • If toxicity worsens, treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, resume tremelimumab after completion of steroid taper.	**For Grade 2:** − Obtain dermatology consult. − Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). − Consider moderate-strength topical steroid. − If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. − Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs
	Grade 3 or 4	**Grade 3:** Hold tremelimumab until resolution to Grade ≤1 or baseline. If no improvement within 30 days,	**For Grade 3 or 4:** − Consult dermatology. − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Consider hospitalization. − Monitor extent of rash [Rule of Nines]. − Consider skin biopsy (preferably more than 1)

		permanently discontinue tremelimumab. **Grade 4:** Permanently discontinue tremelimumab	as clinically feasible. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] − Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, Type 1 diabetes mellitus hypophysitis, hypothyroidism, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	General Guidance **For Any Grade:** − Consider consulting an endocrinologist for endocrine events. − Consider, as necessary, discussing with study physician. − Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c) − For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. − If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.	
	Grade 1	No dose modifications.	**For Grade 1 (including asymptomatic TSH elevation):** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). − If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold tremelimumab until patient is clinically stable. - If toxicity worsens, treat as Grade 3/4. - Tremelimumab can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged steroid replacement can resume tremelimumab on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including symptomatic endocrinopathy):** − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. − For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). − Isolated hypothyroidism may be treated with replacement therapy, without tremelimumab interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without tremelimumab interruption, and without corticosteroids. − Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] − For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated initiate hormone replacement as needed for management.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold tremelimumab until endocrinopathy symptom(s) are controlled.	**For Grade 3 or 4:** − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. − For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, promptly

		Tremelimumab can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged steroid replacement (e.g., adrenal insufficiency) can resume tremelimumab on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones).or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). − For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. − Isolated hypothyroidism may be treated with replacement therapy, without tremelimumab interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without tremelimumab interruption, and without corticosteroids. − Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a] .
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, **excluding** Myasthenia Gravis and Guillain-Barre	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity) General Guidance **For Any Grade:** − Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). − Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). − Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). − Perform symptomatic treatment with neurological consult as appropriate.		
	Grade 1	No dose modifications.	**For Grade 1:** − See "Any Grade" recommendations above.
	Grade 2	**For acute motor** neuropathies or neurotoxicity, hold tremelimumab dose until resolution to Grade ≤1.	**For Grade 2:** − Consider, as necessary, discussing with the study physician. − Obtain neurology consult. − Sensory neuropathy/neuropathic pain may be managed by appropriate medications

		For sensory neuropathy/neuropathic pain, consider holding tremelimumab dose until resolution to Grade ≤1. • If toxicity worsens, treat as Grade 3 or 4. Tremelimumab can be resumed after improvement to Grade ≤1 and after completion of steroid taper.	(e.g., gabapentin or duloxetine). − Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold tremelimumab dose until resolution to Grade ≤1. Permanently discontinue tremelimumab if Grade 3 irAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue tremelimumab.	**For Grade 3 or 4:** − Consider, as necessary, discussing with study physician. − Obtain neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). − Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as **Guillain-Barre and myasthenia gravis**)	**For Any Grade:** − The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. − Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, **it is essential to have a low threshold to obtain a neurological consult.** − Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.		

	− It is important to consider that the use of **steroids as the primary treatment of Guillain-Barre is not typically considered effective.** Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.		
	Grade 1	No dose modifications.	**For Grade 1:** − Consider, as necessary, discussing with the study physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	Hold tremelimumab until resolution to Grade ≤1. **Permanently discontinue** tremelimumab if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** − Consider, as necessary, discussing with the study physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV

			IG.
	Grade 3 or 4	**For Grade 3:** Hold tremelimumab dose until resolution to Grade ≤1. Permanently discontinue tremelimumab if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue tremelimumab.	**For Grade 3 or 4 (severe or life-threatening events):** − Consider, as necessary, discussing with study physician. − Recommend hospitalization. − Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Cardiac* Includes CHF, LV dysfunction, myocarditis, arrhythmia, conduction disorder and others**)**	**General Guidance for Any Grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the study physician. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (*e.g.*, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − Initial workup should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory workup as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.		

	− Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression, other medications, or infections) − **Discontinue tremelimumab permanently if biopsy-proven immune-mediated myocarditis regardless of grade**		
	Grade 1 cardiac AE (asymptomatic with laboratory (*e.g.*, BNP, EKG, troponin)	No dose modifications required unless clinical suspicion is high for myocarditis, in which case hold tremelimumab during diagnostic workup. - If myocarditis is excluded, resume after complete resolution to Grade 0. - If myocarditis is diagnosed, permanently discontinue tremelimumab	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory workup as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 cardiac AE or suspected myocarditis (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (*e.g.*, continuous IV therapy or mechanical hemodynamic support)	**For Grade 2:** - Hold tremelimumab - If toxicity rapidly improves to Grade 0 and no evidence for myocarditis, then the decision to reinitiate tremelimumab is based upon treating physician's clinical judgment and after completion of steroid taper. - If toxicity does not rapidly improve, permanently discontinue tremelimumab - If myocarditis is diagnosed, permanently discontinue tremelimumab regardless of timeline of recovery. - If Grade 3-4, permanently discontinue tremelimumab.	**For Grade 2-4:** − Monitor symptoms daily, hospitalize if myocarditis is suspected. − Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. − Supportive care (*e.g.*, oxygen). − If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

Myositis/Polymyositis ("Poly/myositis")	**For Any Grade:** − Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. − If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. − Consider, as necessary, discussing with the study physician. − Initial workup should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory workup as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).		
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** − Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. − Consider Neurology consult. − Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold tremelimumab dose until resolution to Grade ≤1. Permanently discontinue tremelimumab if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** − Monitor symptoms daily and consider hospitalization. − Obtain Neurology consult, and initiate evaluation. − Consider, as necessary, discussing with the study physician. − If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant − If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue

			additional workup and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**For Grade 3:** Hold tremelimumab dose until resolution to Grade ≤1. **Permanently discontinue** tremelimumab if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4: Permanently discontinue** study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; hospitalization recommended. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If not improvement within 3-5 days after IV methylprednisolone at 2 to 4 mg/kg/day, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow, MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; irAE Immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance **For Any Grade:** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).	
Grade 1 or 2	**For Grade 1:** The infusion rate of tremelimumab may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2:** The infusion rate of tremelimumab should be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2:** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue tremelimumab	**For Grade 3 or 4:** − Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**

Non–Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

6.2.2 Rules for permanent discontinuation of tremelimumab:

- Persistent grade 2 toxicity that does not resolve to grade 1 within 14 days with adequate corticosteroid treatment.

- Any symptomatic grade 3-4 toxicity, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for intravenous hydration for more than 24 hours, gastrointestinal hemorrhage, or gastrointestinal perforation.
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >8 times the upper limit of normal or total bilirubin >3 times the upper limit of normal.
  - Evidence of incipient Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations.
  - Motor or sensory neuropathy (interfering with daily activity) such as Guillain-

Barre like syndrome, or myasthenia gravis.
- Clinically significant immune-mediated reactions involving any organ system (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis).
- Clinically significant immune-mediated ocular disease (uveitis, conjunctivitis, blepharitis, episcleritis, scleritis) that is unresponsive to topical immunosuppressive therapy.

- Any of the above toxicities will be managed by stopping both tremelimumab and olaparib and initiating treatment with corticosteroids until the toxicity is resolved to Grade 1 or less. Olaparib will then be restarted as a single agent.

If tremelimumab is permanently discontinued due to immune related toxicity, subjects may continue treatment on study with olaparib monotherapy.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agents administered in NRG-GY021 are olaparib and tremelimumab, which are being made available under an IND sponsored by DCTD, NCI. For determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.5.1.1 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Olaparib (AZD2281, NSC 747856) (27-AUG-2021)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Olaparib (AZD2281, NSC 747856)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3449 patients.* Below is the CAEPR for Olaparib (AZD2281).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, July 1, 2021[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
Abdominal pain			***Abdominal pain (Gr 3)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		
	Urinary tract infection		
INVESTIGATIONS			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Creatinine increased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
		Platelet count decreased	
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	

NOTE: New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Obstruction gastric; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever; Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Dermatitis radiation; Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle weakness lower limb; Muscle weakness upper limb; Neck pain; Rotator cuff injury; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Treatment related secondary malignancy; Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Erythema multiforme; Pruritus
VASCULAR DISORDERS - Arterial thromboembolism; Flushing; Hot flashes; Hypertension; Hypotension; Peripheral ischemia; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Tremelimumab (CP-675,206, NSC #744483)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1642 patients.* Below is the CAEPR for Tremelimumab (CP-675,206).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.1, March 25, 2019[1]

Adverse Events with Possible Relationship to Tremelimumab (CP-675,206) (CTCAE 5.0 Term) [n= 1642]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		***Anemia[2] (Gr 2)***
CARDIAC DISORDERS			
		Myocarditis[3]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[2]		
Diarrhea			***Diarrhea (Gr 2)***
		Enterocolitis[2]	
		Gastrointestinal disorders - Other (intestinal perforation)[2]	
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***

Adverse Events with Possible Relationship to Tremelimumab (CP-675,206) (CTCAE 5.0 Term) [n= 1642]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		***Alanine aminotransferase increased[2] (Gr 2)***
	Aspartate aminotransferase increased[2]		***Aspartate aminotransferase increased[2] (Gr 2)***
	Lipase increased[2]		***Lipase increased[2] (Gr 2)***
	Lymphocyte count decreased[2]		***Lymphocyte count decreased[2] (Gr 2)***
	Neutrophil count decreased[2]		***Neutrophil count decreased[2] (Gr 2)***
	Platelet count decreased[2]		***Platelet count decreased[2] (Gr 2)***
	Serum amylase increased[2]		***Serum amylase increased[2] (Gr 2)***
	White blood cell decreased[2]		***White blood cell decreased[2] (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hypokalemia		
		Metabolism and nutrition disorders - Other (diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
		Musculoskeletal and connective tissue disorders - Other (Sjogren's syndrome)	
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
	Headache[2]		
		Myasthenia gravis[2,4]	
		Nervous system disorders - Other (encephalitis)[2]	
	Peripheral motor neuropathy[2]		
	Peripheral sensory neuropathy[2]		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
		Nephrotic syndrome[2]	

Adverse Events with Possible Relationship to Tremelimumab (CP-675,206) (CTCAE 5.0 Term) [n= 1642]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Renal and urinary disorders - Other (autoimmune nephritis)[2]		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
	Pneumonitis[2]		
	Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease)[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin[2]		***Dry skin[2] (Gr 2)***
Pruritus			***Pruritus (Gr 2)***
Rash maculo-papular[2]			***Rash maculo-papular[2] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (cutaneous scleroderma-like syndrome)	
		Skin and subcutaneous tissue disorders - Other (Grover's disease)	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***
	Urticaria[2]		
VASCULAR DISORDERS			
		Vascular disorders - Other (giant cell temporal arteritis)[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-related adverse events may occur in any organs including but not limited to the events listed in CAEPR table.

[3]Myocarditis has been reported with other anti-CTLA4 agents; however, it has not yet been observed in clinical trials of tremelimumab (CP-675,206).

[4]Myasthenia gravis was observed in trials of tremelimumab in combination with durvalumab.

Adverse events reported on tremelimumab (CP-675,206) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that tremelimumab (CP-675,206) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Eosinophilia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Endocrine disorders - Other (Graves' disease with ophthalmopathy)

GASTROINTESTINAL DISORDERS - Constipation; Dyspepsia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Ileus; Mucositis oral; Rectal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Pain; Sudden death NOS
INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (oral herpes); Lung infection; Sepsis
INVESTIGATIONS - GGT increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness; Myalgia
NERVOUS SYSTEM DISORDERS - Dizziness; Syncope
PSYCHIATRIC DISORDERS - Confusion; Depression; Insomnia
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Pleural effusion; Respiratory, thoracic and mediastinal disorders - Other (asthma)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Rash acneiform
VASCULAR DISORDERS - Flushing; Hypertension; Thromboembolic event; Vascular disorders - Other (hemorrhage); Vasculitis

Note: Tremelimumab (CP-675,206) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP for this study by telephone at 301-897-7497 and to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by the IND Sponsor for this study (CTEP/DCTD) and NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-230-0159 and to NRG Regulatory Affairs at 215-854-0716.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows

submission of all reports regardless of the results of the assessment.

7.5.1.1 Expedited Reporting Requirements for Adverse Events

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.5.2 Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

Tremelimumab AESIs should be reported through the CTEP Adverse Event Reporting System (CTEP-ARES)

AESIs are of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

An irAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

AESIs observed with tremelimumab requiring reporting through CTEP AERS include:

- Pneumonitis / ILD any grade / ALT/AST increases / hepatitis / hepatotoxicity - **Hy's Law:**
  Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs
- Neuropathy / neuromuscular toxicity (e.g., Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (i.e., events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus)
- Myocarditis, pericarditis, and uveitis.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

7.5.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at

http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

7.6 Secondary Malignancies

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS . In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

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

8. REGISTRATION AND STUDY ENTRY PROCEDURES (24-APR-2020)

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr).

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, activing as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;Act as the site-protocol Principal Investigator (PI) on the IRB approval.

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, must be rostered at the enrolling site with a participating organization. Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit (CTSU) Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the

study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

8.1.1 Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to serach for a protocol is listed below:

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-GY021*.

- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration; and*
- Enter the sties 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.2 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.2.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment during the 1st safety lead-in of this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

8.3 Data Submission / Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

  Rave role requirements:

  - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;

- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. The CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rule's evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
  AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the

Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

8.4 Agent Ordering and Agent Accountability

8.4.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites can order study agents in OAOP when a patient is enrolled to treatment. Agent orders can be expedited overnight Monday-Thursday when sites provide expedited courier information.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.4.2 Investigator Brochure Availability

The current versions of the Olaparib and Tremelimumab IBs will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.4.3 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page.
Store and maintain separate NCI Investigational Agent Accountability Records for each study participant and ordering investigator on this protocol.

8.4.4 PMB Useful Links and Contacts

- *CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/*
- *NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov*

- *PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm*
- *PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP*
- *CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/*
- *CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov*
- *IB Coordinator: IBCoordinator@mail.nih.gov*
- *PMB email: PMBAfterHours@mail.nih.gov*
- *PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)*

9. DRUG INFORMATION

9.1 Investigational Study Agent: Olaparib (AZD2281) (NSC # 747856) (24-APR-2020)

9.1.1 Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one

Other Names: AZD2281; KU-0059436; CO-CE 42

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

Molecular Formula: $C_{24}H_{23}FN_4O_3$ **M.W.:** 434.46

Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range

Mode of Action: Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5' diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

9.1.2 Description: crystalline solid

9.1.3 How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib as green, film-coated tablets in 100 mg and 150 mg strengths.

- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg are 14.5 mm x 7.25 mm oval-shaped

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

Availability: Olaparib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.
Tremelimumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix VIII).

9.1.4 Storage: Store in a secure location below 30° C (86° F).

If a storage temperature excursion is identified, promptly return olaparib (AZD2281) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 Stability: Shelf-life studies are ongoing. Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

9.1.6 Route and Method of Administration: Oral. Take tablets without regard to meals.

9.1.7 Potential Drug Interactions: *In vivo* data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro data shows olaparib is a substrate for P-glycoprotein (P-gp), but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), organic cation transporter 1 (OCT1), multi-drug resistance protein 2 (MRP-2) efflux transporter or breast cancer resistance protein (BCRP). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

Based on *in vitro* data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. *In vitro* studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with

caution when given concomitantly with olaparib.

9.1.8 Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least six (6) months after the last dose of olaparib. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

Lactation is a protocol exclusion criterion and not advised since there is potential for serious adverse reactions in breastfed infants. Advise lactating women to not breastfeed during study treatment and for one (1) month after receiving the last dose of olaparib.

Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery.

There are no data on the effect of olaparib on wound healing, therefore as a precaution, olaparib treatment should be stopped at least 3 days prior to planned surgery. After surgery olaparib can be restarted when the wound has healed. No stoppage of olaparib is required for any needle biopsy procedure.

Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic or palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

9.1.9 Adverse Events: Please see Section 7.3 for the Olaparib CAEPR.

9.2 Investigational Study Agent: Tremelimumab (NSC # 744483) (24-APR-2020)

9.2.1 Other Names: CP-675,206

Classification: Anti-CTLA-4 MAb

Molecular Weight: ~ 149 kDa

Mode of Action: Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), a cell surface receptor that is expressed primarily on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 or CD86 ligands on antigen-presenting cells. Tremelimumab blocks the inhibitory signal resulting from CTLA-4 binding to CD80/86, leading to prolongation and enhancement of T-cell activation and expansion.

9.2.2 Description: Tremelimumab is a human immunoglobulin G2 kappa (IgG2κ) monoclonal antibody.

9.2.3 How Supplied: Tremelimumab is supplied by AstraZeneca, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 400 mg/vial solution for infusion (20 mg/mL). Tremelimumab solution for infusion is formulated in 20 mM histidine/histidine-HCl, 222 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, and 0.27 mM disodium edetate dihydrate, pH 5.5.

Availability: Tremelimumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.
Tremelimumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix VIII).

9.2.4 **Preparation:** Tremelimumab solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature for 30 minutes. Do not shake the vials. To prepare the infusion solution add the dose volume of tremelimumab to an infusion bag containing 0.9% Sodium Chloride Injection or Dextrose 5% in Water Injection, USP and mix by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration must be between **0.10 mg/mL to 10 mg/mL**.

Infusion bags must be latex-free and can be made of polyvinyl chloride (PVC) or polyolefins (eg, polyethylene), manufactured with bis (2-ethylhexyl) phthalate (DEHP) or DEHP free.

9.2.5 **Storage:** Store intact vials between 2-8°C (36-46°F). Do not freeze.

If a storage temperature excursion is identified, promptly return tremelimumab to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.2.6 **Stability:** Stability testing of the intact vials is on-going**.**

Total in-use storage time from needle puncture of tremelimumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If there are interruptions during infusion, the total allowed time should not exceed 4 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.

9.2.7 **Route of Administration:** IV infusion

Method of Administration: Infuse over approximately 60 minutes using IV infusion lines made of PVC/DEHP or PVC/tri octyl trimellitate (TOTM) or polyethylene or polyurethane. All DEHP-containing or DEHP-free lines are acceptable. IV lines should contain a 0.22 or 0.2 µm in-line filter. The in-line filter can be made of polyethersulfone or polyvinylidine fluoride. IV lines containing cellulose-based filters should not be used with tremelimumab. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used at the completion of infusion. Do not co-administer other drugs through the same infusion line.

9.2.8 **Adverse Events:** Please see Section 7.4 for the Tremelimumab CAEPR.

10. PATHOLOGY/BIOSPECIMEN (27-AUG-2021)

Note: The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this

trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens.

10.1 Central Pathology Review Guidelines

Not applicable.

10.2 Biospecimen Selection for Integral Biomarker Testing

Not applicable.

10.3 Biospecimen Selection for Integrated Biomarker Testing

Not applicable.

10.4 Biospecimen Submission Tables

Biospecimens listed below should not be submitted until after patient registration and Bank ID assignment. A detailed description of biospecimen procedures can be found in Appendix VI.

10.4.1 Mandatory Biospecimen Submissions

The patient must give permission to participate in this **mandatory** study component. Participating sites are required to submit the patient's biospecimens as outlined below.

Required Biospecimen (Biospecimen Code)	***Collection Time Point***	***Sites Ship Biospecimens To***
FFPE TUMOR TISSUE ***(Submit one of the following – listed in order of preference)***		
FFPE Recurrent Primary (FRP01) *or* Metastatic (FRM01) Tumor[1] Block must be submitted[2]	Prior to study treatment	NRG Oncology BB - Columbus within 8 weeks of registration[3]
FFPE Persistent Primary (FPP01) *or* Metastatic (FPM01) Tumor[1] Block must be submitted[2]		
FFPE Neoadjuvant Primary (FPT01) *or* Metastatic (FMT01) Tumor[1] Block must be submitted[2]	After patient received neoadjuvant treatment; prior to study treatment	
FFPE Primary (FP01) *or* Metastatic (FM01) Tumor[1] Block must be submitted[2]	Prior to all treatment	
BLOOD BIOSPECIMENS		
Pre-cycle 1		
Pre-cycle 1 T Cell Whole Blood (WB01) 30mL drawn into green top sodium heparin (NaHep) tube(s)	Prior to starting cycle 1 of study treatment	NRG Oncology BB - Columbus the day the biospecimen is collected[3]
Pre-cycle 1 TCR Whole Blood (WB02) 2mL drawn into a purple top (EDTA) tub		
Pre-cycle 1 cfDNA Whole Blood (WB03) 10mL drawn into a Streck (cell-free DNA) tube		
Pre-cycle 3		
Pre-cycle 3 T Cell Whole Blood (WB04) 30mL drawn into green top sodium heparin (NaHep) tube(s)	Prior to starting cycle 3 of study treatment	NRG Oncology BB - Columbus the day the biospecimen is collected[3]
Pre-cycle 3 TCR Whole Blood (WB05) 2mL drawn into a purple top (EDTA) tub		
Pre-cycle 3 cfDNA Whole Blood (WB06)		

10mL drawn into a Streck (cell-free DNA) tube		
Final		
Final T Cell Whole Blood (WB07) 30mL drawn into green top sodium heparin (NaHep) tube(s)	Prior to starting cycle 6 of study treatment or at the time patient progresses or goes off-study (if prior to cycle 6)	NRG Oncology BB - Columbus the day the biospecimen is collected[3]
Final TCR Whole Blood (WB08) 2mL drawn into a purple top (EDTA) tub		
Final cfDNA Whole Blood (WB09) 10mL drawn into a Streck (cell-free DNA) tube		

1 All tissue biospecimens sent to the NRG BB-Columbus must be shipped with a copy of the corresponding pathology report and a completed copy of the FFPE Materials Verification Form (Appendix VII). The FFPE Materials Verification Form should be provided to your Pathology Department when FFPE materials are requested and must be completed by the person providing the FFPE materials.

2 Only blocks will be accepted. Please provide Appendix IX to your pathologist.

3 NRG Oncology BB-Columbus / Protocol NRG-GY021, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

10.4.2 Optional Biospecimen Submissions

Not applicable.

10.5 Exploratory Biomarker Testing (27-AUG-2021)

Note: The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens.

Tumor tissue and blood will be used for the CIMAC assays outlined below. All assays will be done at a CIMAC laboratory using standardized CIMAC testing procedures.

Biospecimen (quantity)	CIMAC Assay	Pre-Cycle 1	Pre-Cycle 3	Final
Tissue				
FFPE Tissue Blocks	IHC/IF	Archival	NA	NA
	RNA-Seq	Archival	NA	NA
	WES	Archival	NA	NA
Blood				
Sodium Heparin (30 mL total)	CyTOF (PBMCs)	X	X	X
	Olink (plasma)	X	X	X
Streck Cell-Free DNA (10 mL)	cfDNA	X	X	X
EDTA (2mL)	TCR-Seq	X	X	X
	WES	X	NA	NA

11. ASSESSMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in 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. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

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, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the

short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

11.1.2 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. 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, subsequent image acquisitions should use the same type of

scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

NRG Oncology will not allow PET-CT use for RECIST 1.1 response criteria.

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.

CA-125 (Ovarian, fallopian tube and primary peritoneal cancer trials): **CA125 cannot be used to assess response or progression in this study**. If CA125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response. Specific guidelines for CA-125 response (in recurrent ovarian cancer) have been published [*JNCI* 96:487-488, 2004]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria that are to be integrated with objective tumor assessment for use only in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

11.1.3 Response Criteria

Determination of response should take into consideration all target and non-target lesions and, if appropriate, biomarkers.

11.1.3.1 Evaluation of Target Lesions **(24-APR-2020)**

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 progression).

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

11.1.3.2 Evaluation of Non-Target Lesions

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

Note: If CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

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

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

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

11.1.3.3 Evaluation of Biomarkers

If serum CA-125 is initially above the upper normal limit, it must normalize for a patient to be considered in complete clinical response.

Progression **cannot** be based upon biomarkers, including serum CA-125 and HE4 for this study.

11.1.3.4 Evaluation of Best Overall Response

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

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	Biomarker CA-125	New Lesions*	Time Point Response
CR ***	CR	Within normal limits	No	CR
CR	Non-CR/Non-PD	Any value	No	PR
CR	NE	Any value	No	PR
PR	Non-PD or NE	Any value	No	PR
SD	Non-PD or NE	Any value	No	SD
NE	Non-PD	Any value	No	NE
PD	Any	Any value	Yes or No	PD
Any	PD**	Any value	Yes or No	PD
Any	Any	Any value	Yes	PD

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion

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

***If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In randomized trials (phase II or III), confirmation of response is not required since it will not add value to the interpretation of results.

For this study, the minimum criteria for SD duration is 12 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.4 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that 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 date of study entry, including the baseline measurements.

11.1.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression per RECIST criteria or death due to any cause, whichever occurs first. Individuals who are progression free at the time of their last assessment will be censored on the date of their last radiographic assessment.

11.1.6 Survival

Survival is defined as the duration of time from study entry to the date of death. For those individuals who are alive, their survival duration is censored on the date last known to be alive.

11.1.7 Dose Limiting Toxicity

Since immune-related adverse events are not classically dose-dependent, no provision is made for a dose reduction of tremelimumab, only treatment delays are permitted. For the purposes of the safety lead-in, a dose-limiting toxicity is a treatment-related adverse event requiring permanent discontinuation of tremelimumab prior to the completion of cycle 3 of treatment. Dose reductions for olaparib are permitted, however if persistent toxicity following olaparib dose-reduction requires a treatment delay of >30 days, then this will also be counted as a DLT.

12. DATA AND RECORDS

12.1 Data Management/Collection

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles in RSS (Regulatory Support System). To access iMedidata/Rave, the site user must have an active CTEP-IAM account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization rosters at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the “accept” link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and will be listed in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave accounts also will receive a separate invitation from iMedidata to activate their account. Account activation

instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2 NRG Data Management Forms

Refer to the CTSU member website for the table of Required Forms and Materials.

12.3 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.5.1 and 7.5.1.1 for information about expedited and routine reporting.

12.4 Global Reporting/Monitoring (24-APR-2020)

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

Treatment Assignment

A web-based enrollment procedure will be used to register patients onto the study. Immediately after an individual has been successfully enrolled, one of the study regimens will be randomly assigned (for this study the date of enrollment is equivalent to the date of randomization). The study regimens: Olaparib with Tremelimumab (OT) or Olaparib-alone (O) will be assigned in a 1:1 ratio within stratum determined by germline and/or somatic BRCA status (mutation vs no mutation or unknown mutation status) and prior treatment with a PARP inhibitor among BRCAm patients (yes vs no). Patients with unknown BRCA status will be stratified as BRCA wild-type. The study treatments will be sequentially drawn from pre-allocated blocks of randomly permuted treatments, which are created for each stratum. The treatment assignment will remain concealed until after

the individual has been successfully enrolled onto the trial, and the interim and final reports will include an accounting of all enrolled individuals.

13.2 Study Endpoints

Primary Endpoint

- The primary endpoint of this study is progression free survival (PFS). PFS is defined in Section 11.1.5. The primary endpoints for the initial safety/efficacy lead-in study will be dose-limiting toxicity (DLT, see Section 11.1.7) and RECIST 1.1 response (Section 11.1.3), respectively.

Secondary Endpoints

- The categories of responses (OR) are defined in section 11.1.3. The objective response rate is the percentage of subjects with a best overall complete response (CR) or partial response (PR) among those with target lesions at the time of enrollment. The duration of response is defined in Section 11.1.4.

- Overall survival (OS) defined as the time from enrollment and randomization to the date of death due to any cause. A subject who has not died will be censored on the date that they were last known to be alive. OS will be followed regularly in accordance with the schedules presented in sections 4.2 and 4.3. Following discontinuation of study treatment, subjects will be evaluated every 3 months via in-person or phone contact for two years and then every 6 months for 3 additional years.

  Safety data will be summarized for all treated subjects. All adverse events, including severe adverse events (SAEs) and treatment-related adverse events, will be categorized and graded for severity according to NCI CTCAE v 5.0.

13.3 Primary Objectives Study Design

13.3.1 Primary Hypothesis

The primary null hypothesis (H0) is that the O+T regimen does not increase the duration of progression-free survival compared to olaparib alone. The primary aim of this study is to assess this hypothesis in the target population.

13.3.2 How Primary Endpoints Will Be Analyzed

The logrank procedure will be used to test the primary study hypothesis. The logrank procedure will be stratified by germline and/or somatic BRCA status (mutation vs no or unknown mutation status) and prior treatment with a PARP-inhibitor (yes vs no). All patients enrolled onto the study will be included in the interim and final analyses of the primary objective regardless of their eligibility or study treatment compliance. The following conditions will censor an individual's PFS duration: 1) In the event that an individual initiates an anticancer therapy that is not prescribed by the protocol, her PFS duration will be censored on the date her last assessment was done prior to beginning that therapy, 2)the PFS duration for an individual who misses 2 consecutive assessments will be censored on the date of her last assessment prior to missing two consecutive

assessments, 3)the PFS duration for those individuals who have no post-enrollment assessments done will be censored 1 day after enrollment.

Interim Analyses:
After at least 58 PFS events (50% information time) have been reported, an interim analysis will be conducted. The purpose of the interim analysis is to assess futility of rejecting H0 at the time of the final analysis. If the estimated relative hazard from a proportional hazards model, adjusted for germline and/or somatic BRCA status and prior PARP-inhibitor treatment, indicates that the hazard of first progression or death (PFS) is greater among those allocated to the O+T treatment group, compared to O, then the Data Monitoring Committee (DMC) will have the option to stop the study early, release the study results and conclude that it is very unlikely that the alternative hypothesis, Ha, is true.

Final Analysis:
The analysis of the primary objective will be conducted on an intention-to-treat basis. A logrank test stratified by BRCA mutation status and prior PARPi use will be used to assess the primary hypothesis. The study will be considered sufficiently mature for assessing the primary objective when at least 115 PFS events occur among all of the enrolled patients. Assuming that the accrual is interrupted for three months at the end of each safety component, this study is expected to mature approximately 2.3 years after the first patient is enrolled.

A proportional hazards model will be used to estimate the treatment hazard ratio and corresponding confidence interval, after adjusting for the patients' BRCA status and prior PARPi usage. Also, an exploratory analysis will be conducted to assess whether the proportional hazards assumption is supported by the study data. A product-limit method will be used to estimate the cumulative distribution of PFS duration for each of the study treatments used in this population.

Descriptive statistics will be used to summarize adverse events (AEs). These analyses will focus on the individuals who initiated their assigned study treatment and summarize maximum grade of adverse events occurring during treatment classified by CTC category. The primary summary of AEs will present counts and percentages, regardless of whether the AE was attributed to any of the study agents.

13.3.3 Sample Size and Power Calculations:

The targeted accrual for this study is 170 eligible individuals, including those enrolled during the safety lead-in components and follow-up of these individuals will continue until at least 115 have experienced either disease progression or death. This sample size provides 80% power for detecting a hazard ratio of 0.625 (Ha) when type I error is set to 0.05 for a one-tail test of H0 (EAST ver 6.4, accounting for the interim analysis of PFS described above). If the true median duration of PFS for patients in this population treated with olaparib is 8 months, then a HR of 0.625, assuming proportional hazards, is comparable to increasing the expected percent of patients alive and progression free for at least 8 months from 50% to 64.8%. Assuming a constant hazard this is comparable to

increasing the median PFS duration from 8 months to 12.9 months.

13.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC
The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis. The stopping boundaries described above provide prospective guidelines based on statistical rationale for early study termination. These guidelines are non-binding and the DMC may use additional ethical, clinical or statistical criteria to recommend early termination of the study.

13.5 Accrual/Study Duration Considerations

The targeted enrollment for this study is 170 eligible patients. During the first safety lead-in, accrual will be limited to NRG's Safety Lead-in institutions and the accrual rate is expected to be about 10 patients per month. Once this component has been completed it is conservatively estimated that at least 20 patients per month will be available for this study. Allowing for a 3 month interruption in accrual following each safety lead-in sub-study (described below), the time from first-patient-in to last-patient-in is expected to be about 1.5 years. The expected time from first-patient-in until data maturity for final analysis is approximately 2.4 years.

13.6 Secondary or Exploratory Endpoints

13.6.1 Definitions of Secondary Endpoints and How These Will Be Analyzed
Overall Survival: The overall survival endpoint is defined in Section 11.1.6. Kaplan-Meier procedures will be used to estimate the cumulative distribution of survival times for each treatment in this population. A proportional hazards model stratified by BRCA status and prior PARPi treatment will be used to estimate the treatment hazard ratio and the corresponding confidence interval.

RECIST Response: The criteria for assessing objective response is defined in Section 11.1.3 and the definition of response duration is defined in section 11.1.4. A logistic model will be used to estimate the relative odds of responding (CR+PR) to O+T relative to O after adjusting for BRCA mutation status and prior PARPi usage. Assuming 90% of these patients have measurable disease, the proposed sample size provides 85% power for detecting a relative odds of 2.5 when type I error is limited to 0.05 for a one-tail test. Assuming the true probability of response to olaparib monotherapy is about 50%, a relative odds of 2.5 is comparable to expecting the true probability of response to increase 21.4% on O+T (i.e. increase from 50% to 71%).

13.6.2 Interim Analysis for All Other Endpoints (Goals):

Two Embedded Safety Lead-in Components of this Study:
In order to limit the number of patients who could be exposed to an excessively toxic treatment regimen, this study includes two embedded safety assessments.

Initial Safety Lead-In*:* The study treatments will be randomly allocated (1:1) to each

individual enrolled during this component of the study. Enrollment will proceed until there are at least 25 patients treated with O+T regimen. Enrollment during this phase of the study will be limited to institutions that are members of the NRG's Phase I Group. These clinics are experienced in conducting phase I trials, and they are adequately staffed and committed to expedited reporting procedures. Once 25 patients have received at least 3 cycles of O+T, the cumulative toxicity data will be reviewed by the Safety Review Committee. Provided no more than 6 of these 25 patients experience dose-limiting toxicities (DLT, see Section 11.1.7 for definition of DLT) during the first 3 cycles of treatment, the O+T regimen will be considered sufficiently safe to continue enrollment onto the second safety assessment component of this study. If the number of patients experiencing a DLT exceeds 6 at any time before the targeted enrollment for the safety lead-in has been completed, then the study's conclusion will be considered ineluctable and the enrollment will be stopped.

If the true probability of a DLT is 0.15 in this population then this decision rule provides a 93% chance of advancing to the next study component. On the other hand, if the true probability of a DLT is 0.35, then there is an 83% chance of stopping the study during or immediately following the first safety lead-in.

Second Safety Lead-in*:* If the O+T regimen is deemed sufficiently safe following the initial safety lead-in, then enrollment will be opened to all approved NRG sites. Enrollment will continue until at least 45 patients have been randomized and treated on O+T (including those enrolled during the first safety lead-in). Following review by the Safety Review Committee, if there are more than 11 DLTs observed among the 45 patients enrolled onto and treated with the O+T regimen then the O+T regimen will be deemed too toxic to warrant further evaluation. In the event that more than 11 DLTs are observed before completing enrollment onto this component of the study, then the study's conclusion will be considered ineluctable and the enrollment will be stopped.

If the true probability of a DLT is 0.15 then the decision rules from the first and second safety assessments provide 92% chance of continuing the study to the completion of its primary objective. However, if the true probability of a DLT is 35%, then these rules provide a 93.5% chance of stopping the study early; that is, during or immediately following one of the two scheduled safety assessments. If the study regimen is deemed to be safe based on this assessment, the protocol will be amended to allow participation of NCTN sites and activation of the full phase II trial.

13.7 Gender/Ethnicity/Race Distribution

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		**Hispanic or Latino**		**Total**
	Female	**Male**	**Female**	**Male**	
American Indian/Alaska Native	**3**	**0**		**0**	**3**
Asian	**12**	**0**	**0**	**0**	**12**

Native Hawaiian or Other Pacific Islander	**1**	**0**	**0**	**0**	**1**
Black or African American	**7**	**0**	**1**	**0**	**8**
White	**141**	**0**	**5**	**0**	**146**
More Than One Race	**0**	**0**	**0**	**0**	**0**
Total	**164**	**0**	**6**	**0**	**170**

Racial Categories	**INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	0	0	0	0	0

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APPENDIX I – FIGO OVARIAN CANCER STAGING 2014

STAGE I: Tumor confined to ovaries

- IA Tumor limited to 1 ovary, capsule intact, no rumor on surface, negative washings.
- IB Tumor involves both ovaries otherwise like 1A.
- IC Tumor limited to 1 or both ovaries
  - IC1 Surgical spill
  - IC2 Capsule rupture before surgery or tumor on ovarian surface
  - IC3 Malignant cells in the ascites or peritoneal washings

STAGE II: Tumor involves 1 or both ovaries with pelvic extension (below the pelvic brim) or primary peritoneal cancer

- IIA Extension and/or implant on uterus and/or Fallopian tubes
- IIB Extension to other pelvic intraperitoneal tissues

STAGE III: Tumor involves 1 or both ovaries with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

- IIIA Positive retroperitoneal lymph nodes and/or microscopic metastasis beyond the pelvis
  - IIIA1 Positive retroperitoneal lymph nodes only
    - IIIA1(i) Metastasis ≤ 10 mm
    - IIIA1(ii) Metastasis > 10mm
  - IIIA2 Microscopic, extrapelvic (above the brim) peritoneal involvement ± positive retroperitoneal lymph nodes
- IIIB Macroscopic, extrapelvic, peritoneal metastasis ≤ 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.
- IIIC Macroscopic, extrapelvic, peritoneal metastasis > 2 cm ± positive retroperitoneal lymph nodes. Includes extension to capsule of liver/spleen.

STAGE IV: Distant metastasis excluding peritoneal metastasis

- IVA Pleural effusion with positive cytology

IVB Hepatic and/or splenic parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity).

Other major recommendations are as follows:

- Histologic type including grading should be designated at staging
- Primary site (ovary, Fallopian tube or peritoneum) should be designated where possible
- Tumors that may otherwise qualify for stage I but involved with dense adhesions justify upgrading to stage II if tumor cells are histologically proven to be present in the adhesions

APPENDIX II – 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 III – GENERAL THERAPY GUIDELINES

- For 21 or 28 day cycles, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.
- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of 21 or 28 day cycles. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).
- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.
- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

Chemotherapy doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

APPENDIX IV: PATIENT DRUG INTERACTIONS HANDOUT AND PATIENT DRUG INTERACTIONS WALLET CARD - OLAPARIB

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Patient Name:	**Diagnosis:**	**Trial #:**
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:
Olaparib interacts with a specific enzyme in your liver and transport proteins. It must be used very carefully with other medicines.

	Explanation
CYP isoenzymes	The enzymes in question are CYP3A4/5, CYP1A2, 2B6, 3A4, and UGT1A1 "Olaparib is broken down by CYP3A4/5 and may be affected by other drugs that inhibit or induce these enzymes. Olaparib inhibits CYP3A4/5 and induces CYP1A2, 2B6, and UGT1A1 which may affect other drugs that are broken down by these enzymes."
Protein transporters	The proteins in question are P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1MATE2K and BCRP. "Olaparib is moved in and out of cells/organs by P-gp transport protein and may be affected by inhibitors or inducers of P-gp. Olaparib inhibits P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP which may affect how other drugs are moved in and out of cells in the body."

These are the things that you need to know:
The study drug Olaparib may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP3A4/5 and Pgp.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
    - Avoid St. John's Wort (Hypericum perforatum).
- Make sure your doctor knows to avoid certain prescription medications.
    - Phenytoin, rifampicin, rifapentine, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

PATIENT DRUG INTERACTION WALLET CARD (24-APR-2020)

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EMERGENCY INFORMATION		**DRUG INTERACTIONS**	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Olaparib interacts with a specific enzyme in your liver and transport proteins. It must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):** Olaparib	**Use caution and avoid the following drugs if possible:** Phenytoin, rifampicin, rifapentin, rifabutin, carbamazepine, phenobarbitone, nevirapine, modafinil, St. John's Wort (Hypericum perforatum) or other herbal supplements.	Your healthcare providers should be aware of any medicines that are strong or moderate inducers/inhibitors of CY3A4/5 and Pgp. Olaparib inhibits "CYP 3A4, UGT1A1 and transport proteins Pgp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP and induces CYP 1A2, 2B6, 3A4, 2C9, 2C19 ." It may change how other medicine works in your body **Before prescribing new medicines,** your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

APPENDIX V: PATIENT DRUG DIARY: OLAPARIB

Today's Date _____ Cycle # _____

1. Complete one form for each cycle (28 days)
2. Record the date, the number of tablets you took, and when you took them.
3. Bring your pill bottles (including empty bottles) and this form to every appointment
4. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
5. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

OLAPARIB

Take (number) mg and (number) mg tablets twice a day 12 hours apart.

Day	Date	100mg	150mg	AM	PM
1	*1/1/19*	*2*	*0*	*8:00*	*8:00*
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature: _____ Date: _____

Patient Name _____

APPENDIX VI – TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES

1. Obtaining a Bank ID for Translational Science Biospecimens

All translational science biospecimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component.

Please contact Support if you need assistance (Email: support@nrgoncology.org).

2. Requesting Translational Science Biospecimen Kits

Upon request, a biospecimen kit including a Streck tube and ambient shipper will be provided for the collection and shipment of cfDNA whole blood biospecimens. A separate kit is needed for each cfDNA whole blood biospecimen.

Sites can order kits online via the Kit Management system (https://kits.bpc-apps.nchri.org/) **(27-AUG-2021).** . Each site may order two kit types per protocol per day (daily max = 6 kits).

Please contact the NRG BB-Columbus if you need assistance (Email: BPCBank@nationwidechildrens.org; Phone: 866-464-2262).

Supplies will not be provided for the collection or shipment of whole blood collected in sodium heparin (NaHep) or EDTA tubes.

Be sure to plan ahead and allow time for kits to be shipped by ground transportation. Kits should arrive within 3-5 business days.

3. FFPE Tissue Shipped to the NRG BB-Columbus

Only one block may be submitted per tissue type. All tissue biospecimens sent to the NRG BB-Columbus must be shipped with a copy of the corresponding pathology report (all PHI must be redacted) and a completed copy of the FFPE Materials Verification Form (Appendix VII) should be provided to your Pathology Department when FFPE materials are requested and must be completed by the person providing the FFPE materials.

3.1 FFPE Biospecimen Requirement

3.1.1 Tumor Tissue Type

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the required type:

- **Recurrent (FRP01) or persistent (FPP01) primary and recurrent (FRM01) or persistent (FPM01) metastatic** tumor should be collected prior to the study treatment and is the preferred tumor type.
- **Neoadjuvant primary (FPT01) or metastatic (FMT01)** tumor should be collected after the patient received neoadjuvant tumor, but prior to the study treatment.
- **Primary (FP01)** or **metastatic (FM01)** tumor should be collected prior to all treatment.

3.1.2 FFPE Type

Only blocks will be accepted. Please provide Appendix IX to your pathologist.

3.1.3 Labeling FFPE Biospecimens

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

REQUIRED FFPE BIOSPECIMEN LABELING
Bank ID (N # # # # # # # # # #)*
NRG ID (X X # # # -GY021- # # # # #)
Biospecimen Code (see section 10)
Collection Date (mm/dd/yyyy)
Surgical Pathology Accession Number
Block Number

*****_Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10._

Failure to label biospecimens with all data fields shown in the sample label above may result in delayed processing and/or inability to utilize biospecimens.

3.1.4 Completing Form TR for FFPE Biospecimens

The type of biospecimen (block) should be specified on Form TR.

The time the tissue was in formalin (i.e., fixation time) should be entered as Estimated Processing Time.

4. Whole Blood Biospecimens Shipped to the NRG BB-Columbus

Labeling Whole Blood

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

REQUIRED WHOLE BLOOD BIOSPECIMEN LABELING
Bank ID (N # # # # # # # # # #)*
NRG ID (X X # # # -GY021- # # # # #)
Biospecimen Code (WB##)
Collection Date (mm/dd/yyyy)

*****_Leading zeros may be omitted when labeling biospecimens with the Bank ID. For example, N000000010 may be written as N10._

Failure to label biospecimens with all data fields shown in the sample label above may result in delayed processing and/or inability to utilize biospecimens.

4.1 T Cell Whole Blood

4.1.1 Collection Time Points

T cell whole blood should be collected as per section 10.4.1.

4.1.2 Collecting T Cell Whole Blood

1. Label the green top sodium heparin (NaHep) collection tube(s) as described above. Multiple tubes may be used to collect the required amount. **Do not use glass blood collection tubes.**
2. Draw 30mL of blood into the labeled green top tube(s).
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and sodium heparin.
4. Whole blood specimens should be kept at room temperature until the specimens can be shipped. Whole blood must be shipped to the NRG BB-Columbus **the day the specimen is collected**. If the specimen cannot be shipped the day it is collected, it should be discarded.

4.2 T Cell Repertoire (TCR) Whole Blood

4.2.1 Collection Time Points

T cell repertoire (TCR) whole blood should be collected as per section 10.4.1.

4.2.2 Collecting T Cell Repertoire (TCR) Whole Blood

1. Label the lavender/purple top (EDTA) collection tube as described above. **Do not use glass blood collection tubes.**
2. Draw 2mL of blood into the labeled lavender/purple top tube.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Whole blood specimens should be kept at room temperature until the specimens can be shipped. Whole blood must be shipped to the NRG BB-Columbus **the day the specimen is collected**. If the specimen cannot be shipped the day it is collected, it should be discarded.

4.3 Cell-Free DNA (cfDNA) Whole Blood

4.3.1 Collection Time Points

Cell-free DNA (cfDNA) whole blood should be collected as per section 10.4.1.

4.3.2 Special Notes Regarding the Collection of Blood in Streck (cf DNA) Tubes

- Heparin should be avoided in pre-collection flush procedures.
- All other blood biospecimens should be drawn *before* the Streck (cell-free DNA) tube when multiple blood biospecimens are collected on the same day.
- Over or under filling a Streck (cell-free DNA) tube will result in an incorrect blood-to-additive ratio.
- No other tube may be substituted for a Streck (cell-free DNA) tube.

4.3.3 Collecting Streck (Cell-Free DNA) Whole Blood

1. Label the **Streck** (cell-free DNA) collection tube as described below.
2. Draw **10mL** of blood into the labeled tube.
3. Immediately after collection, gently invert the tube 5-10 times.
4. Ship whole blood to the NRG BB-Columbus the day the biospecimen is collected. If the whole blood **absolutely** cannot be shipped the day it is collected, the tube must remain at **room temperature** until shipment.

5. Submitting Biospecimen Transmittal Forms

A biospecimen transmittal form for each biospecimen will be available in the **Translational Research Folder in Rave**, once the Specimen Consent (located in the Baseline Folder) has been completed.

An electronically (i.e., Rave) completed copy of the biospecimen transmittal form must accompany each biospecimen shipped to the NRG BB-Columbus. **Handwritten forms will not be accepted.**

Note: A copy does not need to be sent to the NRG BB-Columbus if biospecimens are not collected.

Biospecimen transmittal forms must be printed from the Translational Research Form screen in Rave using the **"PDF File" link at the top of the form**. Clicking this link will generate a single page PDF. Do not use the "Printable Version" or "View PDF" links at the bottom of the form or any other method to print the form, as these formats will not be accepted.

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@nrgoncology.org).

6. Shipping Translational Science Biospecimens

- Translational science biospecimens should not be shipped until after patient registration and Bank ID assignment.
- An electronically completed copy of the biospecimen transmittal form must be included for each translational science biospecimen.
- All translational science biospecimens should be shipped to:

  NRG BB-Columbus / Protocol NRG-GY021
  Nationwide Children's Hospital
  700 Children's Dr, WA1340
  Columbus, OH 43205
  Phone: 614-722-2865
  FAX: 614-722-2897
  Email: BPCBank@nationwidechildrens.org

6.1 FFPE Tissue Shipped to the NRG BB-Columbus

FFPE tissue, a copy of the corresponding pathology report, and a competed copy of the FFPE Materials Verification Form (Appendix VII) should be shipped using your own container at your own expense to the NRG BB-Columbus at the address above.

Do not ship FFPE tissue for Saturday delivery.

6.2 Whole Blood Shipped to the NRG BB-Columbus

- Whole blood biospecimens can be shipped to the NRG BB-Columbus **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Ship biospecimens via FedEx priority overnight.
- When shipping whole blood biospecimens, **your site must comply with IATA standards** (www.iata.org). If you have questions regarding your shipment, contact the NRG BB-Columbus at BPCBank@nationwidechildrens.org or by phoning 866-464-2262.

6.2.1 Whole Blood Collected in Sodium Heparin (NaHep) and EDTA Tubes

To ship whole blood collected in Sodium Heparin (NaHep) and EDTA tubes you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping both whole blood collected in sodium heparin (NaHep) and EDTA, please put each biospecimen in a separate plastic zip-lock bag before placing the biospecimens in the shipping bag.*

If you do not have these materials available at your site, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

6.2.1.1 Shipping Whole Blood in Sodium Heparin (NaHep) and EDTA Tubes

1. Ship whole blood collected in sodium heparin (NaHep) or EDTA tubes using your own shipping container and supplies.
2. Place the whole blood biospecimens in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.
3. Wrap the biohazard envelope in bubble wrap or another padded material.
4. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
5. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).
6. Insert a copy of the Blood Biospecimen Submission Form for each biospecimen.
7. Attach an Exempt Human Specimen sticker to the outside of the shipping container.
8. Print a pre-paid FedEx air bill using the Kit Management link. (https://kits.bpc-apps.nchri.org/). **(27-AUG-2021).** Attach the air bill.
9. Make arrangements for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

6.2.2 Whole Blood Collected in Streck Tubes

To ship whole blood collected in Streck tubes you will need a Streck Cell-Free DNA Ambient Shipper. Refer to Section 2 of this appendix for details.

6.2.2.1 Shipping Whole Blood Using a Streck Cell-Free DNA Ambient Shipper

1. Before packaging cfDNA whole blood biospecimens, verify that each biospecimen is labeled according to the instructions above.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. *Note: If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth.* ***Do not refrigerate, freeze, or microwave.***
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. *Note: The insulated chest must be shipped inside the provided cardboard box.*
4. Place the blood collection tube in zip-lock bags.
5. Next, place zip-lock bag into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal

securely.
7. Place packaged Streck blood collection tube and a completed copy of the Blood Biospecimen Submission Form on top of SAF-T-TEMP Gel Pak.
8. Place the lid on the insulated chest.
9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Print a pre-paid FedEx air bill using the Kit Management link (https://kits.bpc-apps.nchri.org/). **(27-AUG-2021).** Attach the air bill.
13. Make arrangements for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

7. Banking Translational Science Biospecimens for Future Research

Biospecimens will remain in the NRG BB-Columbus and made available for approved research projects if the patient has provided permission for the use of her biospecimens for future health research.

Note: The final biomarker assays and analyses at CIMAC-CIDC will be based on the "Proposal Intake Form for Investigators Using the CIMAC-CIDC Network" for this trial. The Intake Form will be reviewed and approved by NCI and the CIMAC-CIDC coordination center before testing of banked biospecimens. **(27-AUG-2021)**

The patient's biospecimen consent choices will be recorded on the signed informed consent document and electronically via the Specimen Consent form. At the time of biospecimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient's choices regarding the future use of her biospecimens at any time if the patient changes her mind.

If the patient revokes permission to use her biospecimens, the NRG BB-Columbus will destroy or return any remaining biospecimens. The patient's biospecimens will not be used for any further research; however, any biospecimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her biospecimens distributed prior to revoking consent.

Note: If return of biospecimens is requested, shipping will be at the site's expense.

APPENDIX VII - BIOSPECIMEN BANK-COLUMBUS PATHOLOGY MATERIALS VERIFICATION FORM (24-APR-2020)

This form should be completed by the person in the pathology department who provides the FFPE materials to the requestor. ***Please return this form, along with the FFPE materials, to the requestor.*** *The requestor must include this completed form with the shipment of FFPE materials.*

REQUIRED FFPE MATERIALS

One of the following archival tumor types must be submitted (listed in order or preference):

- **recurrent (FRP01)** or **metastatic (FRM01)** – i.e., collected prior to study treatment;
- **persistent primary (FPP01)** or **metastatic (FPM01)** – i.e., collected prior to study treatment;
- **neoadjuvant primary (FPT01)** or **metastatic (FMT01)** – i.e., collected after neoadjuvant treatment, but prior to study treatment; or
- **primary (FP01)** or **metastatic (FM01)** tumor – i.e., collected prior to any treatment.

Only blocks will be accepted. Please provide Appendix IX to your pathologist.

PATIENT INFORMATION (to be completed by person requesting FFPE materials)

Patient ID: _____ **Bank ID:** _____

FFPE MATERIALS (to be completed by person preparing FFPE materials)

Surgical Pathology #: _____ **Block #:** _____

Date Collected: __ __ / __ __ / __ __ __ __

Tissue Type:

□ Recurrent Primary (FRP01) □ Recurrent Metastatic (FRM01)
□ Persistent Primary (FPP01) □ Persistent Metastatic (FPM01)
□ Neoadjuvant Primary (FPT01) □ Neoadjuvant Metastatic (FMT01)
□ Primary (FP01) □ Metastatic (FM01)

Site: □ Ovary □ Other, specify _____

Materials Prepared	**Number Provided**	**Thickness (µm)**
Block	_____	**Not Applicable**

_____ _____
Name of person preparing materials Date

APPENDIX VIII – COLLABORATIVE AGREEMENT

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX IX – LETTER TO PATHOLOGISTS

Dear Pathologist,

Your site is a participant in **NRG GY021**, "A phase II randomized trial of olaparib versus olaparib plus tremelimumab in platinum-sensitive recurrent ovarian cancer."

This study includes exploratory biomarker testing to be **done in collaboration with the NCI Cancer Immune Monitoring and Analysis Centers (CIMACs).**

CIMAC testing requirements mandate that all slides used must be *fresh cut*.

Given the biospecimen requirements for this biomarker testing, **NRG GY021 requires all sites submit FFPE blocks only (i.e., unstained slides will not be accepted).** Blocks may be submitted on a permanent or temporary basis.

If submitted on a temporary basis, blocks will be returned after completion of the CIMAC biomarker testing.

If return of the block is requested, the NRG BB-Columbus will contact your institution for a Fed Ex Account number and shipping address *after* completion of the integral and integrated biomarker testing.

If you should have any questions, please do not hesitate to contact Drs. Sarah Adams (PI) and Heather Lankes (Translational Research Scientist).

We thank you in advance for your participation in this trial and your commitment to the successful completion of this study's objectives.

Sincerely,

Sarah Adams, MD
Heather A Lankes, PhD, MPH