SUMMARY OF CHANGES

For Protocol Amendment #13 to: NRG-GY009

NCI Protocol #: NRG-GY009
Local Protocol #: NRG-GY009

NCI Version Date: 10/13/2022

This amendment is in response to [redacted] notice regarding atezolizumab drug information updates.

#	Section	Comments
1.	Title Pages	• NCI Version Date is now 10/13/2021. • Data Manager contact info has been updated.
2.	9.1	Updated drug information received from CTEP on Atezolizumab has been included throughout section 9.1
3.	10.4.1	Biospecimen table has been updated.
4.	Appendix V	Link to biospecimen ordering kits has been updated to https://kits.bpc-apps.nchri.org/
5.	ICDs	Updated Version Date Only.

NRG ONCOLOGY
NRG-GY009
(ClinicalTrials.gov NCT #02839707)
A RANDOMIZED, PHASE II/III STUDY OF PEGYLATED LIPOSOMAL DOXORUBICIN AND CTEP-SUPPLIED ATEZOLIZUMAB [redacted] VERSUS PEGYLATED LIPOSOMAL DOXORUBICIN, CTEP-SUPPLIED BEVACIZUMAB AND CTEP-SUPPLIED ATEZOLIZUMAB VERSUS PEGYLATED LIPOSOMAL DOXORUBICIN AND CTEP-SUPPLIED BEVACIZUMAB IN PLATINUM RESISTANT OVARIAN CANCER (29-JUN-2020)

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI).

Lead Organization: NRG / NRG Oncology

The Safety Lead-in portion of the study is limited to NRG Oncology Safety Lead-in participants

Participating Organizations
ALLIANCE / Alliance for Clinical Trials in Oncology
ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

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

Study Team	
Study [redacted] (06/29/2017)	**Study [redacted]**
[redacted] M.D.	**[redacted], M.D.**
Memorial Sloan Kettering Cancer Center	Memorial Sloan Kettering Cancer Center
300 East 66th Street	300 East 66th Street
New York, NY 10065	New York, NY 10065
[redacted] / FAX: [redacted]	[redacted] /FAX: [redacted]
[redacted]	[redacted]
Patient Reported Outcomes [redacted]	**Statistician (06/29/2017) (03/19/2018)**
[redacted] PhD	**[redacted] Ph.D.**
University of California, Irvine	NRG Oncology Biostatistical Office-Buffalo
100 Theory, Suite 110	Elm and Carlton Streets
Irvine, CA 92697	Buffalo, NY 14263
[redacted] /FAX: [redacted]	[redacted] /FAX: [redacted]
[redacted]	[redacted]

Research Nurse	**Translational Scientist (10/16/2017)**
[redacted] **RN**	[redacted], **PhD, MPH**
Memorial Sloan Kettering Cancer Center	NRG BB-Columbus
300 East 66th Street	Biopathology Center
New York, NY 10065	Nationwide Children's Hospital
[redacted] /FAX: [redacted]	700 Children's Drive
[redacted]	Columbus, OH 43205
	[redacted]
Data Manager (13-OCT-2022)	
[redacted]	**Translational Research** [redacted] **(10/16/2017) (10/22/2018)**
Elm and Carlton Streets.	[redacted], M.D., Ph.D.
Buffalo, NY 14263	Memorial Sloan Kettering Cancer Center
[redacted] /FAX: [redacted]	300 E. 66th Street
[redacted]	New York, NY 10065
	[redacted] /FAX: [redacted]
Disease Site [redacted] **(10/16/2017) (03/19/2018) (10/22/2018)**	[redacted]
[redacted] **M.D.**	**Protocol Coordinator**
Memorial Sloan Kettering Cancer Center	[redacted], **M.S. (30-OCT-2020)**
Department of Medicine	NRG Oncology
1275 York Avenue	Four Penn Ctr, 1600 JFK Blvd, Ste 1020
New York, NY 10065	Philadelphia, PA 19103
[redacted]	[redacted] /FAX: [redacted]
[redacted]	[redacted]

The following NCTN Group Study [redacted] **has been added to this trial**: **(13-OCT-2022)**
SWOG: [redacted] **M.D.,** University of Mississippi [redacted]

NRG Oncology Contact Information (02/20/2019)	
Data Management For questions concerning data submission	[redacted] NRG Oncology Statistics and Data Management Center Elm and Carlton Streets. Buffalo, NY 14263 716-845-5702/FAX:716-845-8393 [redacted]

Protocol Development For questions concerning protocol and informed consent versions and amendments	Protocol Coordinator [redacted], M.S.**(30-OCT-2020)** NRG Oncology-Philadelphia East Four Penn Center, 1600 JFK Blvd., Ste 1020 Philadelphia, PA 19103 267-295-9476 [redacted]
Biospecimen Bank For questions concerning biospecimen collection and translational research	NRG BB-Columbus Biopathology Center, Nationwide Children's Hospital 700 Children's Dr, WA1340 Columbus, OH 43205 866-464-2262/FAX: 614-722-2897 Email: bpcbank@nationwidechildrens.org
Gynecologic Oncology Committee [redacted]	[redacted] M.D. Memorial Sloan Kettering Cancer Center Department of Medicine 1275 York Avenue New York, NY 10065 646-888-4217 [redacted]

Protocol Agents (29-JUN-2020)

NCI-Supplied Agent(s): *Atezolizumab (NSC 783608)*
Bevacizumab (NSC 704865)

Commercial Agent: *Pegylated liposomal doxorubicin (PLD) (NSC 712227)*

IND #: [redacted]

IND Sponsor: *DCTD, NCI*

Participating Sites

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

Document History

Amendment 13	**October 13, 2022**
Amendment 12	May 17, 2021
Amendment 11	February 24, 2021
Amendment 10	January 08, 2021
Amendment 9	October 30, 2020
Amendment 8	June 29, 2020
Amendment 7	02/20/2019
Amendment 6	10/22/2018
Amendment 5	09/13/2018
Amendment 4	03/19/2018
Amendment 3	08/21/2017
Amendment 2	08/03/2017
Amendment 1	06/01/2017
Activation	04/17/2017

CONTACT INFORMATION (29-JUN-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 the Regulatory Submission sub-tab under the Regulatory tab.) 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. Please see 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 Web page of the CTSU Member Web site located at 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 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.		

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NRG-GY009 SCHEMA (10/22/2018) (24-FEB-2021)
THIS STUDY IS CURRENTLY IN THE PHASE III PORTION (02/20/2019) (29-JUN-2020)

This study consists of four components which will be conducted in sequence:
a) Stage 1 of a safety lead-in
b) Stage 2 of a safety lead-in
c) A randomized phase II study
d) A randomized phase III study

Stage 1 of the safety lead-in

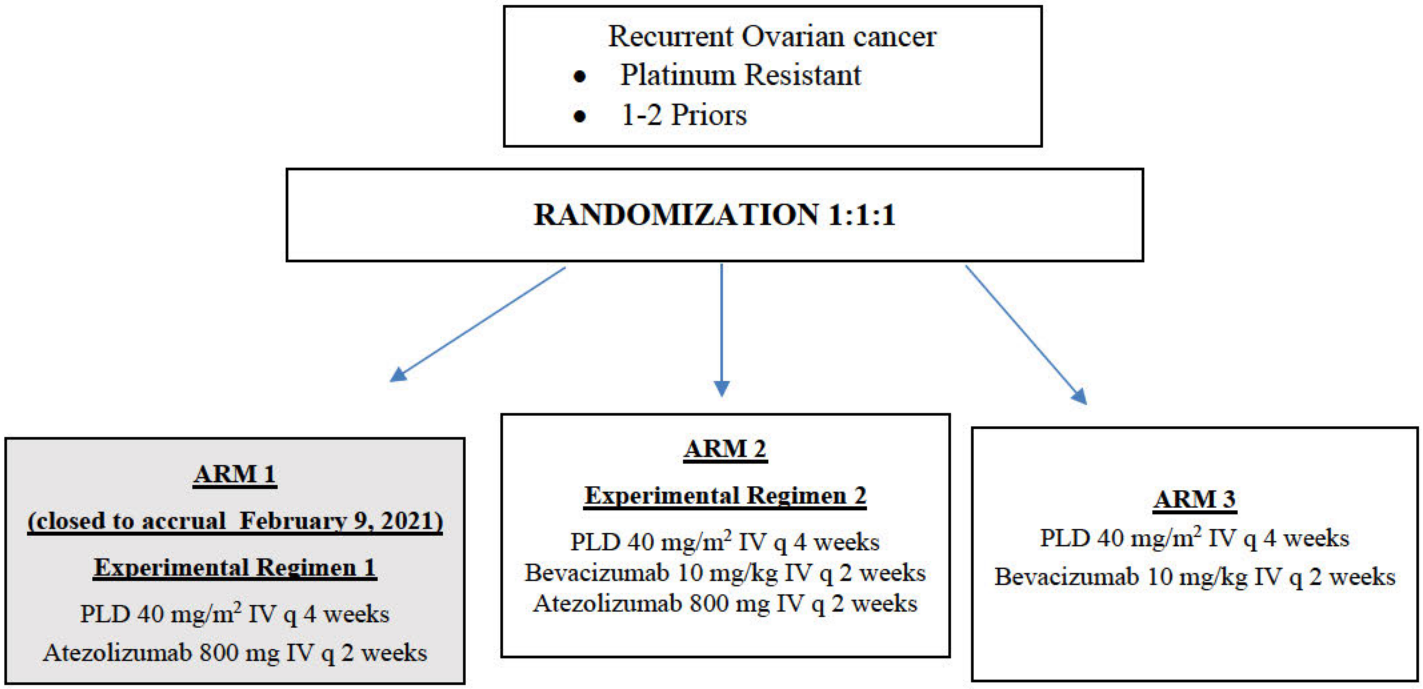
During the first stage of the safety lead-in, treatment assignment will not be randomized. All subjects will receive the PLD + atezolizumab regimen (Accrual: 8 subjects). The safety of this regimen will be assessed when these subjects have been completely evaluated for adverse events following their first cycle of treatment. If the PLD + atezolizumab regimen is deemed sufficiently safe, following this review, then the second stage of the safety lead-in will be initiated

Stage 2 of the safety lead-in

The study treatments will be randomly allocated during the 2nd stage of the safety lead-in until at least 8 subjects are allocated to and initiate PLD + atezolizumab + bevacizumab. The safety of this regimen will be assessed when these subjects have been completely evaluated for adverse events following their first cycle of treatment. If the PLD + atezolizumab + bevacizumab regimen is deemed sufficiently safe, following this review, then the randomized phase II component of this study will be initiated.

Randomized Phase II/III

Note: Arm 1 was permanently closed to accrual with Amendment 11



PLD = pegylated liposomal doxorubicin
Safety Lead-Ins – Limited access (Restricted to NRG Oncology, Participating Institutions for Safety Lead-Ins)
See Section 5.1.1 and Table 4.2 for guidance on PLD dosing if cumulative dose of PLD exceeds 550mg/m^2.

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Safety Lead-in: Estimate the probability of a dose limiting toxicity (DLT) following cycle 1 of experimental regimens (PLD and atezolizumab and PLD/bevacizumab and atezolizumab).

1.1.2 Phase II Study: Estimate and compare the hazard of first progression or death (PFS) of each experimental regimen relative to the reference regimen, PLD and bevacizumab.

1.1.3 Phase III Study: Estimate and compare the hazard of death and the hazard of first progression or death (PFS) of the experimental regimen relative to the reference regimen. **(24-FEB-2021)**

1.2 Secondary Objectives

1.2.1 Phase II Study: ***Secondary efficacy endpoint*****:** Estimate and compare the probabilities of response (ORR, either partial or complete response) defined by RECIST v1.1 criteria on each study regimen. **(24-FEB-2021)**

Safety endpoint**:** Estimate the frequency and severity of adverse events as classified and graded with Common Terminology Criteria for Adverse Events (CTCAE) in those patients who initiate their randomly assigned study treatment. **(03/19/2018)**

1.2.2 Phase III Study: ***Secondary efficacy endpoints:*** Estimate and compare ORR in each treatment group.

Safety endpoints**:** Estimate the frequency and severity of adverse events in those patients who initiate their randomly assigned study treatment.

Patient Reported outcomes (PRO): Estimate and compare mean patient reported outcome scores (PROs) as measured by NFOSI-18 Disease-related symptoms (DRS).

Exploratory endpoints: **Estimate and compare the treatment groups on the basis of the PROs:** Treatment Side Effects (TSE), Function/well-being (FWB), Fatigue (FACIT-Fatigue subscale-) and Abdominal Discomfort (FACT/GOG-AD subscale). **(10/16/2017)**

1.3 Translational Science Objectives

1.3.1 To determine whether biomarker levels in pre-treatment tissue, and pre- or on-treatment peripheral blood, and stool specimens are associated with ORR, PFS and/or OS.

Integrated Biomarker

Estimate pre-treatment PD-L1 expression on tumor cells measured by quantitative immunohistochemistry (IHC), and determine whether it is associated with the duration of PFS or overall survival.

Exploratory Biomarkers (10/16/2017)

Note: Exploratory biomarker testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

(1) Analysis of T cell receptor (TCR) repertoires by deep sequencing of peripheral blood samples;
(2) Tumor "immunogenicity" as determined by the neo-antigen landscape and characterization of the tumor microenvironment using next-generation sequencing, including but not limited to whole exome sequencing and/or RNA sequencing; and
(3) Microbiome analysis via stool sampling.

1.3.2 To determine whether changes in quantitative biomarker parameters after the first 6 and 12 weeks of therapy predict ORR, PFS and/or OS.

2. BACKGROUND

Prior genomic analyses of ovarian cancer have revealed far fewer somatic mutations than in cancers related to chronic mutagenic exposures such as lung (tobacco) and malignant melanoma (UV), with approximately 60 per exome in ovarian cancer compared to >400 per exome in melanoma and lung cancer (http://www.ncbi.nlm.nih.gov/pubmed/23945592, http://www.ncbi.nlm.nih.gov/pubmed/21720365). The Cancer Genome Atlas (TCGA) for ovarian cancer, reporting approximately 61 somatic mutations per tumor, was performed on chemotherapy naïve, primary tumor specimens (http://www.ncbi.nlm.nih.gov/pubmed/21720365). Ovarian cancers treated with DNA damaging chemotherapies (e.g., platinums, doxorubicin) may have more somatic mutations and therefore more neoantigens than untreated cancers. Overall though, ovarian cancers have a substantially lower median mutational burden than other checkpoint blockade sensitive malignancies, yet a subset of patients still benefit clinically in early studies of PD-L1/PD-1 blockade therapies (see Table 1 below).

Tumor infiltrating lymphocytes (TILs) in both cancer stroma and within cancer epithelium have been shown to be associated with improved clinical outcomes in advanced ovarian cancer (http://www.ncbi.nlm.nih.gov/pubmed/16344461, http://www.ncbi.nlm.nih.gov/pubmed/12529460), further indicating the potential importance of immune targeting in this disease.

To increase the proportion of benefiting patients, ovarian cancer must be made "visible" to the immune system, which may require targeting of disease specific immune targets and/or target enhancement through judicious combinations (http://www.ncbi.nlm.nih.gov/pubmed/26205340). Strategies to improve activity of PD-L1/PD-1 blockade include immune combinations (e.g., CTLA4/ipilimumab), chemotherapy combinations and targeted therapy combinations (e.g., anti-angiogenic agents, DNA repair).

NRG-GY003, is a randomized phase II trial of nivolumab vs nivolumab + ipilimumab. This trial has completed the second stage accrual and is in follow-up. This trial will provide preliminary proof of principle concerning the anti-PD-1/CTLA4 combination. **(03/19/2018)**

An industry sponsored phase III trial study is under way evaluating the PD-L1 targeting agent avelumab alone or with PLD, versus PLD alone (NCT02580058). This trial will provide proof of principle concerning the PLD/anti-PD-L1 combination, although will not allow for a concurrent comparator arm for the current concept.

Preclinical and early phase clinical trial data provide the rationale for the combination of the anti-PD-L1 agent atezolizumab with pegylated liposomal doxorubicin (PLD) and bevacizumab.

2.1 Background on Atezolizumab (06/29/2017)

Atezolizumab (MPDL3280A) is a human immunoglobulin (Ig) G1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids) and is produced in Chinese hamster ovary cells (Investigator's Brochure, 2016). Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution (asparagine to alanine) at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells. Atezolizumab targets human programmed death-ligand 1 (PD-L1) and inhibits its interaction with its receptor, programmed death-1 (PD-1). Atezolizumab also blocks the binding of PD-L1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells.

Atezolizumab shows anti-tumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy.

Atezolizumab is approved in the United States for the treatment of locally advanced or metastatic urothelial carcinoma and as well as metastatic non-small cell lung carcinoma. Atezolizumab is being investigated as a potential therapy against additional solid tumors and hematologic malignancies in humans.

Mechanism of Action

PD-L1 expression is prevalent in many human tumors (*e.g.*, lung, bladder, ovarian, melanoma, colon carcinoma), and its overexpression has been associated with poor prognosis in patients with several cancers (Thompson *et al.*, 2006; Hamanashi *et al.*, 2007; Okazaki and Honjo 2007; Hino *et al.*, 2010). PD-L1 binds to two known inhibitory receptors expressed on activated T cells (PD-1 and B7.1), and receptor expression is sustained in states of chronic stimulation such as chronic infection or cancer (Blank *et al.*, 2005; Keir *et al.*, 2008). Ligation of PD-L1 with PD-1 or B7.1 inhibits T-cell proliferation, cytokine production, and cytolytic activity, leading to the functional inactivation or inhibition of T cells. Aberrant expression of PD-L1 on tumor cells has been reported to impede anti-tumor immunity, resulting in immune evasion (Blank and Mackensen, 2007). Therefore, interruption of the PD-L1/PD-1 and PD-L1/B7.1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity. Blockade of PD-L1 or PD-1 with monoclonal antibodies has been reported to result in strong and often rapid antitumor effects in several mouse tumor models (Iwai *et al.*, 2002; Strome *et al.*, 2003). These data suggest that tumor-specific T cells may be present in the tumor microenvironment in an inactive or inhibited state, and blockade of the PD-L1/PD-1 pathway can reinvigorate tumor-specific T-cell responses.

Collectively, these data establish the PD-L1/PD-1 pathway as a promising new therapeutic target in patients with advanced tumors. Immune-related adverse events (AEs) reported from the two recent studies were consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance.

Summary of Nonclinical Experience

The safety, pharmacokinetics (PK), and toxicokinetics of atezolizumab were investigated in mice and cynomolgus monkeys to support intravenous (IV) administration and to aid in projecting the appropriate starting dose in humans. Given the similar binding of atezolizumab for cynomolgus monkey and human PD-L1, the cynomolgus monkey was selected as the primary and relevant nonclinical model for understanding the safety, PK, and toxicokinetics of atezolizumab.

Overall, the nonclinical PK and toxicokinetics observed for atezolizumab supported entry into clinical studies, including providing adequate safety factors for the proposed phase 1 starting doses. The results of the toxicology program were consistent with the anticipated pharmacologic activity of down-modulating the PD-L1/PD-1 pathway and supported entry into clinical trials in patients.
Refer to the Atezolizumab Investigator's Brochure for details on the nonclinical studies.

Summary of Clinical Experience

A summary of clinical data from company-sponsored atezolizumab trials is presented below. Details of all ongoing studies can be found in the Atezolizumab Investigator's Brochure.

Clinical PK and Immunogenicity

On the basis of available preliminary PK data (0.03–20 mg/kg), atezolizumab shows linear PK at doses ≥1 mg/kg (Investigator's Brochure, 2016). Based on an analysis of exposure, safety, and efficacy date, the following factors had no clinically relevant effect: age (21−89 years), body weight, gender, positive ATA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status. No formal PK drug-drug interaction studies have been conducted with atezolizumab, and the interaction potential is unknown. Further details can be found in the current Investigator's Brochure.
The development of anti-therapeutic antibodies (ATAs) has been observed in patients in all dose cohorts and was associated with changes in PK for some patients in the lower dose cohorts (0.3, 1, and 3 mg/kg) (Investigator's Brochure, 2016). Patients dosed at >10 mg/kg maintained C_{min} values well above the target serum concentration of 6 mcg/mL despite the detection of ATAs. Accordingly, the development of detectable ATAs does not appear to have a clinically significant impact on PK for doses above 10 mg/kg. To date, no relationship between the development of measurable ATAs and safety or efficacy has been observed.

Clinical Safety Summary

As of May 10, 2016, atezolizumab has been administered (alone or in combination with other agents) to approximately 6053 patients with solid tumor and hematologic malignancies (Investigator's Brochure, 2016).The first-in-human monotherapy study PCD4989g (in patients

with locally advanced or metastatic solid tumors or hematologic malignancies) provides the majority of monotherapy safety data, with 629 safety-evaluable patients as of the data extraction date. Currently, no maximum tolerated dose (MTD), no dose-limiting toxicities (DLTs), and no clear dose-related trends in the incidence of AEs have been determined. Fatigue, decreased appetite, nausea, diarrhea, constipation, and cough were commonly reported AEs in single and combination therapy (Investigator's Brochure, 2016). AE profiles are similar across tumor types studied, including non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), and urothelial carcinoma (UC), and are consistent with the mechanism of action of atezolizumab. The overall immune-mediated AEs reported were considered moderate in severity, and the majority of patients were able to continue on atezolizumab therapy.

As of the data extraction date of December 15, 2015, there were 629 safety-evaluable patients from the first-in-human phase 1a study PCD4989g (Investigator's Brochure, 2016). The median age was 61 years. Of the 629 patients, 619 patients (98.4%) reported at least one AE of any grade or attribution to atezolizumab, and 316 patients (50.2%) experienced at least one grade 3 or 4 AE of any attribution. A total of 444 patients (70.6%) reported at least one treatment-related AE, and 86 patients (13.7%) experienced at least one treatment-related grade 3 or 4 AE. The most frequently observed AEs of any grade and attribution (occurring in ≥10% of treated patients) include fatigue, decreased appetite, nausea, pyrexia, constipation, cough, dyspnea, diarrhea, anemia, vomiting, asthenia, back pain, headache, arthralgia, pruritus, rash, abdominal pain, insomnia, peripheral edema, and dizziness.

Serious AEs (SAEs) have been reported in 261 patients (41.5%) in study PCD4989g (Investigator's Brochure, 2016). Reported SAEs were consistent with the underlying disease. Treatment-related SAEs (57 patients [9.1%]) included pyrexia, dyspnea, pneumonitis, malaise, fatigue, hypoxia, colitis, and bone pain. Pooled single-agent safety data from 1978 patients with UC, NSCLC, and other indications (including trial PCD4989g) indicate that the most frequent (>1% of patients) serious adverse drug reactions (regardless of grade) include dyspnea (3.0%), back pain (1.2%), and abdominal pain (1.1%). A list of AEs considered "expected" for atezolizumab is presented in the Atezolizumab Investigator's Brochure.

Immune-Related Adverse Events

Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs have been closely monitored during the atezolizumab clinical program (Investigator's Brochure, 2016). To date, immune-related adverse events associated with atezolizumab include hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, and meningoencephalitis.

For further details, see the most recent Atezolizumab Investigator's Brochure.
Clinical Efficacy Summary

Patients with multiple tumor types were included in study PCD4989g, with the largest cohorts consisting of patients with NSCLC, RCC, and UC (Investigator's Brochure, 2016). Objective

responses with atezolizumab monotherapy were observed in a broad range of malignancies, including NSCLC, RCC, melanoma, UC, colorectal cancer, head and neck cancer, gastric cancer, breast cancer, and sarcoma. Both the preliminary and more mature efficacy data available suggest that treatment with atezolizumab as a single agent or in combination with other therapeutic agents results in anti-tumor activity across a range of tumor types and hematologic malignancies (UC, NSCLC, RCC, TNBC, melanoma, CRC, and NHL) and across lines of therapy. Clinical benefit was observed in terms of objective responses, durability of responses, and overall survival (OS). Improved efficacy of atezolizumab was observed in the unselected patient population, as well as in patients with higher PD-L1 expression on TCs or ICs (*e.g.*, NSCLC) or on ICs only (*e.g.*, mUC, RCC).

2.2 Rationale for the use of Atezolizumab in Ovarian Cancer

Checkpoint blockade agents that target CTLA-4, PD-1 and PD-L1 are in widespread use, either for FDA-approved indications or in clinical trials. Atezolizumab, an anti PD-L1 monoclonal, has exhibited tolerability and preliminary signs of efficacy in solid tumors and bladder cancers (http://www.ncbi.nlm.nih.gov/pubmed/25428504, http://www.ncbi.nlm.nih.gov/pubmed/25428503). PD-1 and PD-L1-targeting agents manufactured by other companies have shown preliminary signs of safety and efficacy in ovarian cancer. Programmed cell death one ligand one (PD-L1), the cognate ligand for PD-1, is expressed in a subset of ovarian cancers and is associated with poor prognosis (http://www.ncbi.nlm.nih.gov/pubmed/17360651). In that study, using an antibody generated by the authors, 88.6% of the 70 tumors tested were scored as having PD-L1 expression >0, with 68.6% scored as 2-3.

Promising single agent activity has been seen for anti-PD-1 and anti-PD-L1 agents tested in patients with ovarian cancer (Table 1). The anti-PD-L1 agent avelumab was well-tolerated and showed an overall response rate of 10.7%, and a disease control rate (DCR) of 54.7%, in a Phase 1b study that included 75 patients with ovarian cancer (Disis et al, J Clin Oncol 33, 2015 Abstract 5509). In a more heavily pretreated, PD-L1 positive ovarian cancer population, the anti-PD-1 agent pembrolizumab showed an ORR of 11.5% and a DCR of 34.6% (KEYNOTE-028, Varga et al, J Clin Oncol 33, 2015 Abstract 5510). In addition, the anti-PD-1 agent, nivolumab, showed an ORR of 15% and DCR of 45% in a 20 patient phase I study (http://www.ncbi.nlm.nih.gov/pubmed/26351349). A single agent, phase II study of ipilimumab in recurrent ovarian cancer has completed accrual and is in follow-up (NCT01611558).

Table 1

Study	N	RR	Disease Control Rate	Prior Treatment
Nivolumab Cohort 1: 1 mg/kg Cohort 2: 3 mg/kg IV q 2 weeks	 10 10	 1 (PR)/10 (10%) 2 (CR)/10 (20%) (1 Clear Cell) Overall RR (both cohorts) = 15%	 5/10 (50%) 4/10 (40%)	 ≥ 2 priors; platinum resistant
Avelumab	75	8 (PR)/75 (10.7%)	41/75 (54.7%)	

Phase Ib expansion cohort 10 mg/kg q 2 weeks		(2/2 Clear Cell)		No limit on priors (median 4, range 1-11); platinum resistant
Pembrolizumab Phase Ib expansion cohort 10 mg/kg q 2 weeks	26	3 (1 CR, 2 PR)/26 (11.5%)	9/26 (34.6%)	No limit on priors (>80% ≥ 4 priors); PD-L1 IHC positive*
Ipilimumab 10 mg/kg IV q3 weeks x 4 –> q12 weeks	Results pending			≤ 4 priors

* Positivity defined archival as membranous PD-L1 expression in ≥1% of cells in tumor nests or positive bands in stroma on archived or new biopsies. Assessed at a central laboratory using a prototype assay and 22C3 antibody clone (Merck). Overall 49/96 (51%) of screened patients tested positive.

Rationale for the combination of Bevacizumab and PLD

Bevacizumab is a recombinant, humanized antibody targeting VEGF that has modest single agent activity in ovarian cancer in phase II trials, as shown in Table 2 (BV = bevacizumab; http://www.ncbi.nlm.nih.gov/pubmed/18024863; http://www.ncbi.nlm.nih.gov/pubmed/18024865; GOG186G, ASCO 2014).

Table 2

Study	N	Treatment	RR (%)	PFS at 6 months (%)	Prior Treatment
GOG 170D	62	BV 15 mg/kg IV q 3 wk	21	40	1-2 priors; 58% platinum resistant
Cannistra et al	44	BV 15 mg/kg IV q 3 wk	16	28	1-3 priors; platinum-refractory or resistant AND progression on/within 3 months of topotecan or PLD
GOG186G	75	BV 10 mg/kg IV q 2 wk	9	40	1-3 priors; 68% platinum resistant

The AURELIA study demonstrated that combining bevacizumab with chemotherapy in platinum resistant ovarian cancer significantly improved progression free survival (the primary endpoint) as well as objective response rate and the patient reported outcome end point of abdominal/GI symptoms (results of each arm shown in Table 3), providing the basis for the FDA approval (http://www.ncbi.nlm.nih.gov/pubmed/24637997). PLD with bevacizumab therefore represents a standard of care backbone on which to improve.

Table 3

Agent	Median PFS Chemo Alone (months)	Median PFS Chemo + Bev (months)	HR	Median OS Chemo Alone (months)	Median OS Chemo + Bev (months)	HR
Paclitaxel	3.9	10.4	0.46 (0.30-0.71)	13.2	22.4	0.65 (0.42-1.02)
PLD	3.5	5.4	0.57 (0.39-0.83)	14.1	13.7	0.91 (0.62-1.36)

Topotecan	2.1	5.8	0.32 (0.21-0.49)	13.3	13.8	1.09 (0.72-1.67)

2.3 Rationale for the combination of PLD and Atezolizumab (24-FEB-2021)

From a molecular perspective, in addition to being a mutagenic cytotoxic, doxorubicin is known to exert its anti-tumor effects in part through interferon signaling (http://www.ncbi.nlm.nih.gov/pubmed/25344738). Atezolizumab leads to an increase in activated proliferating CD8+ T cells and a trend to increased circulating interferon gamma (http://www.ncbi.nlm.nih.gov/pubmed/25428504), suggesting a potentially complementary mechanism. With the exception of fatigue, the side effect profiles of these medications are non-overlapping.

Three examples from NSCLC provide evidence that PD-1 and PD-L1-blocking agents can be used safely with chemotherapy. 37 chemotherapy-naive patients with NSCLC were treated with atezolizumab 15mg/kg every 3 weeks in combination with carboplatin and paclitaxel, carboplatin and nab-paclitaxel or carboplatin and pemetrexed (Liu SV et al, 2015). The most common AEs of any grade were fatigue, nausea, constipation and diarrhea, and were similar across arms. The grade 3 AEs occurring in ≥5% of patients were neutropenia, anemia, thrombocytopenia and increased ALT/AST. All but the increased transaminases could be attributed primarily to the chemotherapy component of the combinations. 35/37 patients experienced disease stability or better, but this study design precludes conclusions about efficacy.

In another study, patients with chemotherapy-naïve NSCLC were treated with 4 cycles of pembrolizumab (2 or 10mg/kg) plus carboplatin (AUC 6) and paclitaxel (200mg/m2) every 3 weeks followed by pembrolizumab maintenance, or the same dosing of pembrolizumab with carboplatin (AUC 5) and pemetrexed (500mg/m2) followed by pembrolizumab plus pemetrexed maintenance (Papadimitrakopoulou V et al, 2015). Grade 3-4 toxicities were rare, and including 1-3 cases across cohorts of increased ALT, increased AST, anemia, atrial fibrillation, colitis, diarrhea, rash, fatigue, hypertension, hyponatremia, infectious pleural effusion, and in the carboplatin + paclitaxel cohort, leucopenia, neutropenia, decreased white blood cell count and febrile neutropenia. As in the study above, the disease control rate was high, but conclusions about efficacy are limited given the study design.

A similar study was conducted with nivolumab (platinum-based doublet paired with gemcitabine, pemetrexed or paclitaxel, all with nivolumab followed by nivolumab maintenance (Antonia SJ et al, 2014). Grade 3-4 AE were again rare: of 56 patients, 1-3 across arms experienced fatigue, nausea, anorexia, anemia, rash or diarrhea.

Arm 1 (PLD and atezolizumab) was permanently closed to accrual with amendment 11 as the planned interim analysis for this regimen crossed the futility boundary for early termination, which was based on overall survival compared to standard of care PLD and bevacizumab (Arm 3). The overall survival for patients in Arm 1 (PLD/atezolizumab) was not definitively worse than the standard of Arm 3 (PLD and bevacizumab) and there were no notable additional risks.

2.4 Rationale for the combination of Bevacizumab and Atezolizumab

Preclinical data illustrate the immunosuppressive effects of VEGF, which are reversed by VEGF blockade. VEGF is thought to induce myeloid derive suppressor cells (MDSC), which suppress the anti-tumor T-cell and dendritic cell response (http://www.ncbi.nlm.nih.gov/pubmed/22437938). VEGF blockade may increase T cell trafficking to tumors, increase anti-tumor populations of T cells (CD8+ and CD4+ central memory) and decrease pro-tumor immune populations (myeloid-derived suppressor cells and regulatory T cells) (http://www.ncbi.nlm.nih.gov/pubmed/18566400, http://www.ncbi.nlm.nih.gov/pubmed/24018532, http://www.ncbi.nlm.nih.gov/pubmed/17606729, http://www.ncbi.nlm.nih.gov/pubmed/20631075).
In addition, anti-VEGF therapies may reduce suppressive cytokines, tumor-infiltrating T regulatory cells and MDSC (http://www.ncbi.nlm.nih.gov/pubmed/19888452).

Several clinical studies have illustrated the potential advantage of adding anti-angiogenic agents to checkpoint blockade therapy. A Phase II study of bevacizumab with the anti-CTLA-4 agent ipilimumab in melanoma showed a DCR of 67.4% and median survival of 25.1 months, which was substantially better than historical controls. Furthermore, on-treatment biopsies exhibited inflammation and lymphocyte infiltration (http://www.ncbi.nlm.nih.gov/pubmed/24838938). **In a Phase Ib study of 12 patients with renal cell carcinoma treated with bevacizumab and atezolizumab, 40% had an objective response**, which appeared to occur independent of PD-L1 IHC staining (Figure 1, McDermott et al, ESMO 2014, Abstract 809O; Sznol et al, JClin Oncol 33, 2015 Abstract 410). A phase III trial is in progress (A phase III, open label, randomized study of atezolizumab [anti-PD-L1 antibody] in combination with bevacizumab versus sunitinib in patients with untreated advanced renal cell carcinoma). Renal cell carcinomas (RCC), like ovarian cancers, do not harbor a high mutational burdens (thought to underlie the efficacy of checkpoint blockade agents in melanoma and lung cancers), and are treated with bevacizumab as a standard of care. A Phase III study is also under way of atezolizumab in combination with carboplatin and paclitaxel with or without bevacizumab in stage IV non-squamous NSCLC (NCT02366143).

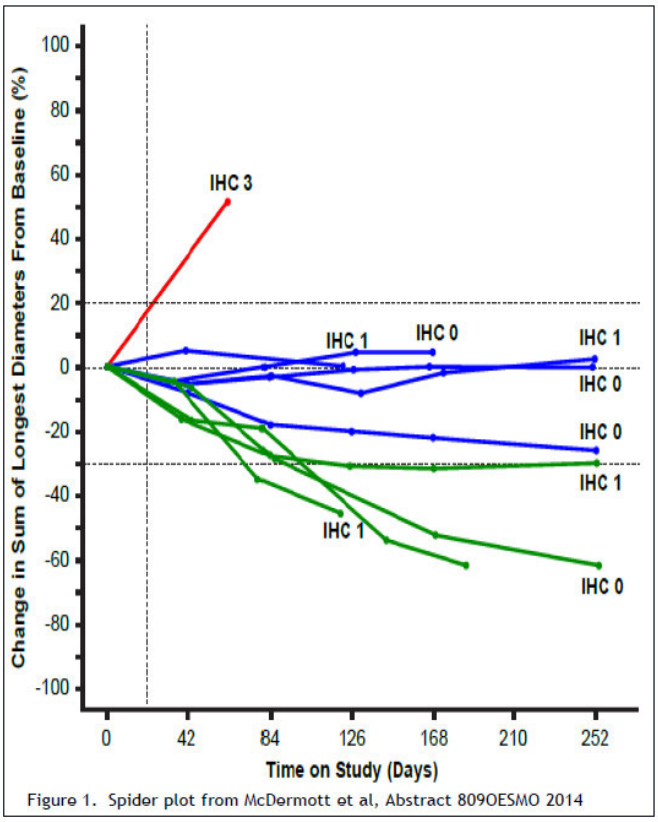


Figure 1. Spider plot from McDermott et al, Abstract 809OESMO 2014

The combination of atezolizumab and bevacizumab has already provided an excellent safety signal. In Study GP28328, the grade 3-5 AE rate was 1/35 patients (2.9%). The one >= grade 3 event was neutropenia.

2.5 Rationale for the combination of PLD, Bevacizumab and Atezolizumab

Based on the safety of single agent atezolizumab alone, atezolizumab plus bevacizumab, and atezolizumab plus chemotherapy; the preliminary evidence for PD-1 and PD-L1-targeting agents in ovarian cancer; the non-overlapping toxicities of these three agents; the scientific rationale for combining PLD and/or bevacizumab with atezolizumab and the need to improve outcomes in patients with platinum-resistant ovarian cancers, we propose a three-arm trial consisting of PLD and bevacizumab (reference arm); the addition of atezolizumab to PLD (Experimental Regimen 1); or the addition of atezolizumab to PLD and bevacizumab (Experimental Regimen 2) in a Phase II/III study.

2.6 Translational Science Background

Note: Exploratory biomarker testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

2.6.1 PD-L1 Expression (Integrated Biomarker) **(30-OCT-2020)**

PD-L1 expression will be evaluated as an integrated biomarker in this study. PD-L1, also known as B7-H1, is an inhibitory ligand expressed in multiple cancer types including ovarian.

In addition to being inherently upregulated in some cancer types, more commonly, PD-L1 expression is upregulated in response to tumor-infiltrating lymphocytes and thus serves as a mechanism of adaptive immune resistance to T cell infiltration (Taube et al., 2014). Expression of PD-L1 on tumor cells and tumor-infiltrating immune cells has been shown to be associated with response to immune checkpoint blocking antibodies targeting PD-1 or PD-L1 in several cancer types (reviewed in https://www.ncbi.nlm.nih.gov/pubmed/24714771). PD-L1 expression in tumor infiltrating immune cells (IC) in particular has been shown to be the strongest predictor of response. Powles *et al.* published a phase I study investigating the anti-PD-L1 antibody atezolizumab for the treatment of metastatic urothelial bladder cancer (Powles et al., 2014). This study showed that atezolizumab had noteworthy activity in metastatic UBC with rapid responses occurring at the first response assessment (6 weeks) and nearly all were ongoing at the data cutoff (Powles et al., 2014). PD-L1 expression is scored in tumor infiltrating immune cells (as percentage of tumor area: IC3≥10%, IC2≥5% and <10%, IC1≥1% and <5%, and IC0<1%).

VENTANA PD-L1 (SP142), is an FDA-approved complimentary diagnostic IHC assay to ascertain tumor PD-L1 status for patients with metastatic urothelial cancer and triple negative breast cancer (TNBC) considering treatment with atezolizumab, with IC1 staining (PD-L1 positivity ≥1%) as a cutoff.

The association of PD-L1 expression with response to PD-L1 blockade in ovarian cancer has not been established. We hypothesize that the tumor microenvironment of the ovarian cancer patients exhibiting higher levels of PD-L1 expression in tumor-infiltrating immune cells is more amenable to immunotherapy with immune checkpoint blockade. As such we hypothesize that patients with higher levels of PD-L1 will exhibit evidence of stronger anti-tumor immune response and improved PFS and OS in the NRG-GY009 trial.

SP142 assay was previously used to evaluate PD-L1 expression in ovarian cancer (Webb et.al., 2016). In the cohort of 490 ovarian cancer cases analyzed by tissue microarray, PD-L1 IC1 positivity (defined as ≥1%) was observed in 57.4% of high-grade serous cases, 24% of endometrioid cases, and 16% of clear cell cases. Internal data provided by Genentech demonstrates IC1 staining in approximately 60% of patients and IC2 staining (>5%) in approximately 20% of patients with ovarian cancer. Based on the study above, we assume that approximately 50% of patients in our population will be PD-L1 positive (defined as ≥1%). In this trial, archival pre-treatment formalin-fixed, paraffin-embedded (FFPE) tumor tissue will be evaluated by immunohistochemistry (IHC) for expression of PD-L1 on tumor and immune cells using the PD-L1 antibody clone SP142. The association of PD-L1 expression and clinical outcome, specifically PFS and OS, will be investigated. Details of PD-L1 testing are available in (section 10.3).

2.6.2 T Cell Receptor (TCR) Repertoires (Exploratory Biomarker)

The analysis of overall changes in TCR repertoires during therapy may help to determine whether certain dominant T cell clones emerge or persist in response to therapy. Cha and colleagues reported that maintenance of specific T cell clonotypes in blood of patients with advanced melanoma treated with ipilimumab was associated with improved survival (https://www.ncbi.nlm.nih.gov/pubmed/24871131). More recently, a study out of Memorial

Sloan Kettering Cancer Center (MSKCC) demonstrated that the baseline peripheral blood mononuclear cell TCR clonality and expansion of tumor-specific TCR in the peripheral blood 3 weeks after initiating treatment were found to correlate with response to atezolizumab in bladder cancer (Funt et al, ASCO 2016). TCR repertoire studies were performed in tumors at MSKCC in the setting of a clinical trial in patients with early stage breast cancer treated with neoadjuvant cryoablation of breast lesion and ipilimumab, where combination therapy demonstrated most significant increase in intra-tumoral T cell clone (Page DB, Diab A, Yuan J, et al., 2014) In this trial DNA will be used for TCR repertoire analysis and deep sequencing of intratumoral and peripheral blood mononuclear cell TCR CDR3 regions (Adaptive Biotechnologies). Peripheral blood DNA will be collected at baseline (prior to initiation of treatment) and at 4 weeks after initiation of therapy in patients participating in the Phase II portion of the study.

2.6.3 Neoantigen Landscape and Characterization of the Tumor Microenvironment (Exploratory Biomarker) **(06/29/2017) (10/16/2017)**
A recent study by the group at Memorial Sloan Kettering Cancer Center (MSKCC) used next-generation whole exome sequencing (NGS) to characterize the neoantigen landscapes in tumors from patients with malignant melanoma and lung cancers (https://www.ncbi.nlm.nih.gov/pubmed/25409260, https://www.ncbi.nlm.nih.gov/pubmed/25765070). In addition, it is known that the tumor microenvironment plays a key role in mediating response as well as immune escape to cancer immunotherapy. To determine whether specific tumor genetic determinants, including predicted mutation burden, as well as immune-modulatory elements or other molecular characteristics of the tumor microenvironment influence the response to either treatment, DNA isolated from archived tumor samples will be processed for NGS and/or RT-PCR to assess for specific driver mutations, for potential neoantigens, and for potential gene expression signatures.

2.6.4 Microbiome Analysis (Exploratory Biomarker) **(10/16/2017)**
As a site of substantial immune activity, the gut (small and large intestines) represents an organ system of known importance to systemic inflammatory conditions (https://www.ncbi.nlm.nih.gov/pubmed/20620945, https://www.ncbi.nlm.nih.gov/pubmed/26102221). Recent studies have demonstrated a role for stool microbiota in influencing response to checkpoint blockade therapy in preclinical models, with a small, retrospective data in human samples to corroborate its importance (https://www.ncbi.nlm.nih.gov/pubmed/26541610, https://www.ncbi.nlm.nih.gov/pubmed/26541606). Manipulation of the gut microbiome by fecal transplant for the treatment of *Clostridium difficile* is safe and effective (https://www.ncbi.nlm.nih.gov/pubmed/23323867). The importance of the gut microbiome to checkpoint blockade outcomes has not yet been studied in a prospective setting. To determine whether the diversity or particular bacterial subtypes in the stool microbiome are associated with clinical benefit from checkpoint blockade therapy, DNA will be isolated from stool samples prior to cycles 1 and 2, using samples from patients participating in the Phase II portion of the study. DNA will undergo 16S Pyrosequencing, organism identification and analyses for prevalence and population shifts using techniques described in the

aforementioned publications (https://www.ncbi.nlm.nih.gov/pubmed/20620945, https://www.ncbi.nlm.nih.gov/pubmed/26102221). **(02/20/2019)**

2.6.5 Additional translational studies may be performed from banked tissues or blood. **(10/16/2017)**

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY 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-Pittsburgh Office: 412-624-2666.

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Administration of study drugs (pegylated liposomal doxorubicin, bevacizumab, atezolizumab) may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of child-bearing potential (WOCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of study agent. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately. **(06/29/2017)**

3.1.3 Submission of tumor tissue is required for all patients. Investigators should check with their site Pathology Department regarding release of biospecimens before approaching patients about participation in the trial.

3.2 Eligibility Criteria (06/29/2017)

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

3.2.1 High grade ovarian cancer, including high grade serous; clear cell; endometrioid, grade 3; and others (adenocarcinoma, NOS; mixed epithelial carcinoma; undifferentiated carcinoma). NOTE: Low grade serous, mucinous and carcinosarcoma histologies are excluded due to their different underlying genomic features and/or clinical behavior. Ovarian cancer = ovarian, fallopian tube or primary peritoneal cancer. Required data element: submission of pathology report.

3.2.2 Recurrent, platinum resistant ovarian cancer (defined as progression within < 6 months from completion of platinum based therapy. The date should be calculated from the last administered dose of platinum therapy).

3.2.3 1-2 prior regimens (including primary therapy). Hormonal therapies (*e.g.*, tamoxifen, aromatase inhibitors) will not count toward the prior regimen limit. PARP inhibitors given in the maintenance setting post response to platinum-based therapy will not count as a separate regimen from the preceding platinum-based therapy. **(30-OCT-2020).**

3.2.4 Measurable disease (defined by RECIST v 1.1) or evaluable disease (defined as solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 definitions for target lesions OR ascites and/or pleural effusion that has been pathologically demonstrated to be disease related in the setting of CA125 ≥ 2xULN).

3.2.5 Age ≥ 18

3.2.6 The trial is open to females only

3.2.7 Performance Status 0, 1 or 2 (see Appendix II)

3.2.8 Adequate hematologic function within 14 days prior to registration defined as follows:

- ANC ≥ 1,500/mcl
- Platelets ≥ 100,000/mcl
- Hgb ≥ 8 g/dl

3.2.9 Adequate renal function within 14 days prior to registration defined as follows:

- Creatinine ≤ 1.5 x institutional upper limit of normal (ULN)
- Urine protein creatinine (UPC) ratio must be < 1.0. If UPC ratio ≥ 1, collection of 24-hour urine measurement of urine protein is recommended (24-hour urine protein level must be < 1000 mg for patient enrollment). If UPC ratio cannot be calculated because the urine protein is below the lower limit of detection of the assay this will not exclude the patient. **(10/22/2018) (30-OCT-2020).**

  UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:
  1. [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
  2. [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L
     (03/19/2018)

3.2.10 Adequate hepatic function within 14 days prior to registration defined as follows:

- Total Bilirubin ≤ 1.5 x ULN (patients with known Gilbert disease who have serum bilirubin level ≤ 3 x ULN may be enrolled)
- AST/ALT ≤ 3 x ULN (AST and/or ALT ≤ 5 x ULN for patients with liver involvement)

3.2.11 INR and aPTT ≤ 1.5 x ULN (or on stable dose of therapeutic anticoagulation, such as low-molecular-weight heparin, warfarin or rivaroxaban) **(10/16/2017)**

3.2.12 TSH within normal limits (Euthyroid patients on thyroid replacement therapy allowed provided TSH < ULN.) **(02/20/2019)**

3.2.13 The patient or 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.

3.3 Ineligibility Criteria (06/29/2017)

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

3.3.1 Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.

3.3.2 Patients who have had systemic anticancer therapy (*e.g.*, chemotherapy, targeted therapy including PARP inhibitors or bevacizumab) within 3 weeks prior to entering the study. **(30-OCT-2020).**

3.3.3 Patients who have had hormonal therapy (*e.g.*, tamoxifen, aromatase inhibitor) within 1 week prior to entering the study.

3.3.4 Patients with prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapeutic antibody or other similar agents. **(10/16/2017)**

3.3.5 Patients with prior treatment with bevacizumab (or any other anti vascular therapy, e.g., cediranib) for platinum resistant recurrence. (Note: Prior bevacizumab in initial therapy and/or platinum sensitive recurrent setting is allowed.) **(10/16/2017)**

3.3.6 Patients with prior treatment with PLD.

3.3.7 Prior radiotherapy to the abdomen or pelvis.

3.3.8 Patients who have not recovered from adverse events to ≤ grade 1 (other than alopecia) due to agents administered more than 3 weeks earlier. **(10/16/2017)**
However, the following therapies are allowed:

- Hormone replacement therapy or oral contraceptives
- Herbal therapy >1 week prior to Cycle 1, Day 1 (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)
- Palliative radiotherapy for bone metastases >2 weeks prior to Cycle 1, Day 1

3.3.9 Treatment with any other investigational agent within 4 weeks prior to Cycle 1, Day 1.

3.3.10 Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-alpha or interleukin [IL]-2) within 6 weeks prior to Cycle 1, Day 1.

3.3.11 Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.

- Patients who have received acute, low dose, systemic immunosuppressant medications (*e.g.*, a one-time dose of dexamethasone for nausea or steroids as CT scan contrast premedication) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

3.3.12 Patients taking bisphosphonate therapy for symptomatic hypercalcemia within the past 28 days. Use of bisphosphonate therapy for other reasons (*e.g.*, bone metastasis or osteoporosis) is allowed.

3.3.13 Patients with known primary central nervous system (CNS) malignancy or symptomatic CNS metastases are excluded, with the following exceptions:

- Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:
  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.
  - No neurosurgical resection or brain biopsy within 28 days prior to Cycle 1, Day 1
- Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:
  - Radiographic demonstration of improvement upon the completion of CNS directed therapy and no evidence of interim progression between the completion of CNS directed therapy and the screening radiographic study
  - No stereotactic radiation or whole brain radiation within 28 days prior to Cycle

1, Day 1
- Screening CNS radiographic study ≥ 4 weeks from completion of radiotherapy and ≥ 2 weeks from discontinuation of corticosteroids

3.3.14 Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.

3.3.15 History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

3.3.16 Patients requiring treatment with a RANKL inhibitor (e.g., denosumab) who cannot discontinue it before treatment with atezolizumab.

3.3.17 Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.
- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

3.3.18 History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. **(02/20/2019)**
- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen or Type 2 diabetes mellitus are eligible.
- Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
  - Rash must cover less than 10% of body surface area (BSA)
  - Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
  - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.3.19 History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.3.20 Patients with active tuberculosis (TB) are excluded.

3.3.21 Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

3.3.22 Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1.

3.3.23 Received oral or intravenous (IV) antibiotics within 2 weeks prior to Cycle 1, Day 1. Patients receiving prophylactic antibiotics (*e.g.*, for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

3.3.24 Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study.

3.3.25 Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of atezolizumab. **(06/29/2017)**

- Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.

3.3.26 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3.27 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial. **(08-JAN-2021)**

3.3.28 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years, with the exception of those with a negligible risk of metastases or death, such as carcinoma in situ of the breast or cervix.

3.3.29 Severe, active co-morbidity defined as follows:

- Current (within 28 days of Cycle 1, Day 1) signs and/or symptoms of bowel obstruction
- Patients who require parental hydration and/or nutrition
- Patients who require drainage gastrostomy tube
- Evidence of bleeding diathesis or clinically significant coagulopathy
- Serious, non-healing or dehiscing wound, active ulcer or untreated bone fracture
- History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month of study enrollment

3.3.30 Significant cardiovascular or cerebrovascular disease including:

- Uncontrolled hypertension (SBP ≥150 and/or DBP ≥90) **(29-JUN-2020)**
- History of myocardial infarction within 6 months
- Unstable angina
- New York Heart Association functional classification II, III or IV (See Appendix III)
- Baseline ejection fraction ≤ 50% as assessed by echocardiogram or MUGA
- Cerebral vascular accident (CVA) or transient ischemic attack (TIA) within 6 months
- Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or peripheral arterial thrombosis) within 6 months

3.3.31 History of abdominal/pelvic or tracheoesophageal fistula or gastrointestinal perforation and/or abdominal/pelvic abscess within 6 months prior to initiation of treatment. **(02/20/2019)**

3.3.32 Pregnant or lactating patients.

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

4.1 PRE-TREATMENT ASSESSMENTS (10/22/2018)

Assessments	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	≤ 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, Bilirubin, Protein, Albumin, Alkaline Phosphatase, AST, ALT)	≤ 14 days	≤ 14 days
TSH	≤ 14 days	≤ 14 days
Hepatitis B Surface Antigen	≤ 28 days	≤ 28 days
Hepatitis B Core Antibody	≤ 28 days	≤ 28 days
Hepatitis C Antibody	≤ 28 days	≤ 28 days
UPCR	≤ 14 days	≤ 14 days
INR and aPTT§ **(06/29/2017)**	≤ 28 days	≤ 28 days
Pregnancy Test (if childbearing potential exists)	≤ 14 days	≤ 24 hours
ECG	≤ 28 days	≤ 28 days
ECHO or MUGA†	≤ 28 days	≤ 28 days
CA-125 **(10/16/2017)**	≤ 28 days	≤ 28 days
Radiographic Tumor Measurement*	≤ 28 days	≤ 28 days
Patient Reported Outcomes (PRO)+		Baseline – prior to any premedication or treatment administration

§ See Sec 3.2.11.**(10/16/2017)**
† The same method should be used for each patient throughout the study.
*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. Images from radiographic studies should be uploaded for future independent radiologic review via TRIAD Digital Image Submission as detailed in Appendix IX. **(03/19/2018)**
+All PRO questionnaires should be completed before any study specific procedures are performed and before the patient sees the physician.

4.2 ASSESSMENTS DURING TREATMENT (29-JUN-2020)

Assessments	Prior to Each Cycle, Day 1 (after Cycle 1, Day 1)	Prior to Every Odd Cycle (i.e., Cycle 3, Day 1; Cycle 5, Day 1; etc.)	Timed (Treatment Cycle Independent)
History and Physical	≤ 1 day		
Concomitant Medications*	≤ 1 day		
Corticosteroid Use (to manage adverse events)	≤ 1 day		
Secondary Immunosuppressive Agent Use (e.g., infliximab)	≤ 1 day		
Vital Signs	≤ 1 day		
Performance Status	≤ 1 day		
Toxicity Assessment	≤ 1 day		
CBC/Differential/Platelets	≤ 3 days		
Chemistries (BUN, Creatinine, Sodium, Potassium, Chloride, CO2, Calcium, Glucose, Bilirubin, Protein, Albumin, Alkaline Phosphatase, AST, ALT)	≤ 3 days		
TSH	≤ 7 days		
UPCR		≤ 7 days	
ECHO or MUGA		[1] ≤ 7 days **(10/22/2018)**	
CA125	X		
Radiographic Tumor Measurement			X[2]
Patient Reported Outcomes (PRO)			X[3]

*** Due to their immunosuppressive effect, administration of systemic steroids (e.g., dexamethasone) as an antiemetic and/or preparative regimen for hypersensitivity reactions should be avoided if other means of treatment are available and medically appropriate.**

[1] Necessary when the cumulative dose of PLD exceeds 550 mg/m^2. Repeat echocardiogram or MUGA scan every other cycle or according to institutional standards. Please include any prior anthracycline therapy when determining the cumulative lifetime dose of anthracyclines. The same method should be used for each patient throughout the study. **(02/20/2019)**

[2] Every 8 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule) for the first 12 months; then every 12 weeks (+/- 7 days) thereafter. 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. Images from radiographic studies should be uploaded for future independent radiologic review via TRIAD Digital Image Submission as detailed in Appendix IX. An excel tool is available on the CTSU website to calculate dates of re-

imaging. Chest imaging is also indicated to monitor for evidence of immune pneumonitis. See below for guidance concerning continuation of treatment in cases of radiologic progression at the first 8 week (+/- 7 days) CT. **(03/19/2018)**

The protocol specifies continuation of treatment in cases of radiologic progression at the first 8 week (+/- 7 days) CT if all of the following criteria are satisfied:

- No decrease in performance status
- No requirement for immediate alternative treatment or urgent palliative treatment
- Progression limited to an increase of 40% in the sum of diameters of target lesions (including the addition of up to 4 new lesions to the sum)
- No more than 4 new lesions included in the sum

For patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT:

- At any subsequent CT scan patients who have stable disease as compared to the 8 week (+/- 7 days) CT scan will be allowed to continue on study treatment.
- Patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT, and later experience a PR or CR (as compared to baseline CT) will be recorded as delayed responses by the Statistics and Data Management Center.

For patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT, must have repeat CT in 4 weeks (+/- 7days) to rule out further progression.

[3] Patient Reported Outcomes (PRO) assessments will be performed every 8 weeks during the first year (which coincides with radiographic tumor assessment and treatment cycles 3, 5, 7, 9, 11, and 13, if on schedule), and every 12 weeks during the second year, unless the patient withdraws from study participation. PRO assessments should continue post-progression. All questionnaires should be completed before any study specific procedures are performed and before the patient sees the physician. **(10/16/2017)**

4.3 ASSESSMENTS IN FOLLOW UP

Assessments	Timed
Vital Status	1
Toxicity Assessment	2
Radiographic tumor measurement	3
Patient reported outcomes (PRO)	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. The Follow-up assessments should include the collection of information regarding non-protocol therapy. **(29-JUN-2020)**

[2] 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.

[3] 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).

[4] Patient Reported Outcomes (PRO) assessments will be performed every 8 weeks during the first year (which coincides with radiographic tumor assessment and treatment cycles 3, 5, 7, 9, 11, and 13, if on schedule), and every 12 weeks for the second year, unless the patient withdraws from study participation. PRO assessments should continue post-progression. All questionnaires should be completed before any study specific procedures are performed and before the patient sees the physician. **(10/16/2017)**

5. TREATMENT PLAN/REGIMEN DESCRIPTION (10/22/2018)

Safety Lead-In for ARM1 (Experimental Regimen 1) will accrue first.
Assignment to treatment arm will then be randomized (1:1:1).

(Note: The SLI was completed as of May 2, 2018.)

TREATMENT SHOULD BEGIN WITHIN 14 DAYS OF REGISTRATION in order to avoid having to repeat pre-treatment assessments as outlined in Section 4.1.

5.1 Treatment Plan (24-FEB-2021)

ARM 1 (Experimental Regimen 1) (Closed to accrual as of February 09, 2021)
PLD 40 mg/m^2 IV Day 1
Atezolizumab 800 mg IV Days 1 and 15

Note: NRG-GY009 was temporarily closed to accrual on February 09, 2021. Arm 1 is permanently closed to accrual as of Protocol Amendment 11. Patients randomized to Arm 1 may continue on the assigned therapy per protocol (or PLD alone) if the treating physician, after discussing with the patient, determines that the patient would benefit from the treatment. Monitoring, assessments, and data collection are to proceed per protocol. Patients choosing to discontinue study therapy should continue to be followed per protocol.

ARM 2 (Experimental Regimen 2)
PLD 40 mg/m^2 IV Day 1
Bevacizumab 10 mg/kg IV Days 1 and 15
Atezolizumab 800 mg IV Days 1 and 15

ARM 3
PLD 40 mg/m^2 IV Day 1
Bevacizumab 10 mg/kg IV Days 1 and 15

ONE CYCLE = 4 weeks

5.1.1 Administration of Pegylated Liposomal Doxorubicin (PLD)

PLD will be administered in a manner consistent with the current labeled dosing regimen. PLD is administered as an intravenous infusion on Day 1 of a 28-day cycle at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related adverse reactions are observed, the rate of infusion can be increased to complete administration of the drug over one hour (60 min).

Do not use with in-line filters. Rapid flushing of the infusion line should be avoided. Do not administer as a bolus injection or undiluted solution.

Acute infusion-related reactions have occurred in up to 10% of patients treated with PLD. Serious and sometimes life-threatening or fatal allergic/anaphylaxis-like infusion reactions have been reported. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use.

The recommended total cumulative dosage of PLD is 550 mg/m^2. Therefore, once this cumulative dose of PLD is reached (with no dose reductions, this would be approximately 13 cycles of therapy), patients will—at the Investigator's discretion—either continue with PLD + other assigned study drugs (ARM1: atezolizumab; ARM2: bevacizumab/atezolizumab; ARM3: bevacizumab) or discontinue PLD and continue other assigned study drugs (ARM1: atezolizumab; ARM2: bevacizumab/atezolizumab; ARM3: bevacizumab). Note that patients who continue to receive PLD beyond a cumulative dose of 550 mg/m^2 must undergo echocardiogram or MUGA scan every 2 cycles or in accordance with institutional standards to monitor for cardiac toxicity. Patients will discontinue treatment should their resting left ventricular ejection fraction (LVEF) demonstrate an absolute decrease of > 10% below the institutional lower limit of normal or should they develop Grade 3 (or greater) left ventricular systolic dysfunction (symptomatic due to drop in ejection fraction responsive to intervention).

Due to their immunosuppressive effect, administration of systemic steroids (e.g., dexamethasone) as an antiemetic and/or preparative regimen for hypersensitivity reactions should be avoided if other means of treatment are available and medically appropriate.

Preparative antihistamine use is allowed (e.g., diphenhydramine 25 mg IV) prior to FIRST dose (and subsequent doses if hypersensitivity reaction is seen with a previous dose).

5.1.2 Administration of Bevacizumab

Administration will be as a continuous IV infusion. Anaphylaxis precautions should be observed during study drug administration. The initial dose will be delivered over 90±15 minutes. If the first infusion is tolerated without infusion associated adverse events (e.g., fever and/or chills), the second infusion may be delivered over 60±10 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be delivered over 30±10 minutes. If a subject experiences an infusion associated adverse event, she may be premedicated for the next study drug infusion; however, the infusion time may not be decreased for the subsequent infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30±10 minutes as long as the subject continues to be premedicated. If a subject experiences an infusion associated adverse event with the 60-minute infusion, all subsequent doses should be given over

90±15 minutes. Similarly, if a subject experiences an infusion associated adverse event with the 30-minute infusion, all subsequent doses should be given over 60±10 minutes.

Due to their immunosuppressive effect, administration of systemic steroids (e.g., dexamethasone) as an antiemetic and/or preparative regimen for hypersensitivity reactions should be avoided if other means of treatment are available and medically appropriate.

5.1.3 Administration of Atezolizumab (06/29/2017) (10/22/2018)

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For the first infusion, if clinically indicated, vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be recorded during the infusion at 15, 30, 45, 60 minutes (±5 minutes for all timepoints) and at 30 minutes (± 10) after the infusion. For subsequent infusions, if the patient experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 minutes (± 10) after the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Premedication is not permitted for the first dose of atezolizumab (Preparative antihistamine use is allowed (e.g., diphenhydramine 25 mg IV) prior to FIRST dose of PLD (and subsequent doses if hypersensitivity reaction is seen with a previous dose; see section 5.1.1). **(10/16/2017)**

Premedication with antihistamines or antipyretics/analgesics (*e.g.*, acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician. The management of Infusion Related Reactions will be according to severity as follows:

- In the event that a patient experiences a Grade 1 Infusion Related Reaction during Cycle 1, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.

- In the event that a patient experiences a Grade 2 Infusion Related Reaction, or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the Infusion Related Reaction. For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for Infusion Related Reactions.

- For Grade 3 or 4 Infusion Related Reactions, the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated (*e.g.*, oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Atezolizumab should be permanently discontinued. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event; retreatment requires consultation with, and consent of, the trial Principal Investigator (PI).

For anaphylaxis precautions, use the following procedure:

Equipment Needed

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

Procedures

In the event of a suspected anaphylactic reaction during atezolizumab infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.

5.1.4 Sequencing and Timing of Drug Administration

PLD will be administered on Day 1. Atezolizumab will be administered on Days 1 and15. Bevacizumab with be administered on Days 1 and 15.

On days where more than one study drug is to be administered, the order of administration should be as follows:

1. PLD
2. Bevacizumab
3. Atezolizumab

If patient requires discontinuation of a study drug(s) (for reason other than protocol defined progression), the patient should continue other assigned study drug(s), if clinically appropriate, until protocol defined progression.

5.2 Radiation Therapy
Not Applicable

5.3 Device
Not Applicable.

5.4 Imaging (for imaging-focused study)
Not Applicable.

5.5 Integral Assay/Biomarker
Not applicable.

5.6 Intervention Not Otherwise Categorized
Not Applicable.

5.7 Quality of Life Component
See Section 11.1

5.8 General Concomitant Medication and Supportive Care Guidelines

5.8.1 Concomitant Medications **(06/29/2017)**
Concomitant therapy includes any prescription medications or over the counter preparations used by a patient between the 7 days preceding the screening evaluation and the treatment discontinuation visit.

Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or cimetidine or another H2 receptor antagonist, as per standard practice. Serious infusion associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (*e.g.*, supplemental oxygen and β_2-adrenergic agonists).

Systemic corticosteroids and TNFα inhibitors may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to corticosteroids should be considered. Premedication may be administered for Cycles ≥2 at the discretion of the treating physician. The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed. Megestrol administered as appetite stimulant is acceptable while the patient is enrolled in the study.

Patients who use oral contraceptives, hormone-replacement therapy, prophylactic or therapeutic anticoagulation therapy (such as low-molecular-weight heparin or warfarin at a

stable dose level), or other allowed maintenance therapy (See Section 3.3) should continue their use.

Females of reproductive potential should use highly effective means of contraception during study treatment and for 5 months following completion of study treatment.

5.8.2 Prohibited Therapies **(06/29/2017)**

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

- Chemotherapy, hormonal therapy, immunotherapy, radiotherapy, investigational agents, or herbal therapy (except for maintenance therapies outlined in Section 3.3).

It is strongly recommended that:

- Traditional herbal medicines not be administered because the ingredients of many herbal medicines are not fully studied and their use may result in unanticipated drug-drug interactions that may cause, or confound assessment of, toxicity.
- The use of a RANKL inhibitor (denosumab) should be discontinued during the study; this agent could potentially alter the activity and the safety of atezolizumab.

Prophylactic use of granulocyte colony-stimulating factors (*e.g.*, granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is prohibited for patients with solid malignancies. **(10/16/2017)**

Patients are not allowed to receive immunostimulatory agents, including, but not limited to, IFN-α, IFN-γ, or IL-2, during the entire study. These agents, in combination with atezolizumab, could potentially increase the risk for autoimmune conditions.

Patients should also not be receiving immunosuppressive medications, including, but not limited to, cyclophosphamide, azathioprine, methotrexate, and thalidomide. These agents could potentially alter the activity and the safety of atezolizumab. Systemic corticosteroids and anti-TNFα agents may attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the treating physician. If feasible, alternatives to these agents should be considered. Inhaled corticosteroids are permitted.

In addition, all patients (including those who discontinue the study early) should not receive other immunostimulatory agents for 10 weeks after the last dose of atezolizumab.

5.9 Duration of Therapy

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw 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.

6. TREATMENT MODIFICATIONS/MANAGEMENT

6.1 PLD Dose Modification Guidelines

Refer to the PLD label for current commendations regarding dose delays and reductions.

Once the dose of PLD has been reduced due to drug-related toxicity, it should not be increased at a later time. If more than 2 dose reductions are required due to PLD-related toxicity, consult the study chair to determine if PLD should be discontinued.

PLD Dose Reduction (30-OCT-2020)

Dose reduction	Dose
1st	30mg/m^2
2nd	22.5mg/m^2
3rd	Consult the study chair to determine if PLD should be discontinued

In the event of a delay in PLD dosing due to drug-related toxicity, doses of atezolizumab and/or bevacizumab should also be delayed.

6.1.1 Modifications for Hematologic Toxicity

The prophylactic use of growth factors is not recommended in this study. Investigators may follow their institutional guidelines/standard practices for use of growth factors for supportive care (e.g., NCCN guideline for management of patients with febrile neutropenia).

PLD Dose Modification Guidelines for Hematological Toxicity*

Toxicity Grade	ANC	Platelets	Modification
1	1,500–1,900	75,000–150,000	Resume treatment with no dose reduction
2	1,000–< 1,500	50,000–< 75,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
3	500 –999	25,000–< 50,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose with no dose reduction
4	< 500	< 25,000	Wait until ANC ≥ 1,500 and platelets ≥ 75,000; redose at 25% dose reduction

*Modification should be guided by the more severe toxicity, if both ANC and platelets are affected.

6.1.2 Modifications for Hand-Foot Syndrome **(02/20/2019)**

PLD Dose Modification Guidelines for Hand-Foot Syndrome (HFS)

Palmar-Plantar Erythrodysesthesia Syndrome (PPE)

Toxicity Grade	Dose Adjustment
1: Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	**Redose unless patient has experienced previous ≥ Grade 3 (PPE)** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2: Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, PLD should be discontinued. If resolved to Grade 0–1 within 2 weeks, and there are no prior ≥Grade 3 PPE, continue treatment at previous dose and return to original dose interval. If patient experienced previous ≥Grade 3 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3: Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no improvement to **Grade 0–1**, PLD should be discontinued.

6.1.3 Modifications for Stomatitis

PLD Dose Modification Guidelines for Stomatitis /Oral Mucositis (30-OCT-2020)

Toxicity Grade	Dose Adjustment
1: painless ulcers, erythema, or mild soreness	**Redose unless patient has experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2: painful erythema, edema, or ulcers, but can eat	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, PLD should be discontinued. –If resolved to Grade 0–1 within 2 weeks and there was no prior Grade 3–4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3–4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3: painful erythema, edema, or ulcers, and cannot eat	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.
4: requires parenteral or enteral support	**Delay dosing up to 2 weeks or until resolved to Grade 0–1.** Decrease dose by 25% and return to PLD original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.

6.1.4 Modifications for Hepatic Toxicity

PLD Dose Modification Guidelines for Impaired Hepatic Function

Limited clinical experience exists in treating patients with hepatic impairment with PLD. Based on experience with doxorubicin HCl, it is recommended that the PLD dosage be reduced if the bilirubin is elevated as follows:

Serum bilirubin 1.2 to 3.0 mg/dL: give ½ normal dose
Serum bilirubin > 3 mg/dL: give ¼ normal dose

6.2 Bevacizumab Dose Modification and Toxicity Management Guidelines

There will be no dose reduction for bevacizumab in this study. Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If bevacizumab is held because of AEs for >84 days beyond the scheduled date of infusion, the patient will be discontinued from bevacizumab.

Bevacizumab dose will not be reduced for reasons other than a >10% change in weight from baseline. Bevacizumab treatment may be either temporarily or permanently suspended in the case of bevacizumab-related events such as fistulae, GI perforation, hypertension, proteinuria, thrombosis/embolism, hemorrhage, CHF, wound healing complications, PRES (or RPLS) and hypersensitivity/allergic reactions in addition to any other serious bevacizumab-related toxicity (grade 3 or 4).

In addition, bevacizumab should be temporarily withheld in the event of febrile grade 4 neutropenia and/or grade 4 thrombocytopenia (regardless of the relationship to treatment), since these conditions are predisposing factors for an increased bleeding tendency. To summarize, bevacizumab should be held temporarily or permanently discontinued in patients (as per the clinical judgment of the treating physician) experiencing any of the following events:

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

Posterior Reversible Encephalopathy Syndrome (PRES/RPLS)
There have been rare reports of patients treated with bevacizumab developing signs and symptoms that are consistent with PRES, a rare neurological disorder. PRES is also known as reversible posterior leukoencephalopathy syndrome or RPLS). PRES can present with following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging. In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing PRES is not known. Adequate brain imaging using MRI must be performed as a follow-up measurement for patients with PRES.

Gastrointestinal Perforation and Fistula
Bevacizumab has been associated with serious cases of GI perforation and a few reports of gallbladder perforation have been reported from the post-marketing experience. The presentation of these events has varied in type and severity, ranging from free air seen only on the plain abdominal X-ray, which resolved without treatment, to a colonic perforation with abdominal abscess and fatal outcome. The common feature among these cases was intra-abdominal inflammation, either from gastric ulcer disease, tumor necrosis, diverticulitis or chemotherapy-associated colitis. Nevertheless, a causal association of an intra-abdominal inflammatory process and GI perforation to treatment with bevacizumab has not been

established. However, caution should be exercised when treating patients with intra-abdominal inflammatory process with bevacizumab.

Bevacizumab should be permanently discontinued in patients who develop GI perforation.

Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae within the GI tract or GI tract and skin are common in patients with mCRC and ovarian cancer, but are uncommon or rare in other indications. Other fistulae (e.g. tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly in bevacizumab clinical trials patients and in post-marketing reports.

Temporarily discontinue bevacizumab in patients with grade 2 or 3 non- tracheoesophageal fistula until resolution to ≤ grade 1.

Permanently discontinue bevacizumab in patients with tracheoesophageal fistula or any grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound Healing Complications
Increased incidences of post-operative bleeding or wound healing complications have been observed in clinical trials of bevacizumab in relapsed glioma and mCRC and BC. Bevacizumab therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed as bevacizumab may adversely impact wound healing.

In patients who experience wound healing complications during bevacizumab treatment, bevacizumab should be withheld until the wound is fully healed. If the wound does not fully heal despite withholding treatment, should be permanently discontinued.

Bevacizumab therapy should be withheld for an interval of at least two half-lives (approximately six weeks) before conducting major elective surgery. Emergency surgery should be performed as appropriate without delay after a careful risk-benefit assessment.

Hypertension
An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest the incidence of hypertension is likely to be dose-dependent.

Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating therapy.

Blood pressure must be assessed before each bevacizumab administration.
In most cases hypertension is controlled adequately using standard antihypertensive treatment appropriate for the individual situation of the affected patient. Bevacizumab should be permanently discontinued if medically significant hypertension cannot be adequately

controlled with antihypertensive therapy, or if the patient develops hypertensive crisis or hypertensive encephalopathy.

Congestive Heart Failure (CHF)
Events consistent with CHF were reported in clinical trials. The findings ranged from asymptomatic declines in left ventricular ejection fraction (LVEF) to symptomatic CHF, requiring treatment or hospitalization. Most of the patients who experienced CHF had metastatic breast cancer and had received previous treatment with anthracyclines, prior radiotherapy to the left chest wall or other risk factors for CHF were present.

Caution should be exercised when treating patients with clinically significant cardiovascular disease such as pre-existing coronary artery disease, concomitant cardiotoxic therapy or CHF with bevacizumab.

Bevacizumab should be permanently discontinued in patients with ≥ grade 3 CHF.

Proteinuria
In clinical studies, the incidence of proteinuria was higher in patients receiving bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. Proteinuria reported as an AE with bevacizumab treatment has ranged in severity from clinically asymptomatic, transient, trace proteinuria to nephrotic syndrome with the great majority as grade 1 proteinuria. The proteinuria seen in bevacizumab clinical trials was not associated with renal dysfunction and rarely required permanent discontinuation of bevacizumab therapy. Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab.

Proteinuria must be assessed by urinalysis as directed by protocol (see section 3.2.9). **(24-FEB-2021)**
Bevacizumab Treatment Management for Proteinuria (03/19/2018) (02/20/2019)

NCI CTCAE	**Urinalysis**	**Treatment Action**
Grade 1	urinary protein < 1.0 g/24 hrs	No bevacizumab dose modification
Grade 2	urinary protein 1.0-3.4 g/24 hrs	No bevacizumab dose modification
Grade 3	urinary protein ≥3.5 g/24 hrs	Suspend bevacizumab. Resume bevacizumab when proteinuria is < 3.5 g/24 hrs.
Nephrotic syndrome		Permanently discontinue bevacizumab

Arterial thrombosis/embolism
Bevacizumab should be discontinued in patients who develop arterial thromboembolic events.

A history of arterial thromboembolic events or age greater than 65 years has been associated with an increased risk of arterial thromboembolic events during bevacizumab therapy. Patients receiving bevacizumab plus chemotherapy with a history of arterial

thromboembolism and age greater than 65 years have a higher risk. Caution should be taken when treating these patients with bevacizumab.

Venous thrombosis/embolism
Bevacizumab should be held in patients developing a grade 3 thrombosis/embolism. Bevacizumab may be resumed once the patient is adequately anti-coagulated for at least 2 weeks prior to restarting study drug treatment. Patients on warfarin should have an INR between 2.0 and 3.0 assessed in two consecutive measurements 1-4 days apart. Patients on full dose low molecular weight heparins should receive the appropriate dose based on the weight of the patient according to package insert.

An increased risk of venous thromboembolic events and bleeding in patients receiving anti-coagulation therapy after first venous thromboembolic event while receiving bevacizumab has been observed.

In the event of recurrent grade 3 thrombosis/embolism, the patient should be discontinued from bevacizumab.

Bevacizumab should be discontinued in patients with life-threatening (grade 4) venous thrombosis/embolism.

Hemorrhage (10/16/2017)
An increased incidence of bleeding events was observed in study patients treated with bevacizumab as compared to control treatment arms. The hemorrhagic events observed in bevacizumab studies were predominantly tumor-associated hemorrhage and minor mucocutaneous hemorrhage.

Patients with untreated CNS metastases were routinely excluded from clinical trials with bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS hemorrhage in such patient has not been prospectively evaluated in randomized clinical studies.

Bevacizumab should be permanently discontinued for:

- grade 3 or 4 bleeding of any kind
- any grade of CNS bleeding. Patients should be monitored for signs and symptoms of CNS bleeding.

Bevacizumab should be temporarily held or permanently discontinued for grade ≥ 2 hemoptysis (defined as ≥ 2.5 mL bright red blood per episode). The safety of re-initiating bevacizumab in patients previously experiencing grade ≥ 2 hemoptysis has not been evaluated.

If hemorrhagic complications occur in patients on full dose anti-coagulation therapy, permanently discontinue bevacizumab treatment and follow guidelines of the treating institution. Standard procedures such as reversal with Protamin or vitamin K and infusion of vitamin K dependent factors should be considered dependent on the severity of the bleeding.

Hypersensitivity/Allergic Reactions and Infusion-Associated Reactions
Bevacizumab should be permanently discontinued in patients exhibiting hypersensitivity/allergic reactions.

The NCI CTCAE distinguishes between hypersensitivity reactions and acute infusion reactions induced by cytokine release. Despite the different possible mechanisms underlying hypersensitivity and infusion reactions, the clinical signs and symptoms associated with these reactions overlap.

Patients may be at risk of developing infusion reactions to bevacizumab. Close observation of the patient during and following the administration of bevacizumab is recommended as expected for any infusion of a therapeutic humanized monoclonal antibody. If an infusion reaction occurs, the infusion should be discontinued and appropriate medical therapies should be administered. A systematic premedication is not warranted.

Osteonecrosis of the Jaw
Osteonecrosis of the jaw was reported in patients receiving bevacizumab mainly in combination with bisphosphonates in the post-marketing setting. The pathogenesis of the osteonecrosis is unclear. For further information, please refer to the Avastin® Investigator' Brochure.

Ovarian Failure
Ovarian failure has been reported more frequently in patients receiving bevacizumab. Ovarian function recovered in the majority of women after bevacizumab discontinuation. For further information, please refer to the Avastin® Investigator' Brochure.

6.3 Atezolizumab Dose Modification and Toxicity Management Guidelines

6.3.1 General AE Management and Dose Modification Guidelines **(06/29/2017)**

There will be no dose reduction for atezolizumab in this study.

Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for >84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the study PI in consultation with CTEP.

Atezolizumab must be **permanently discontinued** if the patient experiences any of the following events, regardless of benefit:

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

Treatment may, under limited and compelling circumstances, be resumed in patients who have recovered from the following events, but only after consultation with the trial Principal Investigator:

- Grade 3 pneumonitis
- Grade 3 ocular inflammatory toxicity
- Grade 3 or 4 infusion-related reactions

Any toxicities associated or possibly associated with atezolizumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, may be used to determine a possible immunogenic etiology. Although most immune-related adverse events (irAEs) observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications (Di Giacomo *et al*., 2010). Discontinuation of atezolizumab may not have an immediate therapeutic effect, and there is no available antidote for atezolizumab. In severe cases, immune-related toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance prior to further administration of atezolizumab. **(03/19/3018)**

For detailed information regarding management of adverse events associated with atezolizumab, please refer to the most current version of the Atezolizumab Investigator's Brochure and the FDA product label.

The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit-risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life-threatening irAEs.

Patients should be assessed clinically (including review of laboratory values) for toxicity prior to, during, and after each infusion. If unmanageable toxicity due to atezolizumab occurs at any time during the study, treatment with atezolizumab should be discontinued.

Systemic Immune Activation (06/29/2017)

Systemic immune activation is a rare condition characterized by an excessive immune response. Given the mechanism of action of atezolizumab, systemic immune activation is considered a potential risk when given in combination with other immunomodulating agents. Systemic immune activation should be included in the differential diagnosis for patients who, in the absence of an alternative etiology, develop a sepsis-like syndrome after administration of atezolizumab, and the initial evaluation should include the following:

- CBC with peripheral smear
- PT, PTT, fibrinogen, and D-dimer
- Ferritin
- Triglycerides
- AST, ALT, and total bilirubin
- LDH
- Complete neurologic and abdominal examination (assess for hepatosplenomegaly)

If systemic immune activation is still suspected after the initial evaluation, contact the Principal Investigator for additional recommendations.

6.3.2 Management of Specific AEs **(06/29/2017) (10/22/2018)**

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, nenigoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure. See Section 5.1.3 and the **AE Management and Dose Interruption Guidelines for Specific Toxicities** table below for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

For recommendations to hold atezolizumab and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab therapy after resolution of the event:

- **Corticosteroids must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If clinically indicated, a shorter course of steroid taper may be appropriate following discussion with the study chair. (02/20/2019)**
- Atezolizumab may be held for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

Pulmonary Events
Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the **AE Management and Dose Interruption Guidelines for Specific Toxicities** table below.

Endocrine Disorders

Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including fatigue, myalgias, impotence, mental status changes, or constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. TSH, prolactin, and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency.

Dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia are described in the **AE Management and Dose Interruption Guidelines for Specific Toxicities** table below.

Meningoencephalitis

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

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the **AE Management and Dose Interruption Guidelines for Specific Toxicities** table below.

Neurologic disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor

neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in the table below.

For recommendations to hold atezolizumab and begin corticosteroid treatment, use the following guidance for tapering the corticosteroid and resuming atezolizumab therapy after resolution of the event:

- Corticosteroids must be tapered over ≥1 month to ≤10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. If clinically indicated, a shorter course of steroid taper may be appropriate following discussion with the study chair.
- Atezolizumab may be held for a period of time beyond 12 weeks to allow for corticosteroids to be reduced to ≤10 mg/day oral prednisone or equivalent.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
Abdominal pain	Acute abdominal pain	Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with administration of other immunomodulatory agents. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for obstruction, as well as serum amylase and lipase tests. See the guidelines for "Amylase and/or lipase increase" and "Immune-related pancreatitis" elsewhere in this table, as needed. Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should be evaluated for potential hepatotoxicity (see the "Hepatotoxicity" guideline elsewhere in this table).
Adrenal insufficiency	Grade 2+ (symptomatic)	Hold atezolizumab. Refer patient to endocrinologist. Perform appropriate imaging. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		If event resolves to grade 1 or better and patient is stable on replacement therapy (if required) within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better or patient is not stable on replacement therapy within 12 weeks.
Amylase and/or lipase increased	Grade 1	Continue atezolizumab. Monitor amylase and lipase prior to dosing.
	Grade 2	Continue atezolizumab. Monitor amylase and lipase weekly. For prolonged elevation (*e.g.*, >3 weeks), consider treatment with 10 mg/day oral prednisone or equivalent.
	Grade 3 or 4	Hold atezolizumab. Consider referral to gastrointestinal (GI) specialist. **(10/16/2017)** Monitor amylase and lipase weekly. **(10/16/2017)** If no improvement, consider treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, permanently discontinue atezolizumab. [c]
Dermatologic toxicity/rash (*e.g.*,	Grade 1	Continue atezolizumab. Consider topical steroids and/or other symptomatic therapy (*e.g.*, antihistamines).

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
maculopapular or purpura)	Grade 2	Continue atezolizumab. Consider dermatologist referral. Administer topical corticosteroids. Consider higher potency topical corticosteroids if event does not improve.
	Grade 3	Hold atezolizumab. Refer patient to dermatologist. Administer oral prednisone 10 mg or equivalent. If the event does not improve within 48–72 hours, increase dose to 1–2 mg/kg/day or equivalent. Restart atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Otherwise, manage as above.
	Persistent and/or severe rash or pruritus, any grade	A dermatologist should evaluate the event. A biopsy should be performed unless contraindicated. **Please refer to Section 6.3.2 regarding duration of steroids. (02/20/2019)**
Diarrhea or colitis	Any grade	Patients should be advised to inform the investigator if any diarrhea occurs, even if it is mild. All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (*e.g.*, increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.
	Grade 1	Continue atezolizumab. Initiate symptomatic treatment.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		Endoscopy is recommended if symptoms persist for >7 days. Monitor closely.
	Grade 2	Hold atezolizumab. Initiate symptomatic treatment. Patient referral to GI specialist is recommended. For recurrent events or events that persist >5 days, initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered, after consultation with the trial PI, in patients who are deriving benefit and have fully recovered from the immune-related event.
	Grade 3	Hold atezolizumab. Refer patient to GI specialist for evaluation and confirmatory biopsy. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks. Resumption of atezolizumab may be considered, after consultation with the trial PI, in

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		patients who are deriving benefit and have fully recovered from the immune-related event.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist for evaluation and confirmation biopsy. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Otherwise, manage as above. **(02/20/2019)**
Hepatotoxicity	Right upper-quadrant abdominal pain and/or unexplained nausea or vomiting	Risk of immune-mediated hepatitis. LFTs should be performed immediately, and LFTs should be reviewed before administration of the next dose of study drug. For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate. Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should also include pancreatitis, as described below.
	Grade 1 hepatic event	Continue atezolizumab. Monitor LFTs until values resolve to within normal limits.
	Grade 2 hepatic event, ≤5 days	Continue atezolizumab. Monitor LFTs more frequently until values resolve to baseline values.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
	Grade 2 hepatic event, >5 days	Hold atezolizumab. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to Grade 1 or better within 12 weeks.
	Grade 3 or 4 hepatic event	Permanently discontinue atezolizumab. Consider patient referral to GI specialist for evaluation and liver biopsy to establish etiology of hepatic injury. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Hyperglycemia	Grade 1 or 2	Continue atezolizumab. Initiate treatment with insulin if needed. Monitor for glucose control.
	Grade 3 or 4	Hold atezolizumab. Initiate treatment with insulin. Monitor for glucose control. Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hyperthyroidism **(02/20/2019)**	Grade 1/2 (asymptomatic)	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:**

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		Continue atezolizumab. Monitor TSH every 4 weeks. **TSH < 0.1 mU/L:** Follow guidelines for symptomatic hyperthyroidism.
	Grade 2+ (symptomatic)	Hold atezolizumab. Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. Consider patient referral to endocrinologist. Resume atezolizumab when symptoms are controlled and thyroid function is improving. Permanently discontinue atezolizumab for life-threatening immune-related hyperthyroidism.
Hypothyroidism **(02/20/2019)**	Grade 1/2 (asymptomatic)	Continue atezolizumab. Start thyroid-replacement hormone. Monitor TSH weekly until improving then resume per assessment schedule 4.2. **(08-JAN-2021)**
	Grades 2+ (symptomatic)	Hold atezolizumab. Start thyroid-replacement hormone. Consider referral to an endocrinologist. Monitor TSH weekly until improving then resume per assessment schedule 4.2. **(24-FEB-2021)** Restart atezolizumab when symptoms are controlled and thyroid function is improving.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
Meningo-encephalitis, immune-related (signs and symptoms in absence of an identified alternate etiology)	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment with 1–2 mg/kg/day IV methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent.
Myasthenia gravis and Guillain-Barré syndrome	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to neurologist. Initiate treatment as per institutional guidelines. Consider initiation of 1–2 mg/kg/day oral or IV prednisone or equivalent.
Myocarditis	All grades	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to cardiologist. **(24-FEB-2021)**
Neuropathy, immune-related (sensory and/or motor)	Grade 1	Continue atezolizumab. Evaluate for alternative etiologies.
	Grade 2	Hold atezolizumab. Evaluate for alternative etiologies. Initiate treatment as per institutional guidelines. Resume atezolizumab if event resolves to grade 1 or better within 12 weeks. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
	Grade 3 or 4	Permanently discontinue atezolizumab. Initiate treatment as per institutional guidelines.
Ocular event (*e.g.*, uveitis, retinal events)	Grade 1	Continue atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If symptoms persist, treat as a grade 2 event.
	Grade 2	Withhold atezolizumab. Patient referral to ophthalmologist is strongly recommended. Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks.
	Grade 3 or 4	Permanently discontinue atezolizumab. Refer patient to ophthalmologist. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. For grade 3 AEs, patient may only resume treatment after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
Pancreatitis, immune related **(10/16/2017)** See Amylase and/or lipase increased section above	Grade 2 (with radiographic findings) or 3 **(10/16/2017)**	Hold atezolizumab. Refer patient to GI specialist. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. Patient may only resume treatment after consultation with the trial PI. For recurrent events, permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit.
	Grade 4	Permanently discontinue atezolizumab. Patient may not resume treatment, regardless of benefit. Refer patient to GI specialist. Initiate treatment with 1–2 mg/kg/day intravenous methylprednisolone or equivalent and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month.
Pulmonary toxicity	All pulmonary events	Evaluate thoroughly for other commonly reported etiologies such as pneumonia/infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease (COPD), or pulmonary hypertension.
	Grade 1	Continue atezolizumab and monitor closely.

AE Management and Dose Interruption Guidelines for Specific Toxicities		
Toxicity	**Severity/ Duration**	**Management**
		Re-evaluate on serial imaging. Consider patient referral to a pulmonary specialist. For recurrent pneumonitis, treat as a grade 3 or 4 event.
	Grade 2	Hold atezolizumab. Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or bronchoscopic alveolar lavage (BAL). Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event resolves to grade 1 or better within 12 weeks, taper corticosteroids and resume atezolizumab according to the guidelines above. Permanently discontinue atezolizumab if event does not resolve to grade 1 or better within 12 weeks. For recurrent events, treat as a Grade 3 or 4 event.
	Grade 3 or 4	Permanently discontinue atezolizumab. Bronchoscopy or BAL is recommended. Initiate treatment with 1–2 mg/kg/day oral prednisone or equivalent. If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. If event resolves to grade 1 or better, taper corticosteroids over ≥1 month. For grade 3 AEs, patient may only resume treatment after consultation with the trial PI; for grade 4, patient cannot resume treatment, regardless of benefit.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents (03/19/2018) (29-JUN-2020)

Investigational Agents

The investigational agents administered in NRG-GY009 are atezolizumab and bevacizumab, which are being made available under an IND sponsored by DCTD, NCI.

Commercial Agents

The commercial agent in NRG-GY009 is pegylated liposomal doxorubicin.

For all patients, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.6.2.1 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 4.0 until March 31, 2018 (CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018) 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. **(03/19/2018)**

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 (CAEPR) List for Study Agents

7.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Bevacizumab (rhuMAb VEGF, NSC 704865) (09/13/2018)

The Comprehensive Adverse Event 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 3540 patients.* Below is the CAEPR for bevacizumab (rhuMAb VEGF).

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, May 2, 2018[1]

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
	Febrile neutropenia		***Febrile neutropenia (Gr 3)***
		Hemolytic uremic syndrome	
CARDIAC DISORDERS			
	Cardiac disorders - Other (supraventricular arrhythmias)[2]		***Cardiac disorders - Other (supraventricular arrhythmias)[2] (Gr 3)***
		Chest pain - cardiac[3]	
		Heart failure	
		Left ventricular systolic dysfunction	
		Myocardial infarction[3]	
		Ventricular arrhythmia	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Colitis		***Colitis (Gr 3)***
	Constipation		***Constipation (Gr 3)***
	Diarrhea		***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
		Gastrointestinal fistula[4]	
	Gastrointestinal hemorrhage[5]		***Gastrointestinal hemorrhage[5] (Gr 2)***
	Gastrointestinal obstruction[6]		
		Gastrointestinal perforation[7]	
		Gastrointestinal ulcer[8]	
	Ileus		
	Mucositis oral		***Mucositis oral (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Fatigue		***Fatigue (Gr 3)***
	Non-cardiac chest pain		***Non-cardiac chest pain (Gr 3)***
	Pain		***Pain (Gr 3)***
HEPATOBILIARY DISORDERS			
		Gallbladder perforation	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[9]		***Infection[9] (Gr 3)***
		Infections and infestations - Other (necrotizing fascitis)	

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Infections and infestations - Other (peri-rectal abscess)		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		***Infusion related reaction (Gr 2)***
		Injury, poisoning and procedural complications - Other (anastomotic leak)[10]	
	Wound complication		***Wound complication (Gr 2)***
	Wound dehiscence		***Wound dehiscence (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 3)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 3)***
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 3)***
	White blood cell decreased		***White blood cell decreased (Gr 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hyperglycemia		
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 3)***
		Avascular necrosis[11]	
	Generalized muscle weakness		
	Musculoskeletal and connective tissue disorder - Other (bone metaphyseal dysplasia)[12]		
	Myalgia		***Myalgia (Gr 3)***
	Osteonecrosis of jaw[13]		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
		Intracranial hemorrhage	
		Ischemia cerebrovascular	
	Peripheral sensory neuropathy[14]		
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
	Hematuria		***Hematuria (Gr 3)***

Adverse Events with Possible Relationship to Bevacizumab (rhuMAb VEGF) (CTCAE 5.0 Term) [n= 3540]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
		Urinary fistula	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
Reproductive system and breast disorders - Other (ovarian failure)[15]			
		Vaginal fistula	
	Vaginal hemorrhage		***Vaginal hemorrhage (Gr 3)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
		Bronchopleural fistula	
		Bronchopulmonary hemorrhage	
	Cough		***Cough (Gr 3)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		***Epistaxis (Gr 3)***
	Hoarseness		***Hoarseness (Gr 3)***
		Pulmonary hypertension	
		Respiratory, thoracic and mediastinal disorders - Other (nasal-septal perforation)	
		Respiratory, thoracic and mediastinal disorders - Other (tracheo-esophageal fistula)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism[3,16]	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 3)***

[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]Supraventricular arrhythmias may include supraventricular tachycardia, atrial fibrillation, and atrial flutter.

[3]The risks of arterial thrombosis such as cardiac or CNS ischemia are increased in elderly patients and in patients with a history of diabetes.

[4]Gastrointestinal fistula may include: Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Gastric fistula, Gastrointestinal fistula, Rectal fistula, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[5]Gastrointestinal hemorrhage may include: Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Intra-abdominal hemorrhage, Oral hemorrhage, Rectal hemorrhage, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[6]Gastrointestinal obstruction may include: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Rectal obstruction, Small intestinal obstruction, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[7]Gastrointestinal perforation may include: Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation.

[8]Gastrointestinal ulcer may include: Duodenal ulcer, Esophageal ulcer, Gastric ulcer, and other sites under the GASTROINTESTINAL DISORDERS SOC.

[9]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

[10]Anastomotic leak may include Gastric anastomotic leak; Gastrointestinal anastomotic leak; Large intestinal anastomotic leak; Rectal anastomotic leak; Small intestinal anastomotic leak; Urostomy leak; Vaginal anastomotic leak.

[11]There have been reports of non-mandibular osteonecrosis (avascular necrosis) in patients under the age of 18 treated with bevacizumab.

[12]Metaphyseal dysplasia was observed in young patients who still have active epiphyseal growth plates.

[13]Cases of osteonecrosis of the jaw (ONJ) have been reported in cancer patients in association with bevacizumab treatment, the majority of whom had received prior or concomitant treatment with i.v. bisphosphonates.

[14]Increased rate of peripheral sensory neuropathy has been observed in trials combining bevacizumab and chemotherapy compared to chemotherapy alone.

[15]Ovarian failure, defined as amenorrhea lasting 3 or more months with follicle-stimulating hormone (FSH) elevation (≥30 mIU/mL), was increased in patients receiving adjuvant bevacizumab plus mFOLFOX compared to mFOLFOX alone (34% vs. 2%). After discontinuation of bevacizumab, resumption of menses and an FSH level <30 mIU/mL was demonstrated in 22% (7/32) of these women. Long term effects of bevacizumab exposure on fertility are unknown.

[16]Arterial thromboembolic event includes visceral arterial ischemia, peripheral arterial ischemia, heart attack, and stroke.

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Bone marrow hypocellular; Disseminated intravascular coagulation; Hemolysis; Thrombotic thrombocytopenic purpura
CARDIAC DISORDERS - Atrioventricular block complete; Atrioventricular block first degree; Cardiac arrest; Myocarditis; Pericardial effusion; Restrictive cardiomyopathy; Right ventricular dysfunction
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (tympanic membrane perforation); Hearing impaired; Tinnitus; Vertigo
ENDOCRINE DISORDERS - Hyperthyroidism; Hypothyroidism
EYE DISORDERS - Blurred vision; Cataract; Dry eye; Extraocular muscle paresis; Eye disorders - Other (blindness); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (corneal epithelial defect); Eye disorders - Other (ischemic CRVO); Eye disorders - Other (macular pucker); Eye disorders - Other (transient increased IOP > or =30 mm Hg); Eye pain; Floaters; Keratitis; Optic nerve disorder; Photophobia; Retinal detachment; Retinal tear; Retinopathy; Vitreous hemorrhage; Watering eyes
GASTROINTESTINAL DISORDERS - Ascites; Cheilitis; Colonic stenosis; Dry mouth; Dysphagia; Enterocolitis; Esophageal pain; Esophageal stenosis; Flatulence; Gastrointestinal disorders - Other (peritonitis); Oral pain; Pancreatitis; Proctitis; Rectal mucositis; Rectal stenosis; Typhlitis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Edema limbs; Edema trunk; Facial pain; Fever; Flu like symptoms; Gait disturbance; Injection site reaction; Localized edema; Multi-organ failure; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder necrosis; Gallbladder obstruction; Hepatic failure; Hepatic necrosis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Arterial injury; Bruising; Burn; Dermatitis radiation; Fracture
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood antidiuretic hormone abnormal; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Electrocardiogram QT corrected interval prolonged; Forced expiratory volume decreased; GGT increased; INR increased; Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Back pain; Bone pain; Chest wall pain; Fibrosis deep connective tissue; Head soft tissue necrosis; Joint effusion; Muscle weakness lower limb; Muscle weakness upper limb; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Neck pain; Osteonecrosis; Pain in extremity; Pelvic soft tissue necrosis; Soft tissue necrosis lower limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Arachnoiditis; Ataxia; Central nervous system necrosis; Cerebrospinal fluid leakage; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Encephalopathy; Extrapyramidal disorder; Facial nerve disorder; Hydrocephalus; Leukoencephalopathy; Memory impairment; Myasthenia gravis; Nervous system disorders - Other (increased intracranial pressure); Paresthesia; Peripheral motor neuropathy; Pyramidal tract syndrome; Seizure; Somnolence; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Insomnia; Libido decreased; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Dysuria; Renal and urinary disorders - Other (ureterolithiasis); Renal hemorrhage; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract obstruction; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain; Erectile dysfunction; Irregular menstruation; Pelvic pain; Vaginal discharge
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Atelectasis; Hypoxia; Nasal congestion; Pulmonary fibrosis; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (dry nares); Respiratory, thoracic and mediastinal disorders - Other (pulmonary infarction)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Hyperhidrosis; Nail loss; Pain of skin; Photosensitivity; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (diabetic foot ulcer); Skin and subcutaneous tissue disorders - Other (skin breakdown/ decubitus ulcer); Skin hyperpigmentation; Skin induration; Skin ulceration; Stevens-Johnson syndrome
VASCULAR DISORDERS - Flushing; Hot flashes; Hypotension; Lymphocele; Phlebitis; Vasculitis

Note: Bevacizumab (rhuMAb VEGF) 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.

7.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Atezolizumab (MPDL3280A, NSC 783608) (06/29/2017) (09/13/2018) (17-MAY-2021)

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 3097 patients*. Below is the CAEPR for Atezolizumab (MPDL3280A).

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 2.3, March 11, 2021[1]

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
	Hyperthyroidism[2]	Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other (hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased[2]		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Encephalopathy[2]	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Myasthenia gravis[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])[2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Skin and subcutaneous tissue disorders - Other (exanthematous pustulosis)[2]	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

*Denotes adverse events that are <3%.

[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]Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) 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 Adverse Events for Commercial Study Agents
Refer to the package insert for detailed pharmacologic and safety information

7.5 Adverse Event Characteristics (06/29/2017) (03/19/2018)

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. **(03/06/2018)**

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Sections 7.3.1 and 7.3.2) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

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

7.6 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 NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.6.1 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 3 days.
- Supporting source documentation is requested by the IND sponsor for this study

(CTEP/DCTD) and NRG as needed to complete adverse event review. When submitting supporting source documentation, 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 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.

7.6.2 Expedited Reporting Requirements for Adverse Events

7.6.2.1 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] (Use for ALL Patients) (29-JUN-2020)

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

Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

Adverse Events of Special Interest in Bevacizumab (24-FEB-2021)

The following AEs are considered of special interest in patients receiving bevacizumab and must be reported expeditiously through CTEP-AERS, irrespective of regulatory seriousness criteria:

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

Adverse Events of Special Interest in Atezolizumab Studies (06/29/2017) (24-FEB-2021)

The following AEs are considered of special interest in patients receiving atezolizumab and must be reported expeditiously through CTEP-AERS, irrespective of regulatory seriousness criteria:

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

7.6.3 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.

7.6.4 Pregnancy **(24-FEB-2021)**

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 5 months 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.

7.6.5 Secondary Malignancy

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 reporting via CDUS unless otherwise specified.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (03/19/2018) (29-JUN-2020)

8.1 CTEP Registration Procedures (03/19/2018)

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) at 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, acting 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 CTSU Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL 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>.

8.2 CTSU Registration Procedures (03/19/2018)

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 RCE 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).

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 and is 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 search 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* tab 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-GY009.
- 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 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 sites 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 given 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.

8.3 Patient Enrollment (03/19/2018)

For the Phase I portion, the SDMC-Buffalo Office web-based patient reservation system will be used, in which slots for particular patients are reserved. Reservations are not transferrable to other patients, and if the patient is not enrolled within the required timeframe, the reservation is cancelled and the slot is then made available to other patients and sites. If all slots are reserved, patients can be added to a waiting list.

The URL for the Phase I reservation system can be found at https://nrg42.nrgoncology.org/phaseireservations. **(10/16/2017)**

8.3.1 Patient Enrollment

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;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar must hold the OPEN Registrar task on the DTL for the site; and
- 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. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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.

8.4 Agent Ordering and Agent Accountability (03/19/2018) (29-JUN-2020)

8.4.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator 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 investigator at that institution.

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. **(10/22/2018) (02/20/2019)**

8.4.2 Investigator Brochure Availability

The current versions of the IBs for the agents 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. **(02/20/2019)**

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 agent, strength, formulation and ordering investigator on this protocol.

8.4.4 PMB Useful Links and Contacts (02/20/2019)

- *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/* **(10/22/2018)**
- *CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/aim/index.jsp*

- *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 Atezolizumab, NSC # 783608, [redacted] (06/29/2017) (13-OCT-2022)

9.1.1 Other Names: Tecentriq™, MPDL3280A

Classification: monoclonal antibody

M.W.: 150 KD

Mode of Action: anti-PD-L1

9.1.2 Description**:**

Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte et al. 2007).

9.1.3 How Supplied**:**

Atezolizumab is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62 mg), polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

Atezolizumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Atezolizumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix VI).

9.1.4 Preparation:

The prescribed dose of atezolizumab should be diluted in 0.9% NaCl to a concentration between 3.2 mg/mL and 16.8 mg/mL and infused with or without a low-protein binding 0.2 or 0.22 micrometer in-line filter. The IV bag may be constructed of polyvinyl chloride (PVC), polyolefin (PO), or polyethylene (PE). The prepared solution may be stored at 2°C-8°C for up to 24 hours or at ambient < 25°C (77°F) for 6 hours from the time of preparation. If the dose

solution is stored at 2°C–8°C (36°F–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. These times include the storage and administration times for the infusion. Do not shake or freeze infusion bags containing the dose solution.**9.1.5**
Storage: 2°C-8°C (36°F-46°F) Vial contents should not be frozen or shaken and should be protected from direct sunlight.

If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-46°F) 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.

9.1.6 Stability: Stability studies are ongoing.
CAUTION: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

9.1.7 Route of Administration: IV infusion

Method of Administration:
Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedications with subsequent infusions.

9.1.8 Potential Drug Interactions:
Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

9.1.9 Patient Care Implications:
Female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 150 days after the last dose of atezolizumab.**9.1.10**
Adverse Events: Please see Section 7.3.2 for the Atezolizumab CAEPR.

9.2 Bevacizumab (rhuMAb VEGF, Avastin®) (NSC #704865) (29-JUN-2020)

9.2.1 Classification: Recombinant humanized monoclonal antibody

9.2.2 Molecular Weight: Approximate molecular weight is 149,000 daltons

9.2.3 Mode of Action: Bevacizumab blocks the binding of vascular endothelial growth factor (VEGF) to its receptors resulting in inhibition of angiogenesis.

9.2.4 Description: Bevacizumab is a recombinant humanized anti-VEGF monoclonal antibody consisting of 93% human and 7% murine amino acid sequences. The agent is composed of human IgG framework and murine antigen-binding complementarity-determining regions.

9.2.5 How Supplied: Bevacizumab is provided by Genentech and distributed by the Pharmaceutical Management Branch, CTEP, NCI. Bevacizumab is supplied as a clear to slightly opalescent, sterile liquid for parenteral administration. Each 400 mg (25mg/ml – 16 mL fill) glass vial

contains bevacizumab with phosphate, trehalose, polysorbate 20, and Sterile Water for Injection, USP.

9.2.6 Preparation: Vials contain no preservatives and are intended for single use only. The calculated dose should be diluted in 0.9% sodium chloride for injection to a final concentration of bevacizumab between 1.4 and 16.5 mg/ml.

9.2.7 Storage: Upon receipt, refrigerate bevacizumab (2°to 8°C). Keep vial in the outer carton due to light sensitivity. Do not freeze. Do not shake.

If a storage temperature excursion is identified, promptly return bevacizumab to 2º-8ºC (36ºF-46ºF) 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.

9.2.8 Stability: Please see the product label for expiration information. The sterile single use vials contain no antibacterial preservatives. Discard vials 8 hours after initial entry.

Once diluted in 0.9% sodium chloride, the product should be used immediately. If not used immediately, in-use storage times are the responsibility of the user and should not be longer than 24 hours at 2ºC-8ºC.

9.2.9 Route of Administration: Intravenous

9.2.10 Method of Administration: Administer the initial dose over a minimum of 90 minutes. If no adverse reactions occur, administer the second dose over a minimum of 60 minutes. If no adverse reactions occur after the second dose, administer subsequent doses over a minimum of 30 minutes. If infusion-related adverse reactions occur, all subsequent infusions should be administered over the shortest period that was well tolerated.

9.2.11 Adverse Events: Please see Section 7.3.1 for the Bevacizumab CAEPR.

9.3 Pegylated Liposomal Doxorubicin (NSC #620212, 712227)

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.3.1 Formulation: Please see the doxorubicin HCl liposome package insert.

9.3.2 Storage: Refrigerate unopened vials of PLD at 2°–8°C (36°–46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on PLD.

9.3.3 Preparation: PLD doses must be diluted in 5% Dextrose Injection, USP prior to administration in accordance with the package insert and/or institutional procedures. . Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in PLD. Diluted PLD should be refrigerated at 2°C–8°C (36°F–46°F) and administered within 24 hours.

Do not mix with other drugs.

Do not use with any diluent other than 5% Dextrose Injection.

Do not use any bacteriostatic agent, such as benzyl alcohol.

PLD is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

9.3.4 Procedure for Proper Handling and Disposal: Caution should be exercised in the handling and preparation of PLD.

The use of gloves is required.

If PLD comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.

PLD should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of PLD, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein.
PLD must not be given by the intramuscular or subcutaneous route.

PLD should be handled and disposed of in a manner consistent with other anticancer drugs.

9.3.5 Adverse Effects: Consult the PLD package insert for the most current and complete information.

9.3.6 Drug Ordering: Commercially Available. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

10. PATHOLOGY/BIOSPECIMEN (10/22/2018)

10.1 Central Pathology Review Guidelines

Not Applicable.

10.2 Biospecimen Selection for Integral Marker Testing

Not applicable.

10.3 Biospecimen Selection for Integrated Marker Testing

10.3.1 Marker to be Tested (30-OCT-2020)

PD-L1 expression will be evaluated as an integrated biomarker in this study. PD-L1, also known as B7-H1, is an inhibitory ligand expressed in multiple cancer types including ovarian. In addition to being inherently upregulated in some cancer types, more commonly, PD-L1 expression is upregulated in response to tumor-infiltrating lymphocytes and thus serves as a mechanism of adaptive immune resistance to T cell infiltration (Taube et al., 2014). Expression of PD-L1 on tumor cells and tumor-infiltrating immune cells has been shown to be associated with response to immune checkpoint blocking antibodies targeting PD-1 or PD-L1 in several cancer types (reviewed in https://www.ncbi.nlm.nih.gov/pubmed/24714771). PD-L1 expression in tumor infiltrating immune cells (IC) in particular has been shown to be the strongest predictor of response. Powles *et al.* published a phase I study investigating the anti-PD-L1 antibody atezolizumab for the treatment of metastatic urothelial bladder cancer (Powles et al., 2014). This study showed that atezolizumab had noteworthy activity in metastatic UBC with rapid responses occurring at the first response assessment (6 weeks) and

nearly all were ongoing at the data cutoff (Powles et al., 2014). PD-L1 expression is scored in tumor infiltrating immune cells (as percentage of tumor area: IC3≥10%, IC2≥5% and <10%, IC1≥1% and <5%, and IC0<1%).

VENTANA PD-L1 (SP142), is an FDA-approved complimentary diagnostic IHC assay to ascertain tumor PD-L1 status for patients with metastatic urothelial cancer and triple negative breast cancer (TNBC) considering treatment with atezolizumab, with IC1 staining (PD-L1 positivity ≥1%) as a cutoff.

The association of PD-L1 expression with response to PD-L1 blockade in ovarian cancer has not been established. We hypothesize that the tumor microenvironment of the ovarian cancer patients exhibiting higher levels of PD-L1 expression in tumor-infiltrating immune cells is more amenable to immunotherapy with immune checkpoint blockade. As such we hypothesize that patients with higher levels of PD-L1 will exhibit evidence of stronger anti-tumor immune response and improved PFS and OS in the NRG-GY009 trial.

SP142 assay was previously used to evaluate PD-L1 expression in ovarian cancer (Webb et al., 2016). In the cohort of 490 ovarian cancer cases analyzed by tissue microarray, PD-L1 IC1 positivity (defined as ≥1%) was observed in 57.4% of high-grade serous cases, 24% of endometrioid cases, and 16% of clear cell cases. Internal data provided by Genentech demonstrates IC1 staining in approximately 60% of patients and IC2 staining (>5%) in approximately 20% of patients with ovarian cancer. Based on the study above, we assume that approximately 50% of patients in our population will be PD-L1 positive (defined as ≥1%).

10.3.2 Testing Requirements and Reporting

A formalin-fixed, paraffin-embedded (FFPE) primary, metastatic, recurrent, or persistent tumor block must be submitted for retrospective PD-L1 testing. **The tumor block must contain at least 50% viable tumor and intact architecture.** See Mandatory Biospecimen Submission Table (section 10.4.1) for details.

10.3.3 Method of Testing (30-OCT-2020) (24-FEB-2021)

VENTANA PD-L1 (SP142), assay is FDA approved as a complimentary diagnostic immunohistochemistry (IHC) assay to ascertain tumor PD-L1 status for patients with metastatic urothelial cancer considering treatment with atezolizumab. In ovarian cancer patients, SP142 detects PD-L1 on immune cells (Webb, et al, 2016).

The Ventana PD-L1 (SP142) assay kit uses the OptiView DAB IHC detection kit and OptiView Amplification kit on a Ventana BenchMark Ultra Instrument along with the specified antibody. PD-L1 expression within tumor tissue will be assessed using (n=6) 4 um sections cut within a 60 day period from the FFPE block.. PD-L1 positive status is defined as ≥ 1% staining of tumor-infiltrating immune cells as a percentage of tumor area using the SP142 Ventana assay. Exploratory PD-L1 positive status is defined as ≥ 5% staining of tumor-infiltrating immune cells as a percentage of tumor area using the Ventana SP142 assay. The details about the assay performance characteristics are available at: **https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160002s009c.pdf**

10.3.4 Location of Testing (30-OCT-2020)

The NRG Oncology Biospecimen Bank (NRG-BB)-Columbus will batch ship fresh cut (not older than 60 days) sections of FFPE tumor to a Genentech designated laboratory (Histogenex) upon closure of each trial phase and receipt of all tumor blocks from sites. The laboratory is specifically set up to perform SP142 testing and quantification and will be used for the assessment of all samples on the study.

10.3.5 Biospecimen Submission for Testing

FFPE tumor **blocks** must be shipped to the NRG BB-Columbus. See Mandatory Biospecimen Submission Table (section 10.4.1) for details.

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 V.

10.4.1 Mandatory Biospecimen Submissions (10/16/2017) (10/22/2018)(13-OCT-2022)

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.

Biospecimen (Biospecimen Code)	Collection Time Point	Ship Biospecimens To
FFPE – Submit *one* (listed in order of preference)		
FFPE Persistent Metastatic Tumor (FPM01)[1] Block containing at least 50% viable tumor and intact architecture[2]	Prior to study treatment *(Preferred FFPE)*	NRG Oncology BB-Columbus within 8 weeks of registration[3]
FFPE Persistent Primary Tumor (FPP01)[1] Block containing at least 50% viable tumor and intact architecture[2]	Prior to study treatment *(Preferred FFPE; optional if another FFPE type is submitted)*	
FFPE Recurrent Metastatic Tumor (FRM01)[1] Block containing at least 50% viable tumor and intact architecture[2]	Prior to study treatment *(Optional if another FFPE type is submitted)*	
FFPE Recurrent Primary Tumor (FRP01)[1] Block containing at least 50% viable tumor and intact architecture[2]	Prior to study treatment *(Optional if another FFPE type is submitted)*	
FFPE Metastatic Tumor (FM01)[1] Block containing at least 50% viable tumor and intact architecture[2]	Prior to all treatment *(Optional if another FFPE type is submitted)*	
FFPE Primary Tumor (FP01)[1] Block containing at least 50% viable tumor and intact architecture[2]	Prior to all treatment *(Optional if another FFPE type is submitted)*	
FFPE Metastatic Neoadjuvant Tumor (FMT01)[1] Block containing at least 50% viable tumor and intact architecture[2]	After receiving neoadjuvant treatment, but prior to study treatment *(Optional if another FFPE type is submitted)*	
FFPE Primary Neoadjuvant Tumor (FPT01)[1] Block containing at least 50% viable tumor and intact architecture[2]	After receiving neoadjuvant treatment, but prior to study treatment *(Optional if another FFPE type is submitted)*	

1 A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-Columbus

2 Due to the complexity of the FFPE requirements, **only blocks will be accepted. Please provide Appendix VII to your pathologist.**

3 NRG Oncology BB-Columbus / Protocol NRG-GY009, 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 (10/16/2017) (10/22/2018) (02/20/2019)

If the patient gives permission to participate in this optional study component, then participating sites are required to submit the patient's biospecimens as outlined below.

Biospecimen (Biospecimen Code)	Collection Time Point	Ship Biospecimens To
ALL PATIENTS		
FFPE Tumor[1]	If the patient agrees, the mandatory block submitted will be used. See section 10.4.1	See section 10.4.1
Pre-Cycle 1 Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to cycle 1 of study treatment	NRG Oncology BB - Columbus the day the specimen is collected[2]
Pre-Cycle 2 Whole Blood (WB02) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to cycle 2 of study treatment; WB02 may be collected even if WB01 was not submitted	
SAFETY LEAD-IN AND RANDOMIZED PHASE II PATIENTS ONLY (This study is currently in the Phase III portion) (29-JUN-2020)		
Pre-Cycle 1 Frozen Stool (ST01) collected using the EasySampler® Stool Collection Kit **and frozen**	Prior to cycle 1 of study treatment and frozen within 1-2 hours of collection; if ***absolutely*** necessary, sample may be collected up to C1D8	NRG Oncology BB-Columbus within 12 weeks of registration[2]
Pre-Cycle 2 Frozen Stool (ST02) collected using the EasySampler® Stool Collection Kit **and frozen**	Prior to cycle 2 of study treatment and frozen within 1-2 hours of collection; ST02 may be collected even if ST01was not submitted	NRG Oncology BB-Columbus within 12 weeks of registration[2]

1 If patient consents to optional FFPE collection for exploratory biomarker studies (see Informed Consent, Additional Studies Section), the block submitted for the mandatory FFPE requirement will also be used to fulfill the optional requirement. See Appendix V for details.

2 NRG Oncology BB-Columbus / Protocol NRG-GY009, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

3 Patient should freeze stool sample within 1-2 hours of collection. Once received at the clinic, it should be placed at -80°C or colder until shipped. See Appendix V for details.

10.5 Exploratory Biomarker Laboratory Testing

Note: Exploratory biomarker testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

10.5.1 T Cell Receptor (TCR) Repertoires (10/16/2017)

DNA isolated from whole blood collected pre-cycles 1 and 2 will be batch shipped by the NRG Oncology BB-Columbus upon trial completion to [redacted] MD, PhD (Memorial Sloan Kettering Cancer Center) for TCR repertoire analysis.
Additionally, DNA and RNA isolated from sections of FFPE tumor* will be batch shipped by the NRG Oncology BB-Columbus upon trial completion to [redacted] MD, PhD for deep sequencing of TCR CDR3 regions. **DNA and RNA will be isolated from one tumor type (order of preference: persistent, recurrent, metastatic, primary).*

10.5.2 Neoantigen Assessment and Characterization of the Tumor Microenvironment (10/16/2017)

DNA and RNA isolated from sections of FFPE tumor* will be batch shipped by the NRG Oncology BB-Columbus upon trial completion to [redacted] MD, PhD for next-generation sequencing, including but not limited to whole exome sequencing and/or RNA

sequencing or alternative methodologies to characterize the neoantigen landscape and the tumor microenvironment. **DNA and RNA will be isolated from one tumor type (order of preference: persistent, recurrent, metastatic, primary).*

10.5.3 Microbiome Analysis

Pre-cycles 1 and 2 frozen stool will be batch shipped by the NRG Oncology BB-Columbus to Dr. [redacted](University of Chicago) for microbiome analysis.

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Quality of Life

Although there is a relatively small body of literature examining quality of life (QoL) with recurrent, platinum resistant ovarian cancer, QOL may be maintained for those receiving further chemotherapy, particularly if they are responding to treatment (Beesley et al., 2014). Similarly, among a sample of recurrent, platinum resistant symptomatic patients, 40% derived a clinical benefit from chemotherapy, and 50% reported symptom improvement (Friedlander et al., 2014). In the AURELIA trial, patients with platinum-resistant ovarian cancer were randomly assigned to chemotherapy alone, or with bevacizumab. Patients who received bevacizumab with chemotherapy reported a significantly greater improvement in abdominal symptoms and QOL during active treatment (Stockler et al., 2014), supporting a role for bevacizumab with chemotherapy in the treatment of women with platinum-resistant ovarian cancer. However, in a recent Cochrane report in which QOL data were deemed insufficient for meta-analyses, authors note that much more research is needed to determine the role of PARP inhibitors in platinum-resistant disease (Wiggans et al., 2015). Adding to this current and significant area of inquiry, we are now considering the AURELIA trial regimen as the new standard care arm, since combining bevacizumab with chemotherapy in platinum resistant ovarian cancer significantly improved progression free survival (the primary endpoint) as well as objective response rate and the patient reported outcome end point of abdominal/GI symptoms and quality of life.

Therefore in this study, PLD with bevacizumab will be the backbone on which to improve and will serve as the reference group. Specific to patient-reported outcomes, we will examine the effects of the addition of atezolizumab to PLD (Experimental Regimen 1); or the addition of atezolizumab to PLD and bevacizumab (Experimental Regimen 2) in a Phase II/III study, compared to the reference group. Given the non-overlapping toxicities of these three agents, with the exception of fatigue, both patient-reported experiences of disease response and treatment side effects are of interest.

In the face of recurrent, platinum resistant disease, and the absence of an OS benefit, it is difficult to place a value upon PFS. On the one hand, delaying cancer progression is likely to confer some benefit to a person's quality of life, not only because of the psychological benefit of knowing one's disease is stable, but also based upon the fact that delaying progression is also likely to delay the onset of life-limiting symptoms. On the other hand, treatment itself carries toxicities which themselves can be distressing and life-limiting. In order to fully appreciate the benefits and risks associated with delaying PFS, these studies require careful assessment of targeted quality of life domains, in particular, disease symptoms, treatment side effects, and patient functioning.

The patient reported outcome (PRO) plan for this trial was assembled to capture disease symptoms, treatment side effects, general function and well-being. Disease related symptom benefit is the primary and only planned PRO analysis. Evaluation of differences in side effects and function are also proposed, in order to estimate the extent to which symptoms and side effects affect function and well-being, and to plan for future study of the relative weight patients place upon each of these endpoints alongside clinical endpoints such as PFS. For this study, the following measures are proposed:

- Disease-related symptoms: The NCCN/FACT-Ovarian Cancer Symptom Index-18 (NFOSI-18; Jensen et al., 2011). Half (9 items) of the NFOSI-18 comprise the Disease-Related Symptom-Physical (DRS-P) scale, which is the primary planned PRO endpoint
- Treatment side effects: Three measures of treatment side effects will be employed: The 5-item Treatment Side Effects (TSE) scale from the NFOSI-18; the 13-item FACIT-Fatigue subscale; and the four-item FACT/GOG-AD subscale.
- Patient function and well-being: Two brief measures of patient function and well-being will be employed: The 3-item function and well-being (F/WB) scale from the NFOSI-18, and the 1-item worry item from the NFOSI-18. **(10/16/2017)**

A proposed PRO assessment comprises a total of 35 questions to measure symptoms, side effects, function, and well-being. This is a shorter assessment than has been used in prior GOG trials that have consistently seen >80% follow-up assessment adherence. Patient time to complete averages less than 10 minutes for the entire set of questions, and this has historically been a very motivated and engaged group of participants. To keep the assessment brief, questions were selected only if they served a specific and planned purpose as described below. *Within the Phase II trial, these same 35 items will be collected for their use rolling into the Phase III trial.* Excluding these in Phase II would compromise the power to detect between-arm differences in Phase III. **(10/16/2017)**

Study Hypotheses and Instrument Selection

It is anticipated that disease-related symptoms, as measured by the DRS-P of each experimental regimen will be significantly better/less than the reference regimen at each of the assessment times during the first year. This is based in part on an underlying assumption that the disease symptom benefit of delaying progression will be greater than any differences in toxicities that might exist between treatments. Therefore, it is critically important that all living patients be assessed, even after progression, for the full follow-up window specified in the protocols. If, as has been the case in many prior trials, PRO assessment stops at the time of progression, this will introduce a bias in the group comparison, one which typically disadvantages the more effective treatment (because it retains more patients, including some who may have progressed on the inferior treatment). Although it is a limitation to attribute QoL changes identified while patients are receiving subsequent therapies after discontinuation of study drug, to the original treatment assignment, there is an even greater limitation imposed by a decision to stop assessment of these patients altogether. That greater limitation is the introduction of bias to any random effects longitudinal model caused by non-ignorable missing data over time. We therefore propose to continue assessment of all living patients during the study observation period. This is consistent with recommendations that have been made by the NCI Symptom and Quality of Life Steering Committee, and with best QoL and

statistical research practices. Limitations associated with subsequent therapies can therefore be explored with available data.

In the PRO component of this trial, the primary emphasis will be placed on symptoms of disease (with the understanding that some symptoms such as fatigue and nausea are caused by both disease and treatment), with exploratory emphases on treatment side effects and function/well-being. Specifically, assessment of disease related symptoms will evaluate the benefit of PFS as experienced by the patient, and address the question of whether symptomatic progression accompanies radiographic progression. Similarly, the patient experience of side effects (at least the more common or consequential ones anticipated in this trial, such as fatigue) will be an important exploratory indicator of the acceptability of one treatment relative to another.

Main PRO Endpoint. The Disease-Related Symptom-Physical (DRS-P) scale from the NCCN/FACT-Ovarian Cancer Symptom Index-18 (NFOSI-18), (Jensen et al., 2011), is a 9-item scale which comprises the first 9 items of the NFOSI-18. This scale was developed using a qualitative methodology with 50 advanced ovarian cancer patients and 10 expert clinicians. Most of the items come from the FACT-O questionnaire (Basen-Engquist et al., 2001), but they have been supplemented, reorganized and validated to create a set of targeted outcome tools for disease related symptoms, treatment side effects, general functioning and well-being. Of note, after establishing that these 9 questions are the most important disease-related symptoms to women with ovarian cancer (Jensen et al., 2011), these questions have been further evaluated and demonstrated through cognitive debriefing interviews with 18 women with ovarian cancer to be understood as intended. The targeted 9-item DRS-P subscale will serve as the main PRO endpoint, and is currently being utilized in GY004 and GY005. Disease-Related Symptoms-Physical, as measured by the DRS-P, have been selected as the main PRO endpoint because we expect that the treatment arm which provides a greater PFS benefit will be demonstrated through a delay or reduction of disease symptoms. The hypothesis, as stated above, is that the treatment arm with the superior PFS benefit will also have a superior DRS-P benefit, lending confirmation as a patient-reported symptomatic benefit associated with delaying disease progression. The 9-item NFOSI-18 DRS-P is the main PRO endpoint for the Phase II and III trials and has a specified analysis plan.

Exploratory endpoints: Additional endpoints are exploratory for the Phase III studies and will be analyzed post-hoc.

Treatment Side Effects (TSE). One measure of treatment side effects will be employed: The 5-item Treatment Side Effects (TSE) scale from the NFOSI-18. As the TSE scale is not intended to cover all, or even most, of the anticipated side effects across these two trials, we propose to use the single summary TSE item ("I am bothered by side effects of treatment") as the unit of analysis comparing overall side effect bother of the treatment arms. There is precedent for this (Cella et al., 2013).

Patient function and well-being (PF/WB). Two brief measures of patient function and well-being will be employed: The 3-item function and well-being (F/WB) scale from the NFOSI-18, and the 1-item worry item from the NFOSI-18.

FACIT-Fatigue subscale. Recent studies of the proposed monoclonal antibody indicate that fatigue is the cardinal treatment side effect, therefore justifying a more detailed investigation of this construct. **(10/16/2017)**
FACT/GOG-AD subscale: is a 4-item subscale used to measure the disease or treatment related abdominal discomfort. **(10/16/2017)**

PRO Assessment Timing. The following PRO assessments will be performed every 8 weeks for the first year, which corresponds to radiographic assessments, and every 12 weeks for the second year. PRO assessments should be conducted on all living patients, even post-progression, for time points as scheduled in the protocol, and will be discontinued after two years on study.

1. (MAIN QOL/PRO endpoint): PRO: DRS-P (from NFOSI-18)
2. (exploratory): PRO: TSE (from NFOSI-18)
3. (exploratory): PRO: Function/Well-Being (from NFOSI-18)
4. (exploratory): PRO: FACIT-Fatigue-13
5. (exploratory): PRO: FACT/GOG-AD subscale **(10/16/2017)**

QOL Data compliance:

In GY009, similar to other trials with very advanced disease populations, the compliance challenge will occur because of the relatively short intervals of PFS and OS. In the platinum-resistant population, the median PFS is 12 weeks and the median OS is less than one year. Our QOL non-compliance is highest among those patients who have stopped study treatment for either progression or adverse events. Importantly, these two reasons do not obviate the need for the research nurses and clinical research associates to continue to collect QOL data as scheduled. It is frequently the case, under these scenarios, that an institutions' research team assumes that if the patient is off of the clinical trial, that she is also finished with her QOL assessments. These "institutional errors" can be remedied by diligent educational efforts and frequent reminders for follow-up, even if the patient is "off study." We are mindful of the fact that even with progressing disease, patients appreciate being asked about their health and well-being, and are compliant with completing the questionnaires. This is especially true for the ovarian cancer patient population. It is worth noting that in previous ovarian trials (e.g., 24 months follow-up) we achieved close to 80% compliance.

NRG will utilize the following strategies to optimize compliance:

TARGET: CLINICAL RESEARCH ASSOCIATES & NURSING

Task 1. **Compliance Task Force**, Chaired by Dr. [redacted] convenes monthly via teleconference to assess compliance of each active protocol and initiate strategies for improvement. **Presentation** at each semi-annual group meeting on compliance updates and challenges, sharing QOL results, and reinforcing the message that QOL should continue to be assessed after the patient progresses or is off the study treatment.

Assigned to: Presenters will include the leadership of the data management and nursing committees.

Task 2. Send an initial **email message, prior to study activation** to all institutions' CRA's, nurses and site PI detailing the requirements, and procedures for QOL data collection, along with the importance of continuing timely assessments.

Assigned to: This message can be prepared by the QOL study chair together with the Data Management and Nursing committee leaders.

Task 3. **Quarterly distribution list email message** to the data management and nursing committees on compliance updates and challenges, reinforcing the message that QOL should continue to be assessed after the patient progresses or is off the study treatment.

Assigned to: Compliance reports will be prepared by the statistical office, and the email message will be sent by the PCOR leaders.

Task 4. **Newsletters** with study updates, including QOL compliance can be prepared semi-annually for activated trials. Sites that are doing especially well with compliance can be featured.

Assigned to: The QOL study Chair, the study statistician and the data management leaders should contribute to individual study updates.

Task 5. The IT staff is developing a **forms-due calendar** in Medidata/Rave to remind clinic staff of upcoming assessments for each patient.

Assigned to: IT Staff with oversight from the Statistical Office

Task 6. A patient **form schedule** is provided to the institution at the time of registration, indicating due dates for QOL assessments.

Assigned to: IT Staff with oversight from the Statistical Office

Task 7. A monthly **forms tracking list** is provided to the institutions, listing all forms due, including QOL, projecting 30 days in advance.

Assigned to: IT Staff with oversight from the Statistical Office

Task 8. A **14-day advance notice** is sent to institutions notifying them of QOL assessments that will be due. **Past due notifications** will be sent out 15, 30, 60 and 90 days to the data management CRAs with site PIs copied.

Assigned to: IT Staff with oversight from the Statistical Office

Task 9. **Delinquency reports** will be generated with expectation of 80% compliance, sent to site PIs and CRAs.

Assigned to: IT Staff with oversight from the Statistical Office

TARGET: PATIENT ADVOCATES

Task 1. Provide advice on **strategies to improve awareness** of the importance of timely and complete QOL data (e.g., brochure, letter, message in the informed consent).

Assigned to: Disease site patient advocates.

12. ASSESSMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using a slightly modified version of 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. The modification to these criteria minimizes the possibility that therapeutic agents that induce T cell infiltration into tumors as an early manifestation of anti-tumor effect could be erroneously interpreted as disease progression on imaging and result in premature discontinuation of a therapeutically effective agent. Therefore, **the protocol specifies continuation of treatment in cases of radiologic progression at the first 8 week (+/- 7 days) CT if all of the following criteria are satisfied:**

- No decrease in performance status
- No requirement for immediate alternative treatment or urgent palliative treatment
- Progression limited to an increase of 40% in the sum of diameters of target lesions (including up to 4 new lesions added to the sum)
- No more than 4 new lesions included in the sum

For patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT:

- At any subsequent CT scan patients who have stable disease as compared to the 8 week (+/- 7 days) CT scan will be allowed to continue on study treatment.
- Patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT, and later experience a PR or CR (as compared to baseline CT) will be recorded as delayed responses by the Statistics and Data Management Center.

For patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT, must have repeat CT in 4 weeks (+/- 7days) to rule out further progression.

12.1.1 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.

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

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.

12.1.3 Response Criteria

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

12.1.3.1 Evaluation of Target Lesions

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

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

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

Note: The protocol specifies continuation of treatment in cases of radiologic progression at the first 8 week (+/- 7 days) CT if all of the criteria are satisfied.

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.

12.1.3.2 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).

12.1.3.3 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.

12.1.3.4 Evaluation of Best Overall Response **(10/22/2018)**

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.

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

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

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

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

12.1.3.5 Best Overall Confirmed Response **(10/22/2018)**

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.

However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of results.

Time Point Response First time point	**Time Point Response Subsequent time point**	**BEST overall confirmed response**
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*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 non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR**

and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.

For this study, the minimum criteria for SD duration is 8 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.

12.1.4 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.

12.1.5 Progression-Free Survival

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

12.1.6 Survival

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

13. DATA AND RECORDS

13.1 Data Management/Collection (29-JUN-2020)

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 an 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.

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.

13.2 NRG Data Management Forms

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

13.3 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 Section 7.5.2 for information about expedited and routine reporting.

13.4 Global Reporting/Monitoring

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, either by FTP burst of data or via the CDS web application. 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 Web site (http://ctep.cancer.gov/reporting/cdus.html)

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

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

a. Stage 1 of a safety lead-in
b. Stage 2 of a safety lead-in
c. A randomized phase II study
d. A randomized phase III study

The first component is a 2-part safety lead-in trial in which the frequency of dose limiting toxicities in the experimental regimens will be evaluated. If the DLT rate on the experimental regimens is deemed acceptable, then the second component, which provides a randomized phase II evaluation of the study regimens, will be initiated. Specifically, the phase II component of this study will assess whether one or both of the experimental regimens increase the duration of progression-free survival adequately to warrant a phase III evaluation. The subjects enrolled onto earlier components of this study will be included in the analyses of subsequent components. That is, the subjects enrolled into the safety lead-in will be included in the analysis of the phase II endpoints and subjects enrolled during the safety lead-in or the phase II component will be included in the analyses of the phase III objectives. This approach is intended to reduce the number of patients required when compared to the strategy of conducting three independent, sequential trials with the same objectives.

Stage 1 of the safety lead-in
During the first stage of the safety lead-in, treatment assignment will not be randomized. Instead, all individuals will receive the PLD + atezolizumab regimen until at least 8 individuals initiate PLD and atezolizumab. The safety of this regimen will be assessed when these individuals have been completely evaluated for adverse events following their first cycle of treatment. If the PLD + atezolizumab regimen is deemed sufficiently safe, following this review, then the second stage of the safety lead-in will be initiated

Stage 2 of the safety lead-in
The study treatments will be randomly allocated during the 2nd stage of the safety lead-in (Randomization procedure described below) until at least 8 individuals are allocated to and initiate PLD and atezolizumab and bevacizumab. The safety of this regimen will be assessed when these individuals have been completely evaluated for adverse events following their first cycle of treatment. If the PLD + atezolizumab + bevacizumab regimen is deemed sufficiently safe, following this review, then the phase II component of this study will be initiated.

Phase II Study (24-FEB-2021)
The target enrollment for the phase II component of the study is 80 additional patients allocated to the reference regimen and each of the experimental regimens selected following the safety lead-in component of this study (see Table below). That is, if both of the experimental regimens are selected following the safety lead-in, then there will be approximately 88 patients randomly allocated to the PLD + bevacizumab, PLD+ atezolizumab and PLD + bevacizumab +atezolizumab regimens, respectively at the end of the phase II study including those enrolled during the stage 2 safety lead-in. Once the targeted number of patients has been enrolled, enrollment will be suspended in order to permit the PFS data to mature for the post-phase II analysis. The purpose of these analyses was to restrict the number of patients treated with experimental regimens that exhibit insufficient evidence of activity to warrant a phase III evaluation at that time.

The enrollment was opened group wide for this component of the study and the expected monthly accrual rate for this component of the study was 14 patients. Therefore, this component of the study was expected to require an additional 17 months of accrual.

Targeted Number of Individuals Enrolled During Each Component of the Study by Study Regimen:

Study Component	PLD+Bev	PLD+Atezo	PLD+Bev+Atezo	Total
Stage 1 of safety lead-in	-	8	-	8
Stage 2 of safety lead-in	8	8	8	24
Randomized Phase II	80	80	80	240
End of Phase II Sub total	88	96*	88	272
Phase III	72	72	72	216
Total	**160**	**168***	**160**	**488**

* Those individuals, who were enrolled during stage 1 of the lead-in, will not contribute to the treatment comparisons following phase II or III.

Treatment Randomization Procedure
Patients are electronically registered and enrolled onto the study via an electronic, web-based procedure. This electronic process also assigns a study treatment to each patient who is successfully enrolled. The treatment allocation procedure will allot approximately 1 patient to each available experimental regimen for each patient allocated to PLD+Bev (reference regimen).

The assigned treatment will be sequentially allotted from a pre-allocated list of treatments that have been randomly permuted within blocks. The assigned treatment will remain concealed until the patient's enrollment procedure has been successfully completed. The same treatment allocation procedure will be used during the second stage of the safety lead-in, as well as the phase II and phase III components of this study. While there is a specific sample size specified for each of these study components, the randomization process will not be constrained to randomize any specific number of individuals to each regimen at the end of each stage.

14.2 Study Endpoints

Safety lead-in (stage 1 and 2)
Dose limiting toxicity (DLT) following cycle 1 of experimental regimens.

Definition of a Dose-Limiting Toxicity (DLT)
For the safety lead-in components of this study a DLT is defined as:

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

A DLT does not include:

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

or symptoms and are reversed with appropriate maximal medical intervention
- Grade 3 hypertension

Phase II and Phase III Study
Progression-Free survival (PFS), defined as time from the date of study enrollment to the investigator determined date of progression (see Section 12.1 for RECIST v1.1 definition of progression), or death due to any cause, whichever occurs first. For individuals who are alive and progression free, the censored time at risk will be defined as the time from the study enrollment date to the date of the patient's last radiographic disease assessment.

The objective tumor response rate is defined as the proportion of patients with complete or partial tumor response by RECIST 1.1. (**10/16/2017)**

Phase III Study
Overall survival (OS), defined as the time from the date of study enrollment to the date of death regardless of the cause. For those individuals, who have no death reported at the time of the analysis, the time at risk of death will be assessed from the date of study enrollment to the date that the patient was last contacted and known to be alive.

14.3 Primary Objectives Study Design

14.3.1 Primary Hypotheses and Type 1 Error Allocation (Phase III)

The *null* hypotheses of therapeutic efficacy for the phase III component of this study are:

$H_{1,os}$: The hazard of death among women in the target population treated with PLD + atezolizumab is equivalent to those treated with PLD + bevacizumab.

$H_{2,os}$: The hazard of death among women in the target population treated with PLD + bevacizumab + atezolizumab is equivalent to those treated with PLD + bevacizumab.

$H_{3,os}$: The hazard of death among women in the target population treated with PLD + atezolizumab is equivalent to those treated with PLD + bevacizumab + atezolizumab.

$H_{1,pfs}$: The hazard of first progression or death among women in the target population treated with PLD + atezolizumab is equivalent to those treated with PLD + bevacizumab.
$H_{2,pfs}$: The hazard of first progression or death among women in the target population treated with PLD + bevacizumab + atezolizumab is equivalent to those treated with PLD + bevacizumab.

$H_{3,pfs}$: The hazard of first progression or death among women in the target population treated with PLD + atezolizumab is equivalent to those treated with PLD + bevacizumab + atezolizumab.

Note: Arm 1 (PLD and atezolizumab) was permanently closed to accrual with amendment 11 as the planned interim analysis for this regimen crossed the futility boundary for early termination, which was based on overall survival compared to the reference regimen of PLD and bevacizumab (Arm 3). The hypotheses $H_{1,os}$, $H_{1,pfs}$, $H_{3,os}$, and $H_{3,pfs}$ will not be open for

further testing since the regimen PLD + atezolizumab is deemed futile (that is, not likely to be declared active against the reference regimen). **(24-FEB-2021)**

Type I error allocation (24-FEB-2021)
The strategy for controlling the overall type I error for these six hypotheses is to allocate 0.0124 type I error (1-sided) to $H_{1,os}$, and 0.0001 (1-sided) to $H_{1,pfs}$ (0.0124 + 0.0001 = 0.0125). Likewise, 0.0124 and 0.0001 type I errors will be allocated to $H_{2,os}$ and $H_{2,pfs}$, respectively, so the type 1 error allocated to all four of these hypotheses is 0.025 (=0.0125+0.0125, 1-sided). These type I errors will *not* be redistributed in the event that one of the experimental regimens are dropped following the phase II component of this trial. Moreover, the type I errors for $H_{1,os}$ and $H_{2,os}$ include the type I errors spent for interim analyses ($H_{1,pfs}$ and $H_{2,pfs}$ will not be assessed at the interim analysis). Dropping the PLD + atezolizumab regimen after the interim analysis does not change the allocation of alpha. The original specifications listed above remain.

If and only if both $H_{1,os}$ and $H_{2,os}$ are rejected, then the type I error allocated to these 2 hypotheses will be "passed-on" to $H_{3,os.}$ In this case the type I error allocated to this hypothesis will be 0.0248 (=0.0124+0.0124, 1-sided). Likewise, if both $H_{1,pfs}$ and $H_{2,pfs}$ are rejected, then type I error allocated to $H_{3,pfs}$ will be 0.0002 (=0.0001+0.0001, sided). This allocation is not relevant if an arm is dropped for futility at an interim analysis.

14.3.2 Power and Sample Size

Safety lead-in (Stage 1 and 2)
The safety lead-in will consist of 2 stages. During the first stage, at least 8 individuals will be assigned (not randomly assigned) to receive the PLD + atezolizumab regimen. The first 8 individuals allocated to and treated with PLD + atezolizumab will form the basis of a safety evaluation. If 2 or more of these individuals experience a dose-limiting toxicity (DLT) then enrollment will be stopped and the doses and schedule will be reconsidered. Otherwise, the regimen will be considered sufficiently safe to continue onto the second stage of the safety lead-in.

During the second stage of the safety lead-in the treatment allocation procedure will begin to allocate all three of the study regimens with nearly equal frequency. The second stage of the safety lead-in will continue until 8 individuals are randomly allocated to and treated with PLD + bevacizumab + atezolizumab. These 8 individuals will form the sample for assessing the safety of the PLD + bevacizumab + atezolizumab regimen. If two or more of these individuals experience a DLT, then consideration will be given to adjusting the doses/schedule or discontinuing the allocation of this regimen to future enrollees.

If the true probability of a DLT is no larger than 0.10, then this criterion provides at least 81% chance of classifying the regimen as acceptable. On the other hand, if the true probability of a DLT is 0.35 then this criterion provides an 83% chance of declaring the regimen as unacceptable.

In the event that 2 individuals experience confirmed DLTs before the target enrollment for the lead-in is attained, then the outcome for this stage of the study will be considered ineluctable and accrual to that experimental regimen will be stopped.

The enrollment during the lead-in component of this trial will be limited to selected institutions. The accrual rate during this period is expected to be about 5 patients per month. Therefore the first stage of the safety lead-in is expected to require 1.5 months following a brief start-up period. If the PLD + atezolizumab regimen is deemed safe, then the second stage of the safety lead-in is expected to require an additional 3-4 months of enrollment.

Phase II Study
The target enrollment for the phase II component of the study is 80 additional patients allocated to the reference regimen and each of the experimental regimens selected following the safety lead-in component of this study (see target accrual table above). That is, if both of the experimental regimens are selected following the safety lead-in, then there will be approximately 88 patients randomly allocated to the PLD + bevacizumab, PLD + atezolizumab and PLD + bevacizumab +atezolizumab regimens, respectively at the end of the phase II study including those enrolled during the stage 2 safety lead-in. These patients will form the basis of the phase II futility assessment. Once the targeted number of patients has been enrolled, enrollment will be suspended in order to permit the PFS data to mature for the post-phase II analysis. The purpose of these analyses is to restrict the number of patients treated with experimental regimens that exhibit insufficient evidence of activity to warrant a phase III evaluation at this time.

The enrollment will be opened group wide for this component of the study and the expected annual accrual rate for this component of the study is 168 patients. Therefore, this component of the study is expected to require an additional 17 months of accrual.

When at least 110 patients who were randomly allocated to receive the reference regimen or the PLD + bevacizumab + atezolizumab have reported either progression or death, the PFS relative hazard for these two regimens will be estimated. A proportional hazards (PH) model will be used to estimate the relative hazards, which is described below. The PLD + bevacizumab + atezolizumab regimen will be considered sufficiently active to warrant phase III evaluation if the estimated relative hazards indicates at least a 21.7% reduction ($HR_{PFS} \leq 0.783$) in the estimated PFS hazard (compared to the reference regimen) at this time. If the true PFS hazard for this regimen is equivalent to the reference regimen (null hypothesis is true), then there is a 90% chance that this regimen will be deemed insufficiently active to warrant a phase III evaluation, based on this criterion. On the other hand, if this regimen truly reduces the PFS hazard 37.5% (HR=0.625) in the target population, then this sample size provides a 88% chance of declaring the PLD + bevacizumab + atezolizumab regimen sufficiently active to advance to the phase III component of the study. If the PLD + bevacizumab + atezolizumab regimen is selected, then the PLD + atezolizumab regimen will also be selected for phase III evaluation. This automatic selection of the experimental doublet is necessary because the triplet regimen may need to ultimately demonstrate definitive superiority over both the reference regimen and the experimental doublet regimen in the phase III study (see below) in order to be declared the overall preferred regimen.

On the other hand, if the PLD + bevacizumab + atezolizumab regimen is not selected, then the PFS hazard of PLD + atezolizumab regimen will be compared to the reference regimen. This regimen will be considered sufficiently active to warrant phase III evaluation if it exhibits at least a 21.7% reduction ($HR_{PFS} \leq 0.783$) in the estimated PFS hazard (compared to the reference regimen) at this time. In this case, the probabilities of selecting (not selecting) this regimen are similar to those for the experimental triplet that are provided above. For the purposes of calculating these selection probabilities, the variance of the log hazard ratio is estimated assuming the null hypothesis is true.

Proportional Hazards Model for Estimating Relative Hazards
A proportional hazards (PH) model (Cox, 1972) will be used to estimate the relative hazards. All of the individuals who have been enrolled during stage 2 of the safety lead-in, the phase II component and the phase III components will be included in these analyses regardless of their eligibility status, or compliance with their assigned study treatment. The proportional hazards model will not be stratified.

Phase III Study (24-FEB-2021)

If at least one experimental regimen is deemed sufficiently active following the phase II study, then 72 additional patients will be enrolled and designated to receive the reference regimen and a nearly equal number of individuals to each of the experimental regimens that were selected following the phase II component of this study in order to evaluate the phase III objectives (the treatment randomization procedure is describe above). Since the expected annual accrual rate is 168 patients, the enrollment period for the phase III component is expected to require approximately 15 months if both experimental regimens are selected.

Hypotheses: $H_{1,os}$ and $H_{2,os}$
When there are at least 128 deaths reported among those patients randomly allocated to the reference regimen, this study will be considered sufficiently mature for evaluating the hypotheses $H_{1,os}$ and $H_{2,os}$. The type I error will be set to 0.0124 (one-tail, see Type I Error Allocation above) for each of these two hypotheses including the type I error spent for interim analyses. If an experimental regimen truly reduces the hazard of death 37.5% (HR=0.625) then the expected number of deaths at this time among those randomly allocated to that experimental regimen is 108. This sample size (128+108=236 deaths for each pairwise comparison) provides approximately 91% power for a true hazard ratio of 0.625 (80% power for HR=0.667). The median duration of survival for women from the target population and treated with PLD+Bev is 14 months. Assuming proportional hazards with exponential survival function, a HR=0.625 is comparable to increasing the median duration of survival by 8.4 (median 14 to median=22.4) months. All of the subjects enrolled, regardless of the whether they were enrolled during the safety the stage 2 lead-in, phase II or phase III components will be included in these final analysis. These power estimates do not account for the chance that a treatment is dropped for safety concerns during the safety lead-in or following the phase II component for exhibiting insufficient activity to warrant a phase III evaluation. Based on simulation where OS and PFS times were generated using a normal copula with correlation 0.70 between event times, it is estimated that the power for $H_{1,os}$, is

0.77, accounting for the chance of dropping an active treatment at the end of the phase II study, if the true PFS and OS hazard ratios are 0.625 (likewise for $H_{2,os}$).

Hypothesis: $H_{3,os}$
See section 14.3.1 regarding $H_{3,OS}$
In the event that both experimental regimens are selected following the phase II component of this study *and both* of these regimens demonstrate statistical superiority over the reference regimen, then the death rates of the two experimental regimens will be compared to each other ($H_{3,os}$). The study will be considered sufficiently mature for an evaluation of this hypothesis when there are 195 deaths reported among those patients who were enrolled and allocated to either of the experimental regimens. The type I error for this comparison will be set to 0.0248 (one-tail). This sample size provides 90% power when the triplet regimen reduces the death rate 37.5% (HR=0.625) relative to the experimental doublet regimen (80% power for HR=0.667), not accounting for the possibility of dropping an active regimen following the phase II component or for the prerequisite for rejecting $H_{1,os}$ and $H_{2,os}$ It is possible for the data for this hypothesis to mature before the data mature for $H_{1,os}$ and $H_{2,os}$. In this case, $H_{3,os}$ will not be assessed until after the data for $H_{1,os}$ and $H_{2,os}$ have matured.

Hypotheses $H_{1,pfs}$ and $H_{2,pfs}$
See section 14.3.1 regarding $H_{1,pfs}$. The hypotheses $H_{1,pfs}$ and $H_{2,pfs}$ will not be assessed until the study has sufficiently matured to assess $H_{1,os}$ and $H_{2,os}$. It is anticipated that approximately 90% of the patients enrolled onto the study will have experienced either a progression or death event at this time. Therefore the expected number of events available for each pairwise treatment comparison of $H_{1,pfs}$ and $H_{2,pfs}$ is approximately 280. With this number of events, each pairwise comparison has 90% power for a true hazard ratio of 0.55 when type I error is 0.0001 (1-sided), not accounting for the possibility of dropping an active regimen at the end of the phase II component.

Hypotheses $H_{3,pfs}$
See section 14.3.1 regarding $H_{3,pfs}$. The hypothesis $H_{3,pfs}$ will not be assessed until the study is sufficiently mature to assess $H_{3,os}$. This hypothesis will not be assessed unless $H_{1,pfs}$ and $H_{2,pfs}$ have been rejected.

Logrank Procedure for Final Analyses of the Phase III Objectives
A logrank test will be used to evaluate the null hypotheses for the phase III objectives. The logrank procedures will involve all of the patients who were enrolled onto the trial during stage 2 of the safety lead-in, phase II or phase III components. Patients will be grouped by their randomly assigned treatment and included in the analysis regardless of their eligibility or compliance with their assigned study treatment. The logrank procedures will not be stratified. The individuals who were enrolled during stage 1 of the safety lead-in will not be included in the testing of these hypotheses, since these individuals do not have their study treatment randomly assigned.

14.4 Study Monitoring of Primary Objectives (24-FEB-2021)

As described in previous sections, there are assessments of safety following stages 1 and 2 of the safety lead-in and an assessment of therapeutic futility following the phase II study

component. Additionally, an interim analysis will be performed when at least half of the number of deaths (128/2=64 deaths among those allocated to the reference regimen) required for the final analysis has occurred. The interim analysis will include an assessment of both futility and superiority for hypotheses $H_{1,os}$ and $H_{2,os}$. O'Brien and Fleming-like ($\beta(t)=2-2\Phi(Z\beta/2/\sqrt{t}$; Lan et al., 1989) Type I and Type II error spending functions (non-binding) will be used for assessing futility and efficacy. These functions require that the percent of information time be specified at the time of the interim analyses. The percent information time will be calculated as the proportion of deaths reported at the time of the interim analyses among those allocated to the reference regimen relative to the required number for the final analysis. The previously described logrank statistic will be calculated and compared to these boundaries. If the logrank statistic does not exceed the futility boundary for $H_{1,os}$ (or $H_{2,os}$) then consideration will be given to stop allocating the PLD + Atezolizumab (or PLD + bevacizumab + atezolizumab) regimen to future enrollees and concluding that it is unlikely that the experimental regimen extends overall survival compared to the reference regimen. These boundaries will restrict the treatment hazard ratio (experimental: reference) for OS to be less than (approximately) 0.90 at the time of the interim analysis.

The interim analysis will also include estimates of the hazard ratios and the corresponding confidence intervals for the experimental regimen relative to the reference regimen, as well as Kaplan-Meier (Kaplan and Meier, 1958) estimates of the survivorship function for each treatment group.

The results of interim analyses are reviewed by the NRG Oncology Data Monitoring Committee (DMC). This DMC meets semi-annually to review the progress of all NRG Oncology ongoing randomized phase II or III trials. The DMC can also schedule additional meetings on an as-needed basis. The dates for the semi-annual DMC meetings are administratively scheduled without any knowledge of the study results. Approximately eight weeks prior to its scheduled meetings, the study database is locked in order to prepare a semi-annual study report. This study report includes summarizes of accrual and adverse event data. If the prerequisite number of deaths for a scheduled interim analysis has been attained, a report summarizing the results of the interim analysis is also prepared and presented to the DMC at their upcoming meeting. The actual decision to terminate accrual or to release study results includes consideration of toxicities, treatment compliance, as well as results from external studies.

14.5 Accrual/Study Duration Considerations (24-FEB-2021)

During the safety lead-in, accrual will be limited to institutions that have experience running multi-center phase I/II studies. The expected accrual rate during this component of the study is 4 patients per month. Therefore, the first and second stages of accrual are expected to require about 1.5 and 4 months after a brief start-up period, respectively, to complete accrual. If the results are not ineluctable at the time when the accrual has completed, then a short interruption may be needed until the last patient enrolled is treated and evaluated.

Enrollment during the phase II and phase III components will be opened to all eligible institutions. Accrual rate is expected to be about 168 patients per year. Therefore, the accrual

periods for the phase II and the phase III components are anticipated to be 17 and 15 months, respectively. A 12- to 18-month post-accrual follow-up period is expected.

Interim Analysis Results and Implications to the Study Accrual Target and Duration

An interim analysis was conducted when 64 deaths were observed in the reference regimen (PLD + bevacizumab). This corresponded to ½ the information time. Tests for efficacy and futility were conducted on the two experimental regimens as described above. The PLD+ atezolizumab regimen (Arm 1) exceeded the futility boundary (i.e. was greater than ─0.435). The DMC recommendation for dropping the PLD+ atezolizumab regimen was accepted. The study will proceed as a two-arm study with equal randomization to each arm (1:1) until about 72 phase III patients are accrued to the reference regimen (160 patients in total for the reference regimen).

As of the study suspension, there were 124, 115, and 116 patients enrolled to Arms 1, 2, and 3, respectively. The study needs 160 patients in Arms 2 and 3. The remaining number of patients needed to finish accrual is 89. The study will have completed accrual when a total of 444 patients are enrolled. The anticipated time it will take to complete recruitment is 6.4 months after study reactivation.

The final analysis will occur when 128 deaths are seen on Arm 3 (the reference regimen) as stated above. Hypotheses $H_{2,os}$ and $H_{2,pfs}$ will be tested at that time in accordance with the original Phase III procedures.

14.6 Secondary or Exploratory Endpoints (including correlative science aims)

14.6.1 Secondary Hypotheses and Endpoints (30-OCT-2020) (08-JAN-2021)

Phase II and Phase III

Safety endpoints: Frequency and severity of adverse events as classified and graded according to Common Terminology Criteria for Adverse Events (CTCAE) assessed among those patients who initiate their randomized study treatment. **(03/19/2018)**

Efficacy Endpoint: The objective tumor response rate is defined as the proportion of patients with complete or partial tumor response by RECIST 1.1. **(10/16/2017)**
The hazard ratios of treatment to reference regimen for death and progression (OS and PFS) will be estimated with a Cox proportional hazards model without stratification variables for both the phase II and III components of the trial. PFS HR will be a primary endpoint for the phase II study. In addition, confidence intervals and KM plots will be provided. Trial stage will be examined in an exploratory manner to see if there is a trial stage influence on these endpoints.

In addition to the formal analyses of the integrated biomarker, we will examine through exploratory analyses response, PFS, and OS by PDL1 (+) status as defined with IC0, IC1/2/3, and IC 2/3. HR estimates with corresponding 95% CI, Chi-square tests, and odds ratio estimates will be reported.

It is common to analyze survival endpoints with log-rank statistics and Cox proportional hazards models. For translational research endpoints, it is common to dichotomize continuous marker values to ease interpretation of results. However, analysis as a continuous variable is

done frequently with care to note influential cases. With large sample sizes, logistic regression often yields satisfactory results when examining tumor response. For TR endpoints obtained after randomization, we propose using landmark analyses when doing survival analyses as well looking at changes of the marker over time (simple paired t-tests for example).

Patient Reported Outcomes: Main endpoint is disease-related symptoms as assessed by the NFOSI-DRS; Exploratory PROs include measurement of treatment side effects, fatigue, function/well-being, and health status.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Efficacy

The objective tumor response rate will be tabulated by treatment group, and 95% confidence intervals will be presented using Wilson's Score Method. Treatment arms will be compared using a likelihood ratio chi-square test. **(10/16/2017)**

Adverse Events

The maximum grade of each adverse event (AE) by system organ class and CTC 4.0 specific term will be tabulated for those individuals who at least initiate study treatment. The number and percent of individuals will be tabulated by the maximum grade of their AE. No specific hypothesis test is pre-specified.

14.6.3 Integrated Biomarker – PD-L1 (30-OCT-2020) (08-JAN-2021) (24-FEB-2021)

There is interest in examining the relative impact of the experimental therapies on OS compared to the control regimen within the patients who express PD-L1 (that is those patients considered to be PD-L1 positive; PD-L1+). The definition of PD-L1 expression within patients is given in the following paragraph:

PD-L1 testing will be performed with the FDA approved Ventana PD-L1 (SP142) assay kit which uses the OptiView DAB IHC detection kit and OptiView Amplification kit on a Ventana BenchMark Ultra Instrument along with the specified antibody. PD-L1 expression within tumor tissue will be assessed using (n=6) 4 um sections cut within a 60 day period from the FFPE block. PD-L1 positive status is defined as $\geq$ 1% staining of tumor-infiltrating immune cells as a percentage of tumor area using the SP142 Ventana assay. Exploratory PD-L1 positive status is defined as $\geq$ 5% staining of tumor-infiltrating immune cells as a percentage of tumor area using the Ventana SP142 assay.

The study is not prospectively stratified before randomization by the patient's PD-L1 level of expression, so an imbalance of the treatment regimen by PD-L1 expression is possible but highly improbable with the sample sizes to be seen in the phase II/III study. Therefore, the odds of randomization of the treatments in this subset should be very close to the wider sample in the entire clinical trial (e.g. randomization in a 1:1:1 fashion or 1:1 in the case that one treatment arm is dropped). What is unknown is the proportion of patients who are PD-L1+ as well as the prognostic or predictive impact of PD-L1 on the hazard of death. The question of the proportion of patients who are PD-L1+ translates into the sample size for this subset analysis. The statistical power of the study for the subset analysis is directly tied to the total number of deaths seen within the subset, and that number is closely related to the sample

size. Because the sample size is largely unknown, it will be difficult to predict the power of the subset analysis based on this factor alone.

In addition to the sample size factor lies an additional complication of the unknown prognostic or predictive effects of PD-L1. For example, PD-L1 may increase or decrease the hazard of death, so the total number of deaths within the PD-L1 + group can be proportionally larger or smaller than the proportion of patients who do not express PD-L1. In the simplest case, we can assume that PD-L1 expression has no prognostic nor predictive effect on OS. Suppose then, for instance, that 50% of patients express PD-L1. Since the final analysis will be triggered when 344 to 384 deaths are observed in the entire study (when the experimental regimens are active or inactive respectively), the total number of deaths observed in the subset would be expected to be between 172 to 192 (and 118 to 128 per treatment comparison when the regimens are active or not, respectively). To be clear, patients will be classified as PD-L1(+) if they express the biomarker to a greater level. Patients who express less biomarker will be classified as PD-L1(-).

To be assured that a subset of patients is not driving the significance of a test for treatment activity (in the case of a positive study), the alpha spent on the primary hypotheses will be forwarded to subset analyses based on whether patients are PD-L1(+) or (-). The alpha will be split equally on each subset only if the primary hypothesis is rejected. The significance of treatment effect will be examined with a log-rank test. These tests will be underpowered but may offer insight into differences in treatment efficacy based on this biomarker level. Approximately 0.0124/2 will be spent on each subset if the regimen of interest rejects the null hypothesis for overall survival. A similar procedure will be done with PFS where 0.0001 is split. If both regimens are considered active, then a test of the regimens against the reference will not be done. Instead, this test will wait to compare the two experimental regimens, and only if that test is significant (H_{3OS} is rejected).

To characterize the power of this part of the study, we used a proportional hazards model as shown below.

The hazard rate is defined through the following function:

$$\lambda = \exp\{\beta_0 + \beta_1 X_t + \beta_2 X_b + \beta_3 X_t \cdot X_b\}$$

where X_t is the treatment indicator, X_b is the biomarker value which is 1 if the patient is PD-L1(+) and zero otherwise, and $X_t \cdot X_b$ is the interaction term between the treatment and biomarker values. If a patient is on the experimental regimen, $X_t = 1$ and 0 otherwise. The $\beta's$ are the log HR values. See the table below for various parameter settings. For sake of providing an example, we will assume the analysis occurred when 128 deaths are observed on the reference regimen. Simulations were conducted assuming exponential survival times. The results were obtained through simulation of 10,000 runs using SAS' proc phreg.

Row	HR Rx	HR Bio	HR Rx*Bio	P(Bio(+)) (%)	$\widehat{HR}$	Power Rx	Power Bio(-)	Power Bio(+)
1	1.000	1.000	1.000	10	1.013	1.05	0.51	0.04
2	1.000	1.000	1.000	30	1.013	1.00	0.27	0.13
3	1.000	1.000	1.000	50	1.012	0.93	0.22	0.13
4	0.625	1.000	1.000	10	0.633	90.72	80.17	6.56
5	0.625	1.000	1.000	30	0.634	91.26	66.54	25.00
6	0.625	1.000	1.000	50	0.634	90.37	47.12	47.59
7	1.000	1.000	0.625	10	0.965	2.52	0.50	0.40
8	1.000	1.000	0.625	30	0.879	11.08	0.54	6.86
9	1.000	1.000	0.625	50	0.802	30.65	0.55	25.31
10	1.000	1.000	0.400	10	0.923	5.54	0.52	2.56
11	1.000	1.000	0.400	30	0.775	39.96	0.54	38.32
12	1.000	1.000	0.400	50	0.653	86.40	0.53	86.01

The column titled HR Rx is the treatment hazard ratio, HR Bio is the hazard ratio associated with the biomarker (often used when prognostic), and the HR Rx*Bio is the hazard ratio for the interaction. This hazard ratio can also be defined as the hazard ratio of treatment to reference among PD-L1(+) patients divided by the hazard ratio of treatment to reference among PD-L1(-) patients. The column titled $\widehat{HR}$ is an estimate of the apparent hazard ratio for the treatment effect when the biomarker is ignored (marginal HR). The value is the mean of 10,000 cases. Rows 1 – 3 show the power of the procedure when the null hypothesis is true and there are no prognostic effects or interactions with the biomarker. The power for the treatment effect is within 1.24%, and the power of the subset analyses are always bounded above by the power of the treatment effect (i.e. Power Rx). Rows 4 – 6 show the power of the procedures when the treatment is equally effective across both strata of biomarkers, and the biomarker has no influence on survival. The power of the treatment effect is about 90% as designed. As the proportion of patients with PD-L1(+) increases, the power of the test within that subset increases as well. Rows 7 – 12 give examples when the treatment is ineffective in the PD-L1(-) patients but adequately or substantially effective in the PD-L1(+) patients. When the HR is 0.625 in the PD-L1 (+) patients only, the power of the treatment effect runs from 3% to 31% as the proportion moves from 10% to 50% of the population. In this instance, the study is not adequately powered to detect this effect. If there is a strong effect in the PD-L1(+) group (HR=0.4), then the subset can drive the primary hypothesis to reject Ho. This would likely be followed by a rejection of Ho in the subset where the treatment is effective (but not in the other group).

In summary, the procedure will limit the probability of declaring the regimen active to the advertised level when the null hypothesis is true and will yield sufficient power to detect treatment activity when PD-L1 is not predictive. In these cases, the power of the subset analysis is heavily dependent on the sample size and typically underpowered. When PD-L1 is predictive (and shows inactivity in one group), then the power of the entire study as well as the subset analyses are underpowered unless the HR is of such a magnitude as to drive the study. In the latter case, a substantial proportion must be PD-L1 (+), in which case the decision rules should be able to correctly identify the active cohorts.

We will define PD-L1(+) patients as those with IC1/2/3 for the analysis described above.

14.6.4 Patient reported outcome (PROs)

The analyses of PROs described here are not intended to be used for regulatory drug approval. These analyses are for research purposes. The primary objective of this component of the study is to assess patient-reported scores of disease-related symptoms (DRS) among the study treatments. The primary measure for symptoms is the NFOSI-DRS-P (Disease Related Symptoms – Physical), which is a 9-item PRO. The DRS-P score for the i^{th} patient-assessment is calculated as

$$S_i = M * \frac{\sum_{j=1}(\delta_{ij} * s_{ij})}{\sum_{j=1}\delta_{ij}}$$

where δ_{ij} is equal to 1 when the j^{th} item has a valid response, otherwise it is equal to 0, s_{ij} is the response score of the jth item and M is the number of items in the subscale. The response score for each item ranges from 0 to 4, where higher values indicate preferred states. The DRS-P score for a particular patient-assessment time is considered valid if the patient provides valid responses to at least 5 of the subscale items, otherwise it is considered incomplete and, for the purposes of analyses, it is treated as if it is missing.

A repeated measures model will be used to estimate and compare the mean DRS-P scores for the treatment groups. Model covariates will include the patients' randomly assigned study treatment, age at enrollment onto the study, initial performance status, pre-treatment DRS-P score, assessment time and treatment-by-time interaction. The primary analyses will include only those treatments selected at the end of the phase II study and all of the patients assigned to one of these treatments during either stage 2 of the safety lead-in, phase II or phase III component of the study regardless of their compliance with the study treatment or eligibility status, provided at least one baseline (pre-treatment) and one follow-up assessment is available. For the primary analysis, patients will be grouped by their randomly assigned study treatment.

The primary analysis of disease related symptoms will use a repeated measures model to compare the mean DRS-P scores for each experimental regimen to the reference regimen at each of the assessment times during the first year. The type I error allocated to each of these two treatment comparisons is 0.025 (0.05/2, two-tail test). The type I error will not be reallocated in the event that only one experimental arm is selected following the phase II component of the study. Hochberg's step-up multiple testing procedure (Hochberg, 1988) will be used to control type I error across the 6 post-baseline assessment times during the first year (see Section 11.1).

Exploratory analyses will include an assessment of the model residuals in order to evaluate the adequacy of modeling assumptions. Additional descriptive analyses will assess whether the differences in mean scores between groups vary systematically with time in a linear or quadratic fashion.

Statistical Power for NFOSI-DRS-P

A previously conducted study involving 51 patients indicates that the expected mean and standard deviation of the DRS-P are approximately 51.6 and 10.7, respectively. The primary analysis of DRS-P will focus on the 6 assessments scheduled during the first year following enrollment onto the study. For the purposes of estimating power, it is assumed that there will be a 10% attrition of patients at the first reassessment time and 15% at each subsequent assessment time, due to death or non-compliance. Also, it is assumed that the correlation between two consecutive assessments on the same individual will be 0.60, and between two assessments separated by 1 and 2 assessments will be 0.40 and 0.20, respectively. The correlation between scores more than 2 assessments apart is assumed to be 0.10. A simulation of 1000 trials indicates that the probability of rejecting the null hypothesis (no difference in mean DRS-P scores) for at least one assessment time when there is a constant 5 unit difference between treatment groups (experimental vs reference) is approximately 99%. The probabilities of rejecting the null hypothesis at each of the 6 post-baseline assessment times are: 98.5%, 94.6%, 82.8%, 73.5%, 67.4% and 62.7%). The drop-off in power with each successive assessment point is due to the anticipated attrition of subjects over time. Alternatively, if the difference in DRS-P scores between treatment groups increases from 0 (at baseline) to 6 units over the first year, then there is an 80% chance of rejecting the null hypothesis for at least one post-baseline assessment time. The probabilities of rejecting the null hypothesis at each assessment time are: 5.4%, 16.4%, 26.1%, 42.8%, 55.1% and 67.3%. In this case, the increase in power with each successive assessment point is due to the postulated increasing difference in mean DRS-P scores between treatment groups over time.

Other PRO Scales
Each of the other general PRO scales will be analyzed with repeated measures models using procedures similar to those described above for the DRS-P.

Missing PRO information
Patient death, noncompliance, missed clinic appointments, and patient illiteracy, can cause observations to be missed. One or more of the PRO assessments may be missing for an individual on any occasion. Missing information is troublesome particularly in studies involving repeated patient assessments. The frequency that assessments are missed will be monitored every 6 months throughout the study. Study Coordinators will be working with the Study Team and the NRG's Patient Centered Outcomes Research Committee to identify reasons that data are missing and recommending remedial actions when possible.

The PRO instruments used in this study have been translated to several different languages. Women who are unable to read or have difficulty reading, will not be required to participate in the PRO component of this study, however, a woman may elect to have the items read to her and be assisted in completing the instruments.

14.7 Interim Analysis for All Other Endpoints (Goals) (24-FEB-2021)

Kaplan-Meier estimates of the treatment-specific cumulative distribution of PFS will be provided to the DMC at the time of the Phase III interim analysis. Tabulations of adverse events by treatment group will also be provided at that time. However, these endpoints are not the primary focus of the interim analysis.

These numbers are based on full accrual to all three study regimens.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	3	0	0	0	3
Asian	10	0	0	0	10
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	13	0	2	0	15
White	403	0	8	0	411
More Than One Race	3	0	1	0	4
Total	433	0	11	0	444

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	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- NYHA CLASSIFICATION

Congestive Heart Failure – New York Heart Association Classification

Class	Definition
I	No limitation: Ordinary physical activity does not cause undue fatigue, dyspnea, or palpitation
II	Slight limitation of physical activity: Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or angina.
III	Marked limitation of physical activity: Although patients are comfortable at rest, less than ordinary physical activity will lead to symptoms.
IV	Inability to carry on physical activity without discomfort: Symptoms of congestive heart failure are present even with rest. With any physical activity, increased discomfort is experienced.

Source: Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis. 6th ed. Boston, Little, Brown and Co, 1964: 114.

- For cycle lengths greater than or equal to 21 days , 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 cycle lengths greater than or equal to 21 days. 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).

- 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. **(02/20/2019)**

- 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 V – TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES (10/16/2017) (02/20/2019)

I. Obtaining a Bank ID for Translational Science Biospecimens
Only one Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational science biospecimens and accompanying paperwork must be labeled with this coded patient number.

Translational science biospecimens should not be submitted until after patient registration and Bank ID assignment.

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. If a patient has previously been assigned a Bank ID, please ensure the Bank ID appearing in Rave is the same as the previously assigned Bank ID.

Please contact Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@nrgoncology.org; Phone: 716-845-7767).

II. Requesting Translational Science Biospecimen Kits
Kits will be provided for the collection and shipment of frozen stool.

Sites can order kits online via the Kit Management link (https://kits.bpc-apps.nchri.org/) . 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).

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

Note: Unused materials and kits should be returned to the NRG BB-Columbus.

III. FFPE Tissue Shipped to the NRG BB-Columbus
Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the biospecimen type (e.g., primary tumor, metastatic tumor, recurrent tumor, persistent tumor).

- **Recurrent** and **persistent** tumor should be collected prior to the study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled **recurrent primary (FRP01)** or **persistent primary (FPP01)**, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic (FRM01)** or **persistent metastatic (FPM01)**, respectively.

- **Primary (FP01)** and **metastatic (FM01)** tumor should be collected prior to all treatment.

- **Primary neoadjuvant (FPT01)** and **metastatic neoadjuvant (FMT01)** tumor should be collected after the patient receives neoadjuvant treatment. Neoadjuvant tumor should only be

submitted if tumor collected prior to receiving any treatment (FP01 or FM01) is not available.

- Only one block may be submitted per tissue type.

- All FFPE tissue should be submitted with the corresponding pathology report.

Special Notes Regarding NRG GY009 FFPE Requirements

- Due to the complexity of the FFPE requirements, **only blocks will be accepted. Please provide Appendix VII to your pathologist.**

- If patient consents to optional FFPE collection for exploratory biomarker studies (see Informed Consent, Additional Studies Section), the block submitted for the mandatory FFPE requirement will also be used to fulfill the optional requirement.

Mandatory FFPE Biospecimen Requirement

- A FFPE primary, metastatic, recurrent, or persistent **tumor block must be submitted**. **The tumor block must contain at least 50% viable tumor and intact architecture.**

- Every attempt should be made to provide a block on a permanent basis; however, if a block cannot be provided on a permanent basis, the block must be submitted on a temporary* basis. **If requested, blocks will be returned after completion of the integrated biomarker testing and at the site's expense.*

- The NRG BB-Columbus will use blocks to fresh cut (within 60 days) four consecutive unstained sections (charged, 4 µm) for shipment to a Genentech designated laboratory for immediate integrated biomarker testing.

Optional FFPE Biospecimen Requirement

- If the patient consents to optional FFPE collection for exploratory biomarker studies, the block submitted for the mandatory FFPE requirement will also be used to fulfill the optional requirement.

- Every attempt should be made to provide a block on a permanent basis; however, if a block cannot be provided on a permanent basis, the block must be submitted on a temporary* basis. **If requested, blocks will be returned after completion of the integrated biomarker testing and at the site's expense.*

- The NRG BB-Columbus will use blocks to fresh cut a scroll (thickness dependent on tumor size) and 10 consecutive unstained sections (charged, 5µm) to be used for exploratory biomarker testing.

Completing Form TR for FFPE Biospecimens

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

Labeling FFPE Tissue

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

REQUIRED FFPE BIOSPECIMEN LABELING
Bank ID (# # # # - # # - G # # #)
Protocol Number (NRG-GY- # # #)
Biospecimen Code (see section 10)
Collection Date (mm/dd/yyyy)
Surgical Pathology Accession Number
Block Number

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.

IV. Whole Blood Shipped to the NRG BB-Columbus

1. Label the lavender/purple top (EDTA) collection tube(s) as described below. Multiple tubes may be used to collect the required amount.
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
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(s) should be refrigerated (4°C) and shipped within 24 hours.

Labeling Whole Blood

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

REQUIRED WHOLE BLOOD BIOSPECIMEN LABELING
Bank ID (# # # # - # # - G # # #)
Protocol Number (NRG-GY- # # #)
Biospecimen Code (WB##)
Collection Date (mm/dd/yyyy)

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.

V. Stool Biospecimens Shipped to the NRG BB-Columbus—Phase II Portion ONLY (29-JUN-2020)

1. Provide patient with stool collection kit several days prior to the treatment visit. **Note: Label the SAMPLE and OUTER stool collection containers with the patient name, date of birth, and date and time of sample collection (as specified in the stool collection kit instructions) prior to providing the kit to the patient. The SAMPLE and OUTER stool collection containers must be relabeled as described below before sending to the NRG BB-Columbus.**
2. Review the EasySampler stool collection instructions (provided with the stool collection kit) with patient and instruct the patient to collect the sample within 24 hours of the treatment visit, as close to the visit as possible. **Note: The patient must freeze the stool sample within one hour of collection (as specified in the patient collection instructions) and keep the sample frozen until it is returned to the clinic. The patient should note the collection time and the time the sample was frozen (as specified in the patient collection instructions).**
3. Upon receipt in the clinic, record the collection date on the label provided and adhere it to the sealing bag.
4. Place the frozen stool in a -70ºC to -80ºC freezer until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.
5. When completing Form TR, the collection time noted by the patient should be recorded as "Collection Time." The "Estimated Processing Time" should be recorded as the amount of time elapsed between sample collection and sample freeze (as noted by the patient).

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

REQUIRED STOOL BIOSPECIMEN LABELING
Bank ID (# # # # - # # - G # # #) Protocol Number (NRG-GY- # # #) Biospecimen Code (ST##) Collection Date (mm/dd/yyyy)

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

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.

VI. Submitting Form TR
An electronically completed copy of Form TR 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.

Form TR should 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; Phone: 716-845-7767).

VII. Shipping Translational Science Biospecimens
Translational science biospecimens should not be shipped until after patient registration and Bank ID assignment.

An electronically completed copy of Form TR must be included for each translational science biospecimen.

A. FFPE Tissue
FFPE tissue, an electronically completed copy of Form TR, and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

NRG BB-Columbus / Protocol NRG-GY009
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

B. Whole Blood
Whole blood biospecimens should be shipped to the NRG BB-Columbus (address above).

Whole blood biospecimens can be shipped to the NRG -Columbus **Monday through Friday for Tuesday through Saturday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to 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.

To ship whole blood biospecimens 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 whole blood biospecimens from more than one patient, please put each biospecimen in a separate plastic zip-lock bag before placing the biospecimens in the shipping bag. You may include up to four different blood biospecimens in one biohazard envelope.*

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).

Shipping Whole Blood Using Your Own Shipping Container

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

C. Frozen Stool

Frozen stool should be shipped on dry ice using the insulated container and shipping instructions provided to the NRG BB-Columbus (address above).

Frozen biospecimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen biospecimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen biospecimens.

Frozen biospecimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold ≤-70ºC freezer, liquid nitrogen, or direct exposure with dry ice) until the biospecimens can be shipped.

VIII. 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: Testing of banked biospecimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The patient's biospecimen consent choices will be recorded on the signed informed consent document and electronically via 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 VI – 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 VII - LETTER TO PATHOLOGISTS (10/16/2017)

Dear Pathologist,

Your site is a participant in **NRG-GY009**, a randomized, phase II/III study of pegylated liposomal doxorubicin and CTEP-supplied atezolizumab versus pegylated liposomal doxorubicin/bevacizumab and CTEP-supplied atezolizumab versus pegylated liposomal doxorubicin/bevacizumab in platinum resistant ovarian cancer.

This study includes **CTEP-approved integrated biomarker testing**. This approved testing will use formalin-fixed, paraffin-embedded (FFPE) tumor to stain for PD-L1 at a sponsor-designated laboratory. The PD-L1 testing requirements mandate that slides used for testing must be *fresh cut*.

Additionally, this study includes several exploratory biomarkers, including analysis of T cell receptor repertoires and neoantigen assessment. DNA and RNA *freshly isolated* from FFPE tumor will be used for this testing.

Given the biospecimen requirements for the approved and exploratory biomarker testing, **NRG-GY009 requires all sites submit FFPE blocks only (i.e., unstained slides will not be accepted). The block submitted must contain at least 50% viable tumor and intact architecture.** Blocks may be submitted on a permanent or temporary basis.

If submitted on a temporary basis, blocks will be returned after the completion of the integrated biomarker testing. The NRG Biospecimen Bank (BB)-Columbus will hold blocks until requested by the study team for the integrated biomarker testing. At that time, the NRG BB-Columbus will fresh cut four consecutive unstained sections (4µm each) for shipment to the sponsor-designated laboratory for immediate integrated 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 integrated biomarker testing.

If you should have any questions, please so not hesitate to contact Drs. Roisin O'Cearbhaill (PI) and [redacted](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 translational research objectives.

Sincerely,
[redacted] MD
[redacted], PhD, MPH

APPENDIX VIII - EXAMPLES ON HOW TO ASSESS TUMOR RESPONSES (10/16/2017)

The methods used to assess tumor response follow to a large extent RECIST 1.1 but are modified especially at week 8 to allow for temporary inflammation of the tumors that could result from activation of an immune response system. Below are examples of hypothetical cases which can be used as a guide for evaluating your patient.

The protocol specifies continuation of treatment in cases of radiologic progression at the first 8 week (+/- 7 days) CT if all of the following criteria are satisfied:

- No decrease in performance status
- No requirement for immediate alternative treatment or urgent palliative treatment
- Progression limited to an increase of 40% in the sum of diameters of target lesions
- No more than 4 new lesions included in the sum.

For patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT:

- At any subsequent CT scan patients who have stable disease as compared to the 8 week (+/- 7 days) CT scan will be allowed to continue on study treatment.
- Patients who continue treatment in the case of radiologic progression at the first 8 week (+/- 7 days) CT, and later experience a PR or CR (as compared to baseline CT) will be recorded as delayed responses.

Example 1

Patient obtains a baseline measurement on 12/31/2015, enrolls onto study, and starts therapy on 01/01/2016.

……

Date of Evaluation: 12/31/2015 Baseline Tumor Measurement

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm

Notes: The nadir is 10 cm. Partial response will occur if the total is ≤ 7 cm (> 30% or greater decrease from nadir of 10). Progression will occur if the total is > 14 cm (>40% or greater increase from nadir of 10). .....

Date of Evaluation: 2/26/2016 Eight Week Assessment

Site of Lesion	Tumor Size
Site 1	6 cm
Site 2	7 cm
Total	13 cm

Time point response: **Neither progression nor response since 7cm < total < =14 cm.** Although the total > 12 cm (> 20% or greater increase from nadir of 10), an allowance is made for this type of therapy at this time. The nadir is revised to 13 cm. The threshold for progression is now > 15.6 cm (> 20% or greater increase from nadir of 13). Partial response can be obtained if the total is ≤ 7 cm, same as before.

.....

Date of Evaluation: 4/22/2016 16 Week Assessment

Site of Lesion	Tumor Size
Site 1	8 cm
Site 2	8 cm
Total	16 cm

Time point response: **Progression** since 16 cm > 15.6 cm. The **date** of **progression** is 2/26/2016, not 4/22/2016.

Example 2

Patient obtains a baseline measurement on 12/31/2015, enrolls onto study, and starts therapy on 01/01/2016.

.....

Date of Evaluation: 12/31/2015 Baseline Tumor Measurement

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm

Notes: The nadir is 10 cm. Partial response will occur if the total is ≤ 7 cm (> 30% or greater decrease from nadir of 10). Progression will occur if the total is > 14 cm (> 40% or greater increase from nadir of 10).

.....

Date of Evaluation: 2/26/2016 Eight Week Assessment

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Site 3	4 cm
Total	14 cm

Time point response: **Neither progression nor response since 7 cm < total <= 14 cm**. Up to 4 additional target tumors are allowed. Nadir revised to 14 cm. The threshold for progression is revised to > 16.8 cm.

.....

Date of Evaluation: 4/22/2016 16 Week Assessment

Site of Lesion	Tumor Size
Site 1	4 cm
Site 2	4 cm
Site 3	3 cm
Total	11 cm

Time point response: **Neither progression nor response** since 7 cm < total < 16.8 cm. Note, the nadir is revised to 11 cm. The threshold for progression is now > 13.2 cm. In order for the patient to respond, all 3 tumors must sum to ≤ 7 cm.

.....

Date of Evaluation: 6/17/2016 24 Week Assessment

Site of Lesion	Tumor Size
Site 1	2 cm
Site 2	2 cm
Site 3	2 cm
Total	6 cm

Time point response: **Partial Response** since total ≤ 7 cm. The patient's response will need to be confirmed ≥ 4 weeks later with a total ≤ 7 cm. If confirmed, her date of partial response will be 6/17/2016. Note, the nadir is now 6 cm. Disease progression would occur if the total is ≥ 7.2 cm.

Example 3

Patient obtains a baseline measurement on 12/31/2015, enrolls onto study, and starts therapy on 01/01/2016.

.....

Date of Evaluation: 12/31/2015 Baseline Tumor Measurement

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm

Notes: The nadir is 10 cm. Partial response will occur if the total is ≤ 7 cm (> 30% or greater decrease from nadir of 10). Progression will occur if the total is > 14 cm (> 40% or greater increase from nadir of 10).

.....

Date of Evaluation: 2/26/2016 Eight Week Assessment

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm
Site of Lesion	Non-Target
Site 3	Present

Time point response: **Neither progression nor response**. This patient's measurable lesions remained the same but she acquired a new non-target lesion.

.....

Date of Evaluation: 4/22/2016 16 Week Assessment

Site of Lesion	Tumor Size
Site 1	5 cm
Site 2	5 cm
Total	10 cm
Site of Lesion	Non-Target
Site 3	Present

Time point response: **Neither progression nor response**. New lesions that appear during week 8 will be carried forward as if they were at baseline.

APPENDIX IX: DIAGNOSTIC IMAGE COLLECTION SUMMARY (03/19/2018) (29-JUN-2020)

Approximate scan collection per subject:

a. ~7 scans per year up to 12 months or until progression
b. After 12 months: ~4 scans per year until progression

1. CT scan or MRI performed once every 8 weeks (+/- 7 days), and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression.
2. If a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 8 weeks (+/- 7 days) until progression.
3. After 1 years of protocol therapy or follow-up (measured from approximately cycle 1, day 1), imaging studies will be conducted every 12 weeks (+/- 7 days).

TRIAD Digital Image Submission:

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

1. TRIAD Access Requirements:

- A valid CTEP-IAM account.
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR). Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

2. TRIAD Installations:

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

APPENDIX X – PARTICIPATING INSTITUTIONS FOR SAFETY LEAD-INS (10/22/2018)

NRG Oncology Participating Institutions for Safety Lead-Ins	
PA075	Abramson Cancer Center at the University of Pennsylvania
AZ151	Arizona Cancer Center
OH027	Cleveland Clinic Foundation
PA086	Fox Chase Cancer Center
MD017	Johns Hopkins University/Sidney Kimmel Cancer Center
GA020	Georgia Regents University
CT009	Hartford Hospital
TX035	M.D. Anderson Cancer Center
NY016	Memorial Sloan Kettering Cancer Center
WI013	Froedtert and the Medical College of Wisconsin
OH007	Ohio State University
OK003	Oklahoma University
NY158	Roswell Park Cancer Institute
PA121	Thomas Jefferson University
CA189	UC Davis Medical Center
CA088	University of California Medical Center at Irvine-Orange Campus
OH274	UHHS – Chagrin Highlands Medical Center
IL057	University of Chicago
CO070	University of Colorado Cancer Center
OH029	Case Western Reserve University
IA018	University of Iowa Hospitals and Clinics
PA015	University of Pittsburgh Cancer Center
VA009	University of Virginia Health Systems
VA010	Virginia Commonwealth University
MO011	Washington University School of Medicine
RI012	Women's and Infants Hospital