For Protocol Amendment #3 to: NRG-GY023

NCI Protocol #: NRG-GY023
Local Protocol #: NRG-GY023

NCI Protocol Version Date: July 25, 2023

This amendment is being submitted in response to an RRA received by Dr. S. Percy Ivy (ivy.p@ctep.nci.nih.gov) received on 7/6/2023.

Section	Comment
7.4	The CAEPR for Olaparib has been updated to version 2.6, June 5, 2023: • Added New Risk: • Rare but Serious: Vascular disorders - Other (venous thromboembolism)
ICD	Please see the ICD for additional changes.

Changes made in addition to RRA:

Section	Comment
Title Page	• The NCI version date is now July 25, 2023 • CTSU language has been updated to agree with current template language
8	• CTSU language has been updated to agree with current template language
8.1	• CTSU language has been updated to agree with current template language
8.2	• CTSU language has been updated to agree with current template language
13.1	• CTSU language has been updated to agree with current template language

NRG-GY023: A RANDOMIZED PHASE II TRIAL OF TRIPLET THERAPY (A PD-L1 INHIBITOR DURVALUMAB (MEDI4736) IN COMBINATION WITH OLAPARIB AND CEDIRANIB) COMPARED TO OLAPARIB AND CEDIRANIB OR DURVALUMAB (MEDI4736) AND CEDIRANIB OR STANDARD OF CARE CHEMOTHERAPY IN WOMEN WITH PLATINUM-RESISTANT RECURRENT EPITHELIAL OVARIAN CANCER, PRIMARY PERITONEAL OR FALLOPIAN CANCER WHO HAVE RECEIVED PRIOR BEVACIZUMAB

ClinicalTrials.gov Identifier NCT #04739800
NCI Version Date: July 25, 2023

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ECOG-ACRIN / ECOG-ACRIN Cancer Research Group
SWOG / SWOG

Participating Sites
☒ U.S.
☐ Canada
☐ Approved International Member Sites
☐ Limited Participation

Protocol Agents:

Agent	Supply	NSC #	IND #	IND Sponsor
Durvalumab	CTEP	778709		DCTD, NCI
Olaparib	CTEP	747856		DCTD, NCI
Cediranib	CTEP	732208		DCTD, NCI
Paclitaxel	Commercial	673089	N/A	N/A
Topotecan	Commercial	609699	N/A	N/A
Pegylated Liposomal Doxorubicin (PLD)	Commercial	712227	N/A	N/A

Document History	
Initial	**April 01, 2021**
Amendment 1	**August 27, 2021**
Amendment 2	**August 23, 2022**
Amendment 3	**July 25, 2023**

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CONTACT INFORMATION (23-AUG-2022)(25-JUL-2023)		
For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trial Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878) , or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page on the CTSU members' website (https://www.ctsu.org). 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 Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
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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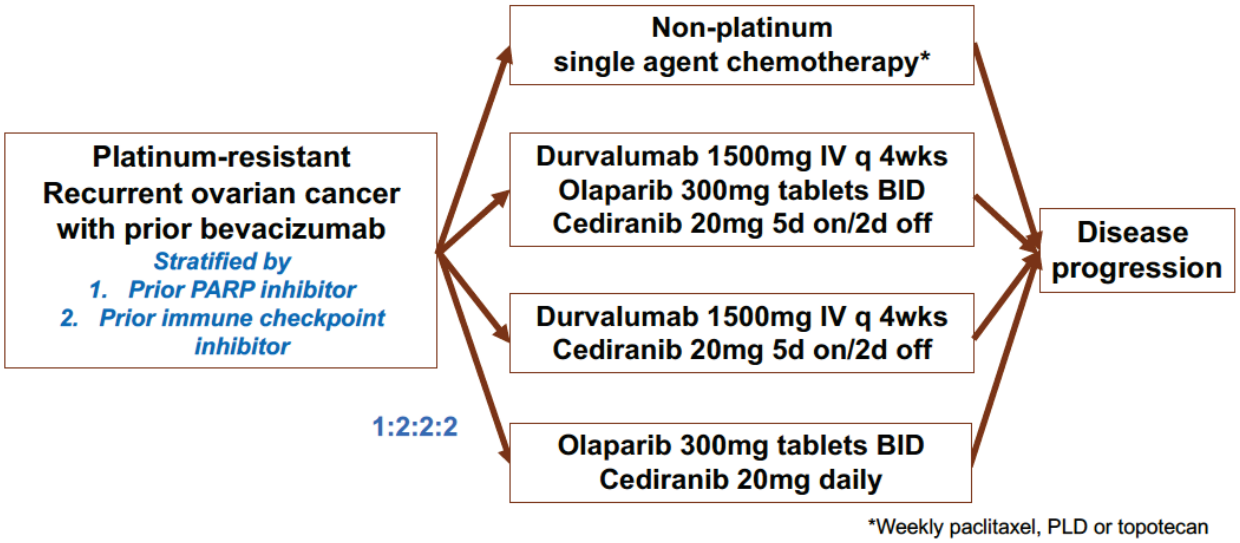
SCHEMA



*Non-platinum single agent chemotherapy includes weekly paclitaxel, topotecan or pegylated liposomal doxorubicin (PLD). There can be no deviance from the prescribed regimens, e.g. addition of bevacizumab or other agents.

Randomization is 1:2:2:2

1. OBJECTIVES

1.1 Primary Objective

1.1.1 To assess the efficacy of the combinations durvalumab (MEDI4736) plus olaparib and cediranib, durvalumab (MEDI4736) plus cediranib, or olaparib and cediranib, as measured by progression-free survival (PFS), as compared to physician's choice standard of care chemotherapy, in patients with recurrent platinum-resistant ovarian, primary peritoneal or fallopian tube cancer who had prior bevacizumab.

1.2 Secondary Objectives

1.2.1 To assess the efficacy of the combinations durvalumab (MEDI4736)) plus olaparib and cediranib, durvalumab (MEDI4736) plus cediranib, or olaparib and cediranib, as measured by overall response rate (ORR) by RECIST version 1.1 criteria, as compared to physician's choice standard of care chemotherapy, in patients with recurrent platinum-resistant ovarian, primary peritoneal or fallopian tube cancer who had prior bevacizumab.

1.2.2 To assess the efficacy of the combinations durvalumab (MEDI4736) plus olaparib and cediranib, durvalumab (MEDI4736) plus cediranib, or olaparib and cediranib, as measured by overall survival (OS), as compared to physician's choice standard of care chemotherapy, in patients with recurrent platinum-resistant ovarian, primary peritoneal or fallopian tube cancer who had prior bevacizumab.

2. BACKGROUND

2.1 Platinum-resistant recurrent ovarian cancer

Ovarian cancer is the deadliest gynecologic malignancy in the United States (Seigel, 2018). The majority of women with epithelial ovarian cancer present at advanced stage, and recurrence is nearly universal leading to incurable disease with limited treatment options (Torre, 2018). There are clear unmet needs for novel treatment approaches for recurrent ovarian cancer.

Platinum resistance is associated with a poor prognosis for women with ovarian cancer and almost all patients with recurrent disease ultimately develop resistance to platinum-based therapy (Naumann, 2011, Tomao, 2017). Several chemotherapeutic options exist for the treatment of recurrent platinum-resistant ovarian cancer, including weekly paclitaxel, pegylated liposomal doxorubicin (PLD), gemcitabine, topotecan, and etoposide. The use of single agent cytotoxic chemotherapy or targeted agent historically resulted in outcome of a median progression-free survival (PFS) of 3-4 months and median overall survival of about 12 months (Tomao, 2017). Added PFS benefit was observed with the addition of bevacizumab to chemotherapy (PLD, weekly paclitaxel, or topotecan) in platinum-resistant recurrent ovarian cancer patients (Cortez, 2018). The combination of bevacizumab and chemotherapy showed improved PFS and objective response rate (RR) compared to chemotherapy alone; RR of 30.9% and a median PFS of 6.7 months vs. RR of 12.6% and a median PFS of 3.4 months (HR 0.48, 95% CI 0.38–

0.60, p<0.001) in bevacizumab-naïve population. Bevacizumab in combination with chemotherapy is now an FDA-approved treatment regimen for patients with platinum-resistant recurrent ovarian cancer who have received no more than two previous lines of chemotherapy. However, patients ultimately acquire resistance to bevacizumab and a critical need remains for new therapeutic strategies for those who progressed on bevacizumab.

VEGF-C and/or VEGF-D mediated activation of VEGFR-2 has been proposed as a potential resistance mechanism following inhibition of VEGF-A by bevacizumab (van der Bilt, 2012). Also, VEGF-C and its receptor VEGFR-3 are shown to be elevated in serum and ascites fluid isolated from ovarian cancer patients and high serum or tumor VEGF-C levels/expression are associated with poor prognosis in ovarian cancer (Cheng, 2013, Nishida, 2004). Similar findings are reported for the related ligand VEGF-D, which also activates VEGFR-3 (Yokoyama, 2003). Thus, it is hypothesized that targeting all 3 VEGFRs (VEGFR-1, -2, -3) activated by different ligands (VEGF-A, -B, -C, -D) can comprehensively suppress the VEGF/VEGFR axis for the treatment of ovarian cancer patients who developed resistance to bevacizumab. A phase II single arm olaparib and cediranib study is now ongoing to test this hypothesis clinically for recurrent platinum-resistant ovarian cancer patients who had prior bevacizumab (NCT02889900; Lee, 2020). Separately, two NRG Oncology phase III studies (GY004 and GY005) are currently ongoing in recurrent ovarian cancer based on the findings from the randomized Phase II study of olaparib and cediranib in platinum-sensitive recurrent ovarian cancer (Liu, 2014). These NRG studies evaluate the combination of olaparib and cediranib compared to standard of care treatment, one in recurrent platinum-resistant ovarian cancer (NRG GY005, NCT02502266) and another in recurrent platinum-sensitive ovarian cancer (NRG GY004, NCT02446600).

2.2 Immunotherapy and targeted agent combinations as a novel therapeutic strategy

Immunotherapy has emerged as a major therapeutic modality in oncology and demonstrated durable long-term response in subsets of ovarian cancer patients. Yet, the majority of patients with recurrent ovarian cancer do not derive benefit from immune checkpoint blockade monotherapy as demonstrated in early clinical trials (RR of 9.6% with avelumab monotherapy (Disis, 2019) [JAVELIN Solid Tumor Trial] and RRs of 7.4-9.9% with pembrolizumab monotherapy (Matulonis, 2019) [KEYNOTE-100], leaving the need to test combination approaches to increase the effectiveness of immune checkpoint inhibitors (Lee, 2018, Mouw, 2018, Mouw, 2017). Other active therapeutic targets in ovarian cancer include the DNA repair and vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) pathways (Lee, 2016).

It has been hypothesized that DNA repair inhibition (e.g., PARP inhibition) may modulate the immune response by increasing DNA damage and tumor mutational burden (TMB). Increased DNA damage promotes local antigen release resulting in systemic anti-tumor immune responses after tumor exposure to radiation or DNA damaging agents (Galluzzi, 2012, Wu, 2014, Gameiro, 2014, Kroemer, 2013). Potential neoantigen expression and associated TMB increase have been correlated with clinical response to

immune checkpoint inhibition in solid tumors, though TMB as a predictive biomarker is still being investigated (Brill, 2017, Hellman, 2018, Lampert 2020). Another possible mechanism of immune modulation by increased DNA damage is constitutive activation of an innate immune STING (stimulator of interferon genes) pathway. PARP inhibition blocks DNA repair, resulting in DNA breaks (Lord, 2017). Fragments of these DNA breaks enter the cytoplasm and bind to cyclic GMP-AMP synthase (cGAS) upregulating the cGAS-STING pathway within the tumor microenvironment, a potent activator of a type I interferons and other immunomodulatory molecules (Chen, 2016). Thus, increased DNA damage from the PARP inhibitor exposure could yield greater TMB, potentially increasing neoantigens (Gajewski, 2013), and affect the immune microenvironment, thus complementing the clinical benefit of immune checkpoint blockade in subsets of recurrent ovarian cancer (Lee, 2017, Lampert 2020). Additionally, results from 3 PARP inhibitor and PD-1/PD-L1 blockade combination trials showed early clinical activity in subsets of recurrent ovarian cancer; 18% RR and 65% disease control rate (DCR, defined by CR+PR+SD) of niraparib and pembrolizumab in platinum-resistant ovarian cancer (TOPACIO) (Konstantinopoulos, 2019), 14% RR and 71% DCR of olaparib and durvalumab (MEDI4736) in heavily-pretreated recurrent ovarian cancer (Lampert, 2020) and 72% RR of durvalumab (MEDI4736) and olaparib in PARP inhibitor-naïve germline BRCA mutant platinum-sensitive ovarian cancer patients (MEDIOLA) (Drew, 2018). These findings suggest potential added benefit of PARP inhibition to PD-1/PD-L1 blockade although additional biomarkers of efficacy are needed.

There are emerging pre-clinical and clinical evidence suggesting synergy between immune checkpoint blockade and VEGF/VEGFR pathway inhibition. VEGF reduces the antitumor immune responses in preclinical models including ovarian cancer models, by suppression of dendritic cell maturation (Sondak, 2011, Ohm, 2001), inhibition of T cell responses (Terme, 2013, Gavalas, 2012), increases in Treg proliferation, and increases in immunosuppressive activity of myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (Huang, 2013, Terme, 2012). VEGF also suppresses lymphocyte trafficking across endothelia into tumor deposits and sites of inflammation to promote vessel growth (Kandalaft, 2011, Tartour, 2011). Wallin *et al.* reported intra-tumoral CD8+ T cells increase (median 5-fold) following combination treatment with bevacizumab and a PD-L1 inhibitor, atezolizumab, in metastatic renal cell carcinoma (RCC) patients (Wallin, 2016), suggesting that the anti-VEGF and anti-PD-L1 combination improves antigen-specific T cell migration. Consistent with these preclinical evidences, axitinib, an oral VEGFR- tyrosine kinase inhibitor (TKI) and pembrolizumab combination is approved by FDA as a front-line therapy in patients with advanced RCC, independent of PD-L1 status. Also, lenvatinib, another oral VEGFR TKI, and pembrolizumab was recently FDA-approved in advanced endometrial cancer, independent of mismatch repair instability (MSI) status (Makker, 2019). In recurrent ovarian cancer, Liu and colleagues reported phase II single arm study of bevacizumab and nivolumab which demonstrated a median PFS of 9.4 months (RR of 40% and clinical benefit rate [CBR] of 75% defined by CR+PR+SD> 6months) in platinum-sensitive patients (20 patients) and a median PFS of 5.3 months (RR of 16.7% and CBR of 55.3%) in platinum-resistant patients (18 patients) (Liu, 2019).

Further, angiogenesis pathways interact with both immune activity and DNA repair mechanisms. Tumor hypoxia induces downregulation of genes involved in DNA repair, e.g., RAD51 and BRCA1, leading to further DNA damage, genomic instability, and cell death (Hegen, 2010). These data support VEGFR TKI as an optimal drug for the immune checkpoint blockade and/or PARP inhibitor combination therapy in ovarian cancer. As such, it has been hypothesized that 3-pathway (DNA repair, angiogenesis and immune checkpoints) modulation would enhance the anti-tumor activity of PD-1/PD-L1 inhibitor, by creating higher mutational loads and a more immunogenic microenvironment in recurrent platinum-resistant patients.

2.3 Phase I/II single arm study of the PD-L1 inhibitor, durvalumab (MEDI4736) in combination with olaparib and cediranib in recurrent ovarian cancer (NCT0248440)

Preclinical data suggest potential synergy between the PARP inhibitor or anti-angiogenic agents with immune checkpoint inhibition in breast, lung and renal cell carcinoma models (Jiao, 2017, Pircher, 2017). durvalumab (MEDI4736) is a human immunoglobulin G1κ monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80 (B7.1) (Lee, 2017). A phase I/II study is currently evaluating activity signal by combining durvalumab (MEDI4736) with olaparib and cediranib for recurrent ovarian cancer patients at the NCI Clinical Center (NCT0248440). Evaluation of toxicity and early clinical activity of the two durvalumab (MEDI4736) doublets [durvalumab (MEDI4736) plus olaparib or cediranib] was conducted prior to launching the durvalumab (MEDI4736) triplet [durvalumab (MEDI4736) plus olaparib and cediranib because there were anticipated overlapping toxicities such as diarrhea and fatigue. Durvalumab (MEDI4736) was given intravenously monthly with olaparib and/or cediranib until disease progression, patient withdrawal of consent, or intolerable toxicities.

Lee *et al.* reported that durvalumab (MEDI4736) and olaparib combination was tolerable and yielded durable response in recurrent women's cancer patients (Lee, 2017). Adverse events (AEs) were mostly grade 1 and 2, including fatigue, nausea, and rash. There were no reports of colitis of any grade in the durvalumab (MEDI4736) and olaparib or durvalumab (MEDI4736) and intermittent cediranib combinations. In contrast, daily cediranib dosing scheduling was not tolerable due to recurrent grade 2 and non-dose limiting toxicities (DLT) grade 3 and 4 AEs of fatigue and dyspnea. Preplanned pharmacokinetic analysis identified exposure to durvalumab (MEDI4736) increased cediranib exposure including area under the curve [AUC] and maximum plasma concentration (C_{max}) on the daily scheduling due to decreased clearance of cediranib. This led to the protocol amendment modifying the dose schedule of cediranib daily to an intermittent (5 days on/2 days off) schedule. An intermittent cediranib schedule was found to be tolerable and did not increase AUC or C_{max} of cediranib after durvalumab (MEDI4736) infusion. It is important to note that lower dose (20mg 5days on/2days off schedule) did not attenuate clinical activity when combined with durvalumab (MEDI4736) (Lee, 2017).

The tolerability and preliminary activity data of the triplet therapy durvalumab

(MEDI4736) plus olaparib and cediranib) was also reported (Zimmer, 2019). These established doses and schedules durvalumab (MEDI4736) 1,500mg every 4 weeks with olaparib tablets 300mg BID and/or cediranib 20 mg daily 5 days on/2 days off) are now being used in ongoing single arm phase II studies for recurrent ovarian cancer at the NCI Clinical Center (NCT0248440). In the triplet therapy durvalumab (MEDI4736) plus olaparib and cediranib) phase I study, 9 patients were enrolled (Table 1) and most AEs were grade 1 or 2, including fatigue, nausea, diarrhea, hypertension. Grade 3/4 adverse events included hypertension (1/9), anemia (1/9) and lymphopenia (3/9). No grade 4 AEs were observed.

Patient Characteristics	**Durvalumab (MEDI4736) plus olaparib and cediranib Phase I study (n=9)**
Age: median (range)	59 years (44-73)
Tumor types Ovarian cancer (platinum-resistant/-sensitive recurrent disease) Endometrioid endometrial cancer (MSI-low) Triple negative breast cancer	 7 (5/2) 1 1
Number of prior treatment regimens: median (range) Prior PARP inhibitor Prior bevacizumab	2 (2-6) None 2

Four patients had PR (44%) and 3 had SD lasting ≥ 6 months, yielding a 67% CBR (**Figure 1**). All patients were *BRCA* wild type (BRCAwt) except one patient with platinum-sensitive disease and PR of 9 months (*BRCA1* 187delAG). Three of 5 platinum-resistant patients had durable clinical benefit >1.5 year without unanticipated new AEs.

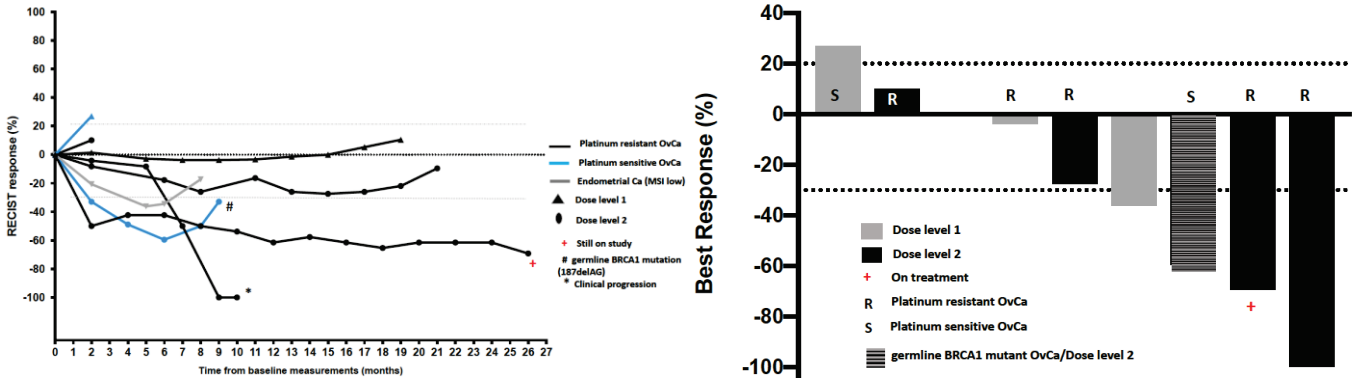


Figure 1. Spider plot and waterfall plot of durvalumab (MEDI4736) plus olaparib and cediranib phase I study. Triplet combination resulted in durable long-term response in heavily pretreated women's cancer patients, mostly platinum-resistant recurrent ovarian cancer. R: platinum-resistant recurrent ovarian cancer, S: platinum-sensitive recurrent ovarian cancer. One endometrial cancer patient who achieved PR had MSI-low tumor.

Additionally, pharmacokinetic data showed no significant changes of olaparib AUC or C_{max} when durvalumab (MEDI4736) was given to the patients with steady-state exposure to olaparib and cediranib. The presence of durvalumab (MEDI4736) also did not

significantly affect cediranib PK, consistent with the previous report (Lee, 2017), where demonstrated the lack of a drug interaction between durvalumab (MEDI4736) and cediranib alone when cediranib was given on the intermittent schedule.

2.4 Phase II single arm study of olaparib and cediranib in recurrent ovarian cancer patients who had prior anti-angiogenic agents (NCT0248440).

CONCERTO (**C**ediranib maleate and **O**laparib or sta**N**dard Chemotherapy in treating patients with r**E**current platinum-**R**esistan**T** or -refractory **O**varian, fallopian tube, or primary peritoneal cancer) is a single arm multi-center phase II study evaluating the activity of the olaparib and cediranib combination in platinum-resistant recurrent ovarian cancer patients who have no germline *BRCA* mutation. Eligibility includes at least 3 prior lines of chemotherapy and exposure to prior antiangiogenics, *e.g.,* bevacizumab. This eligibility criteria represent the difficult-to-treat patient population in the platinum-resistant disease setting. The primary endpoint is objective RR (ORR) by Independent Central Review using RECIST 1.1 criteria.

The study findings were recently presented at the 2020 ASCO virtual meeting (Lee, 2020). 60 women were enrolled and received olaparib and cediranib. Although olaparib and cediranib combination did not meet the target of 20% confirmed ORR, the combination treatment showed the evidence of antitumor activity in this heavily-pretreated (≥4 lines of chemotherapy), non-gBRCAm platinum-resistant ovarian cancer patients, with 88.3% of the patients already exposed to a VEGF inhibitor, bevacizumab. ORR was 15.3% including 1 CR and 8 PR and a total of 4/9 responders had a measurable response for more than 9 months. Furthermore, 14 out of 59 patients evaluable for response remained in disease control at 6 months; median overall survival was 13.2 months and median PFS was 5.1 months (**Figure 2**). Overall, the safety findings of this

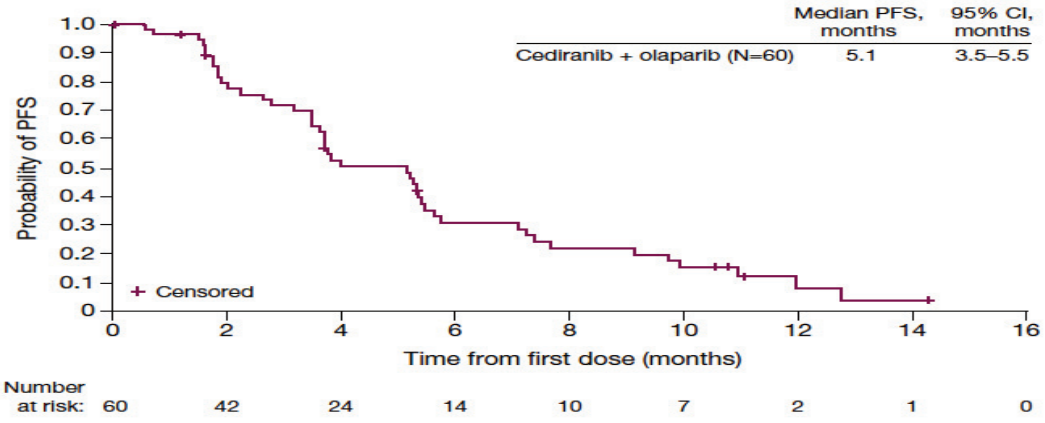


Figure 2. Kaplan-Meier PFS curves in patients treated on olaparib and cediranib in Phase II CONCERTO trial

study were consistent with the known safety profiles of olaparib and cediranib.

Biomarker studies were also presented. % global loss of heterozygosity (gLOH)

measured at Foundation Medicine was available for 47 patients in the evaluable for response set. Of these, 15 had a tumor BRCAm and/or gLOH score ≥16% ($gLOH^{high}$) and 32 had a gLOH score <16% ($gLOH^{low}$). The ORR was 26.7% (4/15; 95% CI 7.8–55.1%) in the $gLOH^{high}$ group and 12.5% (4/32; 95% CI 3.5–29.0%) in the $gLOH^{low}$ group, requiring further investigation.

2.5 Translational Science Background

2.5.1. Tumor PD-L1 and tumor infiltrating lymphocytes (TIL)

The expression of PD-L1 and presence of CD8+ TILs have been previously characterized as prognostic biomarkers in ovarian cancer. In certain settings across different tumor types, tumor PD-L1 expression has been described as potential predictive biomarkers for response to immune checkpoint blockade (Topalian 2012; Garon 2015; Motzer 2015 (1); Rosenberg 2016). However, in other studies, no association has been reported (Brahmer 2015; Motzer 2015 (2)). In ovarian cancer, associations between PD-L1 expression and response to immune checkpoint therapy have been limited. In the Phase II study of avelumab in ovarian cancer, PD-L1 expression did not clearly correlate with activity of the drug (Disis 2019). In contrast, in the KEYNOTE-100 study, a higher RR was reported for ovarian cancer tumors with higher PD-L1 expression as measured by a combined positive score (CPS) of ≥10 (Matulonis 2019).

Immune checkpoint blockade activity is thought to be in part mediated by re-activating a tumor immune response; as such, it has been hypothesized that the presence of TILs could also be a predictive biomarker of response. Tumors that are "immune-inflamed" with the presence of both CD8+ and CD4+ TILs have been reported to experience a better response to immune checkpoint blockade (Herbst 2014; Tumeh 2014; Lee 2017). The significance of PD-L1 and TILs as potential predictive biomarkers in ovarian cancer when immune checkpoint inhibitors are combined with other agents remains unclear. In JAVELIN Ovarian 200, the performance of avelumab together with liposomal doxorubicin appeared to be more robust compared to liposomal doxorubicin alone in patients who were PD-L1+ (Pujade-Lauraine 2018). However, this was a subgroup analysis, and the activity of the avelumab and liposomal doxorubicin combination was similar in both the PD-L1+ and PD-L1- cohorts; rather, the activity of liposomal doxorubicin was slightly decreased in the PD-L1- tumors. In JAVELIN Ovarian 100, in newly diagnosed ovarian cancer, neither PD-L1 nor CD8 status appeared to be a predictive biomarker for activity of combined chemotherapy and avelumab (Ledermann 2020). In this study, PD-L1 and TILs in archival tissue samples will be evaluated to correlate with responses to the treatment.

2.5.2. Homologous recombination deficiency (HRD) assessment

Homologous recombination (HR) is a DNA damage repair pathway responsible for repairing double-strand DNA breaks. Key proteins that are intrinsic to proper function of this pathway include BRCA1, BRCA2, and other members of the Fanconi anemia pathway. Cells that are homologous recombination deficient (HRD) lack the ability to

perform double-strand break repair via HR; as a consequence, they can be more sensitive to the effects of drugs such as PARP inhibitors and platinum.

In the clinical setting, assessment of HRD status has been primarily performed by evaluation of patterns of "genomic scarring", which occurs as cells lacking HR acquire specific patterns of mutations and structural aberrations of chromosomes. Three separate types of genomic scarring patterns have been described to be associated with HRD: loss of heterozygosity (LOH), large-scale state transitions (LST), and telomeric-allelic imbalance (TAI) (Abkevich 2012; Popova 2012; Birkbak 2012). Various assays to assess these genomic instability patterns exist, including measurement of percent genomic LOH, which is utilized by the FoundationFocus CDx BRCA LOH test, and a composite score with measurement of LOH, LST, and TAI, which is utilized in the Myriad MyChoice CDx test.

The presence of HRD has been associated with activity of PARP inhibitors in ovarian cancer. The strongest association of PARP inhibitor activity has been with the presence of a *BRCA1/2* mutation, as seen in both monotherapy studies of PARP inhibitors for treatment of relapsed disease (Gelmon 2011; Swisher 2017; Moore 2019), and trials of PARP inhibitor maintenance therapy (Ledermann 2014; Mirza 2016; Coleman 2017; Gonzalez-Martin 2019; Coleman 2019; Ray-Coquard 2019). In non-mutated *BRCA* tumor populations within these trials, exploratory analyses have suggested that assays of HRD provide some additional information regarding the likelihood of deriving benefit from PARP inhibitor therapy, although these assays do not clearly differentiate populations that will or will not derive benefit (Mirza 2016; Coleman 2017; Gozalez-Martin 2019; Ray-Coquard 2019), and in one study, no difference was seen with regards to PARP inhibitor activity in *BRCA* wild-type tumors that were deemed HRD on the Myriad MyChoice assay and those that did not (Coleman 2019, Swisher 2020). In studies of combined olaparib and cediranib, higher RRs have been reported in those patients with platinum-resistant tumors where the LOH score was more elevated, although these are small studies and require further validation (Liu 2019; Lee 2020). Other mechanisms of HRD may be a functional biomarker for response. As such, it is important to identify which ovarian cancer patients have germline or somatic mutations in HRD genes and to examine their potential as predictive biomarkers.

2.6 Rationale for trial design

Patients with recurrent platinum-resistant ovarian cancer who had prior bevacizumab remain a patient population with significant unmet needs. There are no effective therapeutic options currently available for this population. Single agent olaparib has shown limited activity in patients with non-BRCA mutant platinum-resistant ovarian cancer with RR of 4% (1/26) (Gelmon, 2011). Single agent cediranib has shown an objective RR of 17% and a median PFS of 5.2 months in patients with platinum-resistant ovarian cancer, treated in 2nd or 3rd line setting (Matulonis, 2009). Given the limited activity of single agent olaparib or cediranib in platinum resistant recurrent ovarian cancer patients who do not carry a deleterious or suspected deleterious BRCA mutation, it is considered appropriate to evaluate the combination of olaparib and cediranib with

and without durvalumab, a PD-L1 inhibitor in this population. The proposed study will identify potential benefit of the 3-pathway modulation for recurrent platinum-resistant ovarian cancer patients who had prior bevacizumab.

More importantly, given that the number of patients exposed to immune checkpoint inhibitors and/or PARP inhibitors has significantly increased over the past few years, this study will provide insights on the optimal use of a triplet therapy in patients who previously received these therapies by stratifying them based on the prior immune checkpoint inhibitors and/or PARP inhibitors. Also, given that PARP inhibitors are now widely used in various clinical settings for ovarian cancer patients, it is important to test whether the combination of durvalumab (MEDI4736) and cediranib without olaparib yields a similar clinical activity to the triplet therapy in this population. Furthermore, the activities of these combinations compared to standard of care chemotherapy need to be defined in this previously unstudied population.

Women with recurrent platinum-resistant ovarian cancers, who had prior bevacizumab and/or PARP inhibitors are the enriched patient population with unmet medical needs. There is an urgent need for the development of targeted therapies for this patient population. The results of this randomized phase II trial could lead to future randomized phase III trials, and potentially produce practice-changing results, given the limited options for therapy in recurrent platinum-resistant ovarian cancer who had prior bevacizumab. Additionally, if positive, the results of this trial may provide a non-chemotherapy treatment alternative for patients, with the potential for increased tolerability.

The purpose of this phase II randomized study is to test the hypothesis that olaparib and cediranib in combination with durvalumab, or durvalumab (MEDI4736) plus cediranib, or olaparib plus cediranib may result in greater clinical benefit for women with recurrent platinum-resistant ovarian cancer who previously received bevacizumab compared to standard of care chemotherapy. Preliminary clinical data of a triplet therapy showed potential durable anti-tumor activity in a subset of heavily pretreated recurrent ovarian cancer patients (Zimmer 2019). It was thus hypothesized that creating a more immunogenic milieu via increased DNA damage and reduced VEGF signaling would complement the anti-tumor activity of an immune checkpoint inhibitor in this difficult-to-treat population.

Rationale for a fixed dosing of durvalumab (MEDI4736):

A population PK model was developed for durvalumab (MEDI4736) using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of MEDI4736 (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab (MEDI4736) was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients

were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen. Similar findings have been reported by others (Ng et al 2006, Wang et al 2009, Zhang et al 2012, Narwal et al 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009)]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al 2012). A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, it was considered feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W MEDI4736 (equivalent to 20 mg/kg Q4W) is included in the current study

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

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

3.1 Eligibility Criteria

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

3.1.1 Women with recurrent/persistent platinum-resistant ovarian, primary peritoneal, or fallopian tube cancers; platinum-resistant disease is 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.

3.1.2 Patients must have histologically or cytologically confirmed ovarian cancer, peritoneal cancer or fallopian tube cancer and must have a histological diagnosis of high grade serous, grade 3 endometrioid or clear cell carcinoma based on local histopathological findings.

Patients with low grade serous, grade 1 or 2 endometrioid, mixed epithelial, undifferentiated carcinoma, or mucinous carcinoma histologies are also eligible, provided that the patient has a known deleterious BRCA1 or BRCA2 mutation identified through testing at a clinical laboratory.

Histologic confirmation of the original primary tumor is required via the pathology report *(upload of report required).*

Confirmation of BRCA1 and BRCA2 germline and/or somatic mutation status and HR status is required for all entered patients (if available) via testing report (upload of

report[s] required). **(27-AUG-2021)**

3.1.3 Evaluable disease – defined as RECIST 1.1 measurable disease OR non-measurable 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 a CA125 ≥ 2x upper limit of normal (ULN)).

3.1.4 Prior therapy:

- At least two prior treatment regimens (including primary therapy) but up to 5 lines of systemic anticancer therapy. Hormonal therapy (such as tamoxifen, aromatase inhibitors) will not count as a previous treatment regimen.
- Prior use of bevacizumab in the upfront or recurrent setting ***is required.***
- Prior use of PARP inhibitor is allowed.
- Prior use of immune checkpoint blockade (e.g., a PD-L1/PD-1inhibitor or a CTLA-4 inhibitor) is allowed.

3.1.5 ECOG Performance Status of 0, 1, or 2 (see Appendix I).

3.1.6 Patients must have adequate organ and marrow function as defined below

- Absolute neutrophil count (ANC) ≥ 1,500/mcL
- Hemoglobin ≥ 10 g/dL
- Platelets ≥ 100,000/mcL
- Creatinine clearance (CrCL) or estimated Glomerular filtration rate (eGFR) of >50 mL/min estimated using either the Cockcroft-Gault equation, the Modification of Diet in Renal Disease Study, or as reported in the comprehensive metabolic panel/basic metabolic panel (eGFR). **(27-AUG-2021)**
- Urine protein: creatinine ratio (UPC) of ≤1
- Total serum bilirubin level ≤ 1.5 x ULN (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled)
- AST and ALT ≤ 3 x ULN

3.1.7 Age ≥ 18 years.

3.1.8 Body weight > 30 kg

3.1.9 Adequately controlled blood pressure (SBP ≤ 140; DBP ≤ 90 mmHg) on a maximum of three antihypertensive medications. Patients must have a BP of ≤ 140/90 mmHg taken in the clinic setting by a medical professional within 2 weeks prior to study registration. It is strongly recommended that patients who are on three antihypertensive medications be followed by a cardiologist or a primary care physician for management of BP while on protocol. Patients must be willing and able to check and record daily blood pressure readings. BP cuffs will be provided to patients randomized to the cediranib-containing arms (Appendix X).

3.1.10 Adequately controlled thyroid dysfunction with no symptoms of thyroid dysfunction and normal TSH. If TSH is not within normal range despite no symptoms of thyroid dysfunction, normal free T4 level is required.

3.1.11 Able to swallow and retain oral medications and no GI illnesses that would preclude absorption of olaparib and cediranib as judged by treating physician.

3.1.12 Toxicities of prior therapy (excepting alopecia and vitiligo), should be resolved to less than or equal to Grade 1 as per CTCAE v5.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

3.1.13 Women of childbearing potential (WOCBP) must agree to use two forms of birth control (hormonal or barrier method of birth control; abstinence).

Note: Definition of women of no longer having childbearing potential: Postmenopausal or evidence of non-childbearing status for women of childbearing potential as confirmed by a negative urine or serum pregnancy test within 7 days prior to start of study treatment.

Postmenopausal is defined as: Age ≥60 years, or
Age <60 with any one or more of the conditions below:

- Amenorrheic for ≥1 year in the absence of chemotherapy and/or hormonal treatments,
- Luteinizing hormone and/or Follicle stimulating hormone and/or estradiol levels in the post-menopausal range,
- Radiation-induced oophorectomy with last menses >1 year ago,
- Chemotherapy-induced menopause with >1 year interval since last menses,
- Surgical sterilization (bilateral oophorectomy or hysterectomy).

3.1.14 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and authorization permitting release of personal health information.

3.2 Ineligibility Criteria

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

3.2.1. Primary platinum-refractory disease defined as progression during first-line platinum-based chemotherapy.

3.2.2 Rising CA-125 only without RECIST 1.1 evaluable disease.

3.2.3 Prior therapy:

- Patients who have had chemotherapy, investigational drugs or radiotherapy within 3 weeks prior to study registration or those who have not recovered from adverse

events due to agents administered more than 3 weeks earlier.

- Patients may not have had hormonal therapy within 2 weeks of study registration. Patients receiving raloxifene for bone health as per FDA indication may remain on raloxifene absent other drug interactions.
- Prior use of concurrent olaparib and cediranib combination.
- Patients who have experienced immune-mediated adverse events requiring dose modification or discontinuation. **(23-AUG-2022)**
- For patients who have received prior PARP inhibitor:
    - Patients who have required dose modification or dose reduction of olaparib will not be eligible, as they will not be able to start this study at full dose.
    - Patients who have required dose reduction of non-olaparib PARP inhibitors for hematologic adverse events will not be eligible (Note: niraparib that is initiated at 200mg daily per weight and platelet guidelines is not considered a dose reduction).
    - Patients who required dose-reduction of non-olaparib PARP inhibitors for non-hematologic adverse events may be eligible after discussion with the Study Chair if the treating investigator feels that they could appropriately receive olaparib at full dose. **(23-AUG-2022)**

3.2.4 History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 3 months prior to study registration.

3.2.5 Current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months of study registration except temporary (<24hr) improved with medical management, within last 3 months.

3.2.6 Any prior grade ≥ 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE > grade 1.

3.2.7 Dependency on IV hydration or TPN.

3.2.8 Pregnant women. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with these drugs, breastfeeding should be discontinued. These potential risks may also apply to other agents used in this study.

3.2.9 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.2.10 Patients with untreated brain metastases, spinal cord compression, or evidence of symptomatic brain metastases or leptomeningeal disease as noted on CT or MRI scans should not be included on this study, since neurologic dysfunction may confound the evaluation of neurologic and other adverse events. Patients with treated brain metastases and resolution of any associated symptoms must demonstrate stable post-therapeutic

imaging for at least 6 months following therapy prior to starting study registration.

3.2.11 Patients who have the following clinical conditions are considered to be at increased risk for cardiac toxicities. Patients with any cardiac history of the following conditions:

- History of myocardial infarction or myocarditis within six months of study registration
- Unstable angina
- Resting ECG with clinically significant abnormal findings.
- New York Heart Association functional classification of III or IV (Appendix II)

3.2.12 If cardiac function assessment is clinically indicated or performed: LVEF less than normal per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines.

Patients with the following risk factors should have a baseline cardiac function assessment:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab or T-DM1
- Prior central thoracic radiation therapy (RT), including RT to the heart
- History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)
- Prior history of impaired cardiac function

3.2.13 History of stroke or transient ischemic attack within six months of study registration.

3.2.14 Clinically significant peripheral vascular disease or vascular disease (aortic aneurysm or aortic dissection).

3.2.15 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of study treatment. Patients must have recovered from any effects of any major surgery and surgical wound should have healed prior to starting treatment.
Note: Local surgery of isolated lesions for palliative intent is acceptable.

3.2.16 Evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events, including warfarin, is permitted. Patients receiving warfarin are recommended to have careful monitoring of international normalized ratio (INR), as detailed in Section 4 and Section 9.

3.2.17 Evidence suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.

No prior allogeneic bone marrow transplant or double umbilical cord blood transplantation (dUBCT).

3.2.18 Human Immunodeficiency Virus (HIV) positive patients due to potential drug and drug

interactions

3.2.19 Patients may not use any complementary or alternative medicines including natural herbal products or folk remedies as they may interfere with the effectiveness of the study treatments.

3.2.20 Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment.

Note: Patients, if enrolled, should not receive live vaccine whilst receiving study treatment and up to 30 days after the last dose of study treatment.

3.2.21 Uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia (other than atrial fibrillation with controlled ventricular rate), or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring adverse events or compromise the ability of the patient to given written informed consent.**(27-AUG-2021)**

3.2.22 Patients receiving any medications or substances that are strong inhibitors or inducers of CYP3A4. Dihydropyridine calcium-channel blockers are permitted for management of hypertension.

3.2.23 Current or prior use of immunosuppressive medication within 14 days of study registration. The following are exceptions to this criterion:

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

3.2.24 History of allergic reactions attributed to compounds of similar chemical or biologic composition to durvalumab, olaparib, or cediranib.

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

3.2.26 Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), or hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for

hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA.

3.2.27 Patients who have a history of (non-infectious) pneumonitis that required steroids, or current pneumonitis. **(27-AUG-2021)**

Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf

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

4.1 Pre-Treatment Assessments (27-AUG-2021)

The following assessments are to be performed and recorded on the appropriate form(s). Please note: Each entry refers to the corresponding footnote at the end of the table. **Cycle 1 Day 1 treatment should begin within 7 days of registration.**

Assessments See Section 10.4.1 for Mandatory Biospecimen Submission Information.	**Prior to Registration (calendar days)**	**Prior to Treatment (calendar days) (Cycle 1, Day 1)**
History and Physical	≤ 14 days	≤ 14 days
Concomitant Medications	≤ 14 days	≤ 14 days
Vital Signs (Blood Pressure, Heart Rate, Temperature and Pulse Oxygen Saturation)	≤ 14 days	X
Height*	X	-
Weight	≤ 14 days	≤ 14 days
Performance Status (ECOG)	≤ 14 days	≤ 14 days
Toxicity Assessment	≤ 14 days	≤ 14 days
CBC/Differential/Platelets	≤ 14 days	≤ 14 days
Chemistries (BUN, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)	≤ 14 days	≤ 14 days
Urine protein: creatinine ratio (UPCR)	≤ 14 days	≤ 14 days
TSH	≤ 28 days	≤ 28 days
CA-125	≤ 28 days	≤ 28 days
Pregnancy test (for women of childbearing potential) Urine or serum testing is permitted	≤ 14 days	≤ 72 hours
Electrocardiogram (ECG)	≤ 28 days	≤ 28 days
MUGA or echocardiogram[a]	≤ 28 days	≤ 28 days
Radiographic Tumor Measurement[b]	≤ 28 days	≤ 28 days

[a] MUGA or echocardiogram should be performed at baseline for patients at increased risk for compromised LVEF, including patients with (1) prior treatment with anthracyclines, (2) prior treatment with trastuzumab or T-DM1, (3) prior central thoracic RT, (4) history of myocardial infarction within the 12 months prior to registration or (5) prior history of impaired cardiac function. LVEF assessment by MUGA or echocardiogram should be performed on every 16-week (+/-1 week) basis for patients with these risk factors on cediranib-containing arms. Should the patients discontinue cediranib-containing arm therapy due to progression or toxicities within the 16-week (+/- 1 week) time frame before the next LVEF assessment, the treating physicians should follow cardiac symptoms and assess LVEF as clinically indicated until another therapy is initiated.

[b] Radiographic tumor measurements should be obtained via imaging of at least the chest, abdomen, and pelvis at baseline. If chest imaging at baseline reveals evidence of measurable disease, then subsequent radiographic tumor assessments must also include chest imaging. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline and subsequent assessments. Contrast CT is the preferred modality. **Tumor reassessment will be time-based at 9 weeks +/- 1 week throughout the study for the first year and every 12 weeks (+/- 7 days) after the first year.**

***** Height measurement is performed on adult participants during admission or at initial visit to an

outpatient facility per clinical practice. As height measurement on adults is not routinely performed during follow up visits, the height measurement previously recorded for adult participants may be used for calculating drug dosages or body surface area as applicable and can be used for baseline and follow up visits data capture.

4.2 Assessments During Treatment

The following assessments are to be performed and recorded on the appropriate form(s). Timing of assessments prior to Cycle 1 Day 1 may be as per pre-treatment assessments schedule. Please note: Each entry refers to the corresponding footnote at the end of the table. Please refer to Section 10.4.1 for Specimen Requirements.

ARM I (Non-platinum single agent chemotherapy) (27-AUG-2021):

Assessments	Prior to day 1 of each cycle of therapy	Weekly Topotecan Days 8 and 15 (if applicable)	Timed (Treatment Cycle Independent)
History and Physical	≤ 3 days		
Concomitant Medications	≤ 3 days		
Toxicity Assessment	≤ 3 days		
Vital Signs, weight required	≤ 3 day		
Performance Status	≤ 3 days		
CBC/Differential/Platelets	≤ 3 days	≤ 1 days	
Chemistries[1]	≤ 3 days		
CA125	≤ 3 days		
Radiographic Tumor Measurement			See footnote[2]
MUGA or echocardiogram			See footnote[3]

[1] Serum chemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin.

[2] **Tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI performed once every 9 weeks (+/- 7 days),** for the first 12 months, then every 12 weeks (+/- 7 days) thereafter, 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 is confirmed according to RECIST 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 9 weeks (+/- 7 days) until progression. Utilize **same** imaging modality of abdomen and pelvis +/- chest (for patients with evidence of measurable disease on baseline chest imaging; then subsequent radiographic tumor assessments must also include chest imaging. A tool is provided to calculate dates of re-imaging. Utilize same imaging modality of abdomen, pelvis and chest (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. PET CT should not be used.

[3]For patients receiving PLD, when the cumulative dose of PLD exceeds 550 mg/m^2, it is recommended that repeat echocardiogram or MUGA scan be performed every other cycle or according to institutional standards.

ARMS II, III, IV (27-AUG-2021)(23-AUG-2022):

Assessments	Prior to day 1 of each cycle of therapy	Every week for first 8 weeks of study therapy (in person, telemedicine, or phone)	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]	≤ 1 day			
Toxicity Assessment	≤ 1 day	X		
Vital Signs[2], weight required	≤ 1 day			
Performance Status	≤ 1 day			
CBC/Differential/Platelets	≤ 3 days			
Chemistries[3]	≤ 3 days			
TSH			≤ 7 days	
Urine protein:creatinine ratio (UPCR)			≤ 7 days	
CA125	≤ 3 days			
MUGA or echocardiogram	See footnote[4]			
Radiographic Tumor Measurement				See Footnote[5]
Home BP assessment[6]	See footnote[6]	See Footnote[6]		

[1] Because of a potential for interaction of olaparib and cediranib with other drugs through the cytochrome P450 system, special attention should be paid to other medications known to affect P450 isoenzymes, in particular CYP3A4. Please see Appendix VI for a list of these medications.

[2] Monitoring of vital signs before/during/after the infusion of durvalumab (see Section 6.2.4.1).

[3] Serum chemistry includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin.

[4] MUGA or echocardiogram should be performed at baseline for patients at increased risk for compromised LVEF, including patients with (1) prior treatment with anthracyclines, (2) prior treatment with trastuzumab or T-DM1, (3) prior central thoracic RT, or (4) history of myocardial infarction within the 12 months prior to registration or (5) prior history of impaired cardiac function. LVEF assessment by MUGA or echocardiogram should be performed on every 16-week (+/-1 week) basis for patients with these risk factors on cediranib-containing arms. Should the patients discontinue cediranib-containing arm therapy due to progression or toxicities within the 16-week (+/- 1 week) time frame before the next LVEF assessment, the treating physicians should follow cardiac symptoms and assess LVEF as clinically indicated until another therapy is initiated.

[5] **Tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI performed once every 9 weeks (+/- 7 days),** for the first 12 months, then every 12 weeks (+/- 7 days) thereafter,

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 is confirmed according to RECIST 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 9 weeks (+/- 7 days)**,** for the first 12 months, then every 12 weeks (+/- 7 days) thereafter until progression (or initiation of subsequent therapy). Utilize **same** imaging modality of abdomen and pelvis +/- chest (for patients with evidence of measurable disease on baseline chest imaging; then subsequent radiographic tumor assessments must also include chest imaging. A tool is provided to calculate dates of re-imaging. Utilize same imaging modality of abdomen, pelvis and chest (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. PET CT should not be used.

[6] Because of the rapid changes in blood pressure that can occur and the potential for severe life-threatening complications if hypertension is not appropriately managed, patients on Arms II, III and IV should check their blood pressure twice daily for at least the first 8 weeks after starting study drug, or, if anti-hypertensive management is required, until a stable anti-hypertensive regimen has been established, even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, blood pressure monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib hold/dosing delay for two weeks or until the patient is re-established on a stable anti-hypertensive regimen, whichever takes longer. **Patient blood pressures should be reviewed with the study team on a weekly basis for the first 8 weeks of study treatment to ensure that blood pressure guidelines are being correctly followed**. Blood pressures can be reviewed by phone between clinic visits.

4.3 Assessments in Follow-up

The following assessments are to be performed and recorded on the appropriate form(s). Vital status and patient-reported outcome assessments should be continued per the schedules noted below unless the consent is withdrawn. Removal from study treatment and remaining in follow-up is preferred to collect the continued outcome information.

Assessments	**From end of treatment:** Follow-up forms are collected for the 5- year follow-up period or until study termination, whichever occurs first.
Vital Status	Every 3 months (+/- 1 week) x 2 years, then every 6 months (+/- 1 week) x 3 years or until death.
Toxicity Assessment	Report all adverse events that occur within 30 days of last protocol treatment on the Toxicity form for the last cycle of therapy administered. For reporting of delayed toxicity, see Section 7
Radiographic tumor measurement	Every 9 weeks (+/- 7 days) x 1 year, then every 12 weeks (+/- 7 days) until progression (or initiation of subsequent therapy). **(27-AUG-2021)**

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Patients will be randomized to one of four study arms.

See Appendix III-General Therapy Guidelines

5.1 Treatment Plan

Day 1 of the cycle is the first day of the cycle if there is a delay, and the next cycle is to be a complete 21 or 28 days.

No modification of the regimens is allowed.

Patients randomized to ARM I may be treated with one of the three regimens specified in this section per investigator discretion (the planned regimen must be specified prior to randomization). The number of cycles of therapy should be administered as clinically appropriate.

The patients on cediranib intermittent schedule (5 days on/2 days off) may begin with 2-4 days on/2 days off during the first week of the cycle to have weekdays (Monday through Friday) weekend (Saturday and Sunday) on/off schedule, subsequent administrations are then adjusted to maintain a 5 days on/2 days off-interval.

Patients on Arms II, III and IV will need to keep medication and blood pressure diaries. A blood pressure cuff will be provided to patients randomized to Arms II, III and IV.

5.1.1 ARM I (Standard of Care/Control Arm) – Physician's choice Standard of Care Chemotherapy

Patients randomized to the non-platinum-based chemotherapy arm may be treated with one of the three regimens specified in this section per investigator discretion (the planned regimen must be specified prior to randomization). The number of cycles of therapy should be administered as clinically appropriate.

- Regimen 1 (Standard of Care/Control Arm): Paclitaxel 80 mg/m^2 intravenously (IV) over approximately 60 minutes on days 1, 8, and 15 every 28 days until disease progression or adverse events prohibit further therapy.

- Regimen 2: Pegylated liposomal doxorubicin 40 mg/m^2 IV over approximately 60 minutes on day 1, every 28 days until disease progression or adverse events prohibit further therapy.

- Regimen 3: Topotecan 4 mg/m^2 IV over approximately 30 minutes on days 1, 8, and 15 every 28 days or 1.25 mg/m^2 IV over approximately 30 minutes on days 1 to 5 every 21 days until disease progression or adverse events prohibit further therapy.

- ***No modification of the assigned regimens, such as addition of bevacizumab or other agents is allowed.***

5.1.2 Arm II durvalumab (MEDI4736) plus olaparib and cediranib (27-AUG-2021)

Durvalumab (MEDI4736) 1500mg fixed dose IV over approximately 60 minutes, Day 1.

NOTE: Patients must be at least 30 kg in order to be eligible for this study; however, should a patient lose weight during treatment and fall at or below 30 kg, patients less than or equal to 30 kg actual body weight will be dosed at 20 mg/kg every 4 weeks. When patient weight increases to over 30 kg, resume the fixed dosing of durvalumab (MEDI4736) at 1500 mg every 4 weeks.

Cediranib 20 mg PO Monday through Friday every week. Cediranib should be taken on an empty stomach in the morning, approximately one hour before taking the morning dose of olaparib.

Olaparib 300 mg PO BID. Olaparib should be taken with a light meal or snack twice a day approximately 12 hours apart.

One cycle = 28 days. Cycles are continuously numbered regardless of any dose holds or interruptions.

Patients will be treated until disease progression or adverse events prohibit further treatment.

5.1.3 Arm III durvalumab (MEDI4736) plus cediranib (27-AUG-2021)

Durvalumab (MEDI4736) 1500 mg fixed dose IV over approximately 60 minutes, Day 1, every 28 days until disease progression, patient withdrawal or toxicities.

NOTE: Patients must be at least 30 kg in order to be eligible for this study; however, should a patient lose weight during treatment and fall at or below 30 kg, patients less than or equal to 30 kg actual body weight will be dosed at 20 mg/kg every 4 weeks. When patient weight increases to over 30 kg, resume the fixed dosing of durvalumab (MEDI4736) at 1500 mg every 4 weeks.

Cediranib 20 mg PO Monday through Friday every week. Cediranib should be taken on an empty stomach in the morning.
One cycle = 28 days. Cycles are continuously numbered regardless of any dose holds or interruptions.

Patients will be treated until disease progression or adverse events prohibit further treatment.

5.1.4 Arm IV Olaparib and cediranib

Cediranib 20 mg PO daily. Cediranib should be taken on an empty stomach in the morning, approximately one hour before taking the morning dose of olaparib.

Olaparib 300 mg PO BID. Olaparib should be taken with a light meal or snack twice a day approximately 12 hours apart.

One cycle will be considered 28 days. Cycles are continuously numbered regardless of any dose holds or interruptions.

Patients will be treated until disease progression or adverse events prohibit further treatment.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of calcium with vitamin D and/or minerals, basic multivitamins, or melatonin oral supplements will be permitted either at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins, medical marijuanas or probiotics oral supplements are not allowed.

Concomitant use of know strong cytochrome (CYP) 3A inhibitors or inducers should be prohibited while on olaparib monotherapy or olaparib and cediranib combination given olaparib is a substrate for CYP3A.

- Concomitant use of known strong cytochrome (CYP) 3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil).
- Concomitant use of known strong CYP3A inducers (e.g., phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (eg. bosentan, efavirenz, modafinil).

5.3 Duration of Therapy (27-AUG-2021)

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to discontinue treatment. If a patient may decide to discontinue study treatment not to withdraw consent, she will be followed up for AEs/disease status as per Section 4.3

- 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

Dose delays and modifications will be made using the following recommendations.

- Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE v.5). CTCAE is identified and located on the CTEP website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).
- For adverse events (AEs) that are unrelated to the study drugs, study treatment may be held for up to 14 days at the discretion of the treating investigator. Drug holds of greater than 14 days for unrelated AEs where the patient is experiencing ongoing clinical benefit may be considered after discussion with the Study Chair.
- All AEs experienced by participants will be collected from the time of the first dose of study treatment, through the study and until the final study visit. Participants continuing to experience toxicity at the off-study visit may be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.
- There will be no dose escalations or re-escalations on this study.
- Dose modifications for Arm 1 should follow “institutional and compendium guidelines”.

Hematologic Issues

Use of hematopoietic agents

- Myeloid growth factors (filgrastim or pegfilgrastim) may be used per institutional standards. It is recommended that National Comprehensive Cancer Network (NCCN) and/or ASCO guidelines be consulted. Filgrastim should be administered subcutaneously starting 24 to 72 hours after the last dose of chemotherapy and continuing through hematopoietic recovery, but should not be administered within the 48 hours preceding the next dose of cytotoxic chemotherapy. Pegfilgrastim should be administered at 6mg subcutaneously 24 to 72 hours after the last dose of chemotherapy and should not be administered within 2 weeks preceding the next dose of cytotoxic chemotherapy. Pegfilgrastim should not be used for patients receiving chemotherapy that is given less than every 2 weeks.
- Use erythropoietin (EPO) per standard of care NCCN and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these

agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

- Transfusions may be administered as clinically indicated for management of anemia.
- Patients will NOT receive prophylactic thrombopoietic agents.
- Patients may NOT receive amifostine.
- Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below for each regimen.
- Management of prolonged hematological toxicities while on olaparib and/or cediranib

  If a patient develops prolonged hematological toxicity such as:

  - ≥2 week interruption/delay in olaparib due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
  - ≥2 week interruption/delay in 1 or both investigational drugs due to CTCAE Grade ≥3 neutropenia (ANC <1 x 10^9/L)
  - ≥2 week interruption/delay in 1 or both investigational drugs due to CTCAE Grade ≥3 thrombocytopenia and/or development of platelet transfusion dependence (Platelets <50 x 10^9/L)

  Check weekly differential blood counts including reticulocytes and peripheral blood smear. If any blood parameters remain clinically abnormal after 3 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered at this stage according to standard hematological practice. Both investigational drugs should be discontinued if blood counts do not recover to CTCAE Grade ≤1 within 3 weeks of dose interruption.

- **All Arms require ANC of 1500 mcl and platelets of 100,000 mcl for treatment initiation, the start of each cycle (Day 1), and treatment resumption after holding treatment.**

6.1 Arm I (Reference regimen)

6.1.1 Hematologic toxicity

For patients who do not achieve hematological recovery on scheduled day of the cycle, complete blood counts should be performed twice weekly until the above defined limits are achieved. If hematological recovery is achieved within 14 days after the scheduled beginning of the cycle, the full dose of therapy adjusted for the previous nadir should be administered immediately. If hematological recovery is not achieved 14 days or more after the scheduled day of the course, the patient will discontinue treatment.

6.1.2 Non-hematologic toxicity

- Management of non-hematologic toxicities on the reference arm should be per institutional practice and guidelines. Criteria for dose holds and modifications on the reference arms for non-hematologic toxicity should follow institutional practice and prescribing information.
- Other Major Organ Toxicity (not evaluated as disease related): If the patient has any clinically significant non-hematological drug related toxicity CTCAE grade > 3, the patient should discontinue protocol therapy unless strong clinical benefit is observed and after discussion with the Study Chair.
- Dose modifications for alopecia, nausea, constipation, or electrolyte abnormalities are not recommended.
- If treatment is delayed for greater than 3 weeks due to a drug-related non-hematologic toxicity, the patient may be discontinued from protocol-directed therapy after consultation with the Study Chair.

6.2 Arms II [durvalumab (MEDI4736) plus olaparib and cediranib], III durvalumab (MEDI4736) plus cediranib alone], and IV [olaparib and cediranib]

For Arms II-IV, at the discretion of the investigator, the study drugs may be held or dose modified independently if the observed toxicity is attributed to only one of the drugs, while the patient continues to receive the drug not associated with the observed toxicity.

The time cediranib or olaparib is held should not exceed 14 days.

Dose modification/hold of durvalumab) should follow Section 6.2.4.1, below.

Patients experiencing ongoing clinical benefit who experience a related AE where continuation of one of the drugs is considered, **in the judgment of the treating Investigator and the Study Chair**, to be potentially life-threatening or with the potential for long-term harm to the patient, may be allowed to continue on the unrelated drug(s) **after discussion with the Study Chair**.

Arm II

The dose levels and the general approach to dose modification of durvalumab, cediranib and olaparib combination therapy are shown below. AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form. **Dose reductions are not permitted for durvalumab (MEDI4736). Dose may be delayed or permanently discontinued as directed in Section 6.2.4.1.**

Dose Level	Durvalumab
1	A fixed dose of 1500 mg every 4 weeks

Dose level	Cediranib tablets
1	20 mg Monday through Friday (weekend off)
-1	15 mg Monday through Friday (weekend off)

Dose Level	Olaparib tablets
1	300 mg twice daily
-1	200 mg twice daily
-2	150 mg twice daily

Arm III

Dose Level	Durvalumab
1	A fixed dose of 1500 mg every 4 weeks

Dose level	Cediranib tablets
1	20 mg Monday through Friday (weekend off)
-1	15 mg Monday through Friday (weekend off)

Arm IV

Dose level	Cediranib tablets
1	20 mg daily
-1	20 mg Monday through Friday (weekend off)
-2	15 mg daily
-3	15 mg Monday through Friday (weekend off)

Dose Level	Olaparib tablets
1	300 mg twice daily
-1	200 mg twice daily
-2	150 mg twice daily

6.2.1 Hematologic toxicity

6.2.1.1 Use of hematopoietic agents

Use erythropoietin-stimulating agents per standard of care NCCN and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Treating physicians should be aware of the recent changes in prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) which note that there is a potential risk of shortening the time to tumor progression or disease-free survival, and that these agents are administered only to avoid red blood cell transfusions. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. They can cause an increased incidence of thrombotic events in cancer patients on chemotherapy. The updated package inserts should be consulted.

Use of granulocyte-colony stimulating factors will not be allowed in Arms II, III and IV.

6.2.2 Dose modifications for hematologic events

Table 6.2.2 A: Management of neutropenia or thrombocytopenia		
	Olaparib dose	**Cediranib dose**
CTCAE Grade 1-2 ANC >1.0 G/L or Platelet count >50 G/L	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 2 weeks; appropriate supportive treatment and causality investigation	Investigator judgement to continue treatment or allow dose interruption; dose interruptions should be for a maximum of 2 weeks; appropriate supportive treatment and causality investigation
CTCAE grade 3-4 ANC <1.0 G/L or Platelet count <50 G/L	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 2 weeks. Upon recovery, olaparib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both drugs	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 2 weeks. Upon recovery, cediranib dose should be reduced by one dose level. If repeat CTCAE Grade 3-4 occurrence, further dose reduce one or both drugs.

Table 6.2.2 B: Management of anemia		
	Olaparib dose	**Cediranib dose**
Hb <10 but ≥8 g/dL	Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib or interrupt dose for a maximum of 2 weeks. If repeat Hb **<10 but ≥8** g/dL, dose interrupt until Hb ≥10 g/dL for maximum of 2 weeks and upon recovery, olaparib dose should be reduced by one dose level.	No change
Hb < 8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt olaparib until improved to Hb ≥10 g/dL. Upon recovery, olaparib dose should be reduced by one dose level.	No change

- For AEs that are unrelated to the study drugs, study drug may be held for up to 14 days at the discretion of the treating investigator. Drug holds of greater than 14 days for unrelated AEs where the patient is experiencing ongoing clinical benefit may be considered after discussion with the Study Chair.

- Patients experiencing ongoing clinical benefit who experience a related AE where continuation of one of the drugs is considered, in the judgment of the treating investigator AND the Study Chair, to be potentially life-threatening or with the potential for long-term harm to the patient, may be allowed to continue on the unrelated drug after discussion with the Study Chair.

6.2.3 Dose modifications for Non-Hematologic toxicity

Table 6.2.3 A: General Management of Non-Hematologic Toxicity, Arms II - IV	
Observation	**Action**
AE resolves promptly with supportive care	Maintain dose level
Any ≥ grade 3 non-hematologic (excluding grade 3 fatigue, or easily correctable asymptomatic grade 3 laboratory abnormalities)	Hold study drug(s)[1] for up to 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.2.3, at the treating investigator's discretion[2]. The Study Chair should be informed regarding all dose modifications.
Any grade 2 non-hematologic AE or grade 3 fatigue, that persists despite maximal support.	Hold study drug(s)[1] for up to 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.2.3, at the treating investigator's discretion[2]. The Study Chair should be informed regarding all dose modifications. Patients whose toxicity has not resolved after 14 days will be removed from the study treatment.
1. Grade 3 or 4 non-hematologic AE that does not resolve to grade 0-2 within 14 days (excluding weight loss) despite maximum supportive care after treating patient at the lowest reduced dose level.[3] 2. Grade 3 or 4 non-hematologic AE lasting > 14 days (excluding weight loss) despite maximum supportive care and treatment being held.	Discontinue study drug(s)
[1]**At the discretion of the investigator, one drug may be held or dose modified or discontinued independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the second drug not associated with the observed toxicity.** The time a given drug is held should not exceed 14 days. [2]Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the Study Chair if evidence of clinical benefit. [3]For thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic.	

The management of general AEs not otherwise specified in the following sections should be as per Table 6.2.3.A. Management of specific toxicities, including durvalumab-related infusion reaction, immune-mediated AEs, hypertension, diarrhea, proteinuria, decrease in LVEF, fever and neutropenia, nausea and vomiting, thyroid toxicities, reversible posterior leukoencephalopathy syndrome (RPLS) and gastrointestinal perforation should

be as further outlined in the below specific subsections and not per Table 6.2.3.A.

* Management of olaparib-induced nausea and vomiting

Events of nausea and vomiting are known to be associated with olaparib treatment. These events are generally mild to moderate (CTCAE grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie 2 pieces of toast or a couple of biscuits).

Olaparib dose reduction should be considered for patients requiring consistent anti-emetic intervention despite supportive cares per ASCO PARP inhibitor guidelines (Tew et al, J Clin Onc, 2020).

6.2.4 Durvalumab-related adverse events

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

All toxicities will be graded according to NCI CTCAE, Version 5.0.

6.2.4.1 Monistoring of durvalumab (MEDI4736) administration:

- Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessments. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

- Standard infusion time is one hour, however if there are interruptions, the total allowed time must not exceed 8 hours at room temperature (otherwise requires new infusion preparation).

- For management of patients who experience an infusion reaction, please refer to the Section 6.2.4.2. As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if

necessary.

6.2.4.2 Infusion-related reaction with durvalumab

- In the event of grade 1 or 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with grade 1 or 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications may be administered at the discretion of the investigator.
- If the infusion-related reaction is grade 3 or higher OR recurrent grade 2 or higher in severity, durvalumab (MEDI4736) will be discontinued

Table 6.2.4.2 Management of Infusion-Related Reactions

Dose Modifications	**Toxicity Management**
Any Grade	• Management per institutional standard • Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1 The infusion rate of durvalumab (MEDI4736) may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: • Acetaminophen and/or antihistamines may be administered at the discretion of the investigator • Consider premedication prior to subsequent doses • Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 2 The infusion rate of durvalumab (MEDI4736) may be decreased 50% or temporarily interrupted until resolution of the event (up to 4 hours). Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3 or 4 Permanently discontinue durvalumab	For Grade 3 or 4: Manage severe infusion-related reactions (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

6.2.4.3 Immune-related adverse events

- Based on the mechanism of action of durvalumab (MEDI4736) leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects

should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or progression) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

- Dose modification recommendations and toxicity management guidelines for durvalumab, immune-mediated reactions are detailed below.

Table 6.2.4.3 A. General Considerations for immune-related AEs (irAEs)

General guidelines for treatment modifications: Treatment modifications will be made to manage potential immune-related AEs (irAEs) based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0.

In addition to the criteria for permanent discontinuation of study drugs as described in the table below, **permanent discontinuation of durvalumab (MEDI4736) is also required for the following conditions**:

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

AE Grade:

Grade 1 No dose modification

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

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

Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.

Grade 4 Permanently discontinue study drug/study regimen.

Note: For asymptomatic amylase or lipase levels of >2× ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.

Note: Durvalumab (MEDI4736) should be permanently discontinued in Grade 3 events with high likelihood for morbidity or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper.

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

Toxicity Management – general guidelines

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

- Adverse events with an inflammatory or immune mediated mechanism could occur in all organs, not all of which are noted specifically in these guidelines.
- Patients should be thoroughly evaluated to rule out alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, **all such events should be managed as if they were immune related. General recommendations follow.**
    - Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events.

Table 6.2.4.3 A. General Considerations for immune-related AEs (irAEs)

- For persistent (≥3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
- **Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if not currently noted in the guidelines**. Initiate high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2 when clinical suspicion is high or there has been clinical confirmation. Consider, as necessary, discussing with the study chairs and promptly pursue specialist consultation.
- **Steroid tapering should be gradual over at least 4 weeks**. If symptoms recur or worsen during tapering, increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).
- If no improvement after steroids, consider more potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive). Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity or mortality – e.g., myocarditis, or other similar events even if not currently noted in the guidelines.
- **With long-term steroid and other immunosuppressive use**, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring (refer to current NCCN guidelines for treatment of cancer-related infections)[a]

- Discontinuation of durvalumab (MEDI4736) is not mandated for Grade 3/4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

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

6.2.4.3 B. Dose Delay Treatment modifications for Specific Immune-Mediated Reactions

Adverse Events	Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)[1]	**For Any Grade**: − Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. − Initial workup may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory workup, and high- resolution CT scan.		
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug(s) as clinically appropriate pending workup for other etiologies.	**For Grade 1 (radiographic changes only):** − Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory workup and then as clinically indicated. − Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting	Hold study drug(s) until resolution to Grade ≤1. • If toxicity worsens, treat as Grade 3/4 • If toxicity improves to Grade ≤1, then the	**For Grade 2 (mild to moderate new symptoms):** − Monitor symptoms daily and consider hospitalization. − Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). − Reimage as clinically indicated.

	instrumental ADL)	decision to retreat will be based upon treating physician's discretion and after completion of steroid taper.	− If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day − If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start additional immunosuppressive agent such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment Consider pulmonary and infectious disease consult. − Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. − Hospitalize the patient and Supportive care − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a]
Diarrhea/ Colitis	**For Any Grade:** − Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). − When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. − Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. − Use analgesics carefully; they can mask symptoms of perforation and peritonitis.		
	Grade 1 (Diarrhea: stool frequency of	No dose modifications.	**For Grade 1:** − Monitor closely for worsening symptoms. − Consider symptomatic treatment, including

	<4 over baseline per day) Colitis: asymptomatic; clinical or diagnostic observations only)		hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	Hold durvalumab(MEDI473) until resolution to Grade ≤1 • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then study drug(s) can be resumed after completion of steroid taper.	**For Grade 2:** − Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. − Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 3 to 5 days or worsens, obtain GI consult for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. Promptly start IV methylprednisolone 2 to 4 mg/kg/day. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. − Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a]
	Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥7 over baseline per day; limiting self-care ADL; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences,	<u>Grade 3</u> Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. <u>Grade 4</u> Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. − Monitor stool frequency and volume and maintain hydration. − Urgent GI consult and imaging and/or colonoscopy as appropriate. − If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

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

			infections) [a]
	Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20×baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0×baseline if baseline abnormal) **Grade 4** (AST or ALT >20xULN if baseline normal, >20xbaseline if baseline abnormal; an/or TB >10xULN if baseline normal, >10.0×baseline if baseline abnormal)	**For Grade 3:** For transaminases elevations ≤8 × ULN, or bilirubin elevations ≤5 × ULN: • Hold durvalumab (MEDI4736) until resolution to Grade ≤1 or baseline • Resume durvalumab (MEDI4736) if LFT elevations resolve to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • **Permanently discontinue** durvalumab (MEDI4736) if no resolution within 14 days **Permanently discontinue** durvalumab (MEDI4736) for: • Transaminases elevation >8 × ULN or bilirubin >5 × ULN. • Any case meeting Hy's law criteria (AST or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause[b]	**For Grade 3 or 4:** − Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. − If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** − Perform hepatology consult, abdominal workup, and imaging as appropriate. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Nephritis or renal dysfunction (elevated serum creatinine)	**For Any Grade:** − Consult with nephrologist. − Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.		
	Grade 1 (Serum creatinine > ULN to 1.5 × ULN)	No dose modifications.	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular

			monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to >1 to 1.5 × baseline, consider following recommendations in this row.
	Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)	Hold durvalumab (MEDI4736) until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If improvement to Grade ≤1 or baseline, resume study drug(s) after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO/IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol
	Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum creatinine >6.0 × ULN)	Permanently discontinue durvalumab (MEDI4736)	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO/IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v5.0 for definition of severity/grade depending on type of skin rash) General Guidance **For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**		
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).

	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold durvalumab (MEDI4736) until resolution to Grade ≤1 or baseline. • If toxicity worsens, treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, resume drug(s) after completion of steroid taper.	**For Grade 2:** − Obtain dermatology consult. − Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). − Consider moderate-strength topical steroid. − If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. − Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs
	Grade 3 or 4	**Grade 3:** Hold durvalumab (MEDI4736) until resolution to Grade ≤1 or baseline. If no improvement within 30 days, permanently discontinue durvalumab (MEDI4736) **Grade 4 (or life-threatening):** Permanently discontinue durvalumab (MEDI4736)	**For Grade 3 or 4:** − Consult dermatology. − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Consider hospitalization. − Monitor extent of rash [Rule of Nines]. − Consider skin biopsy (preferably more than 1) as clinically feasible. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] − Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, Type 1 diabetes mellitus hypophysitis, hypothyroidism, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	General Guidance	**For Any Grade:** − Consider consulting an endocrinologist for endocrine events. − Consider, as necessary, discussing with study physician. − Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). − Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c) − For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. − For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation − If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody

	testing.	
Grade 1	No dose modifications.	**For Grade 1 (including asymptomatic TSH elevation):** − Monitor patient with appropriate endocrine function tests. − For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). − If TSH < 0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold durvalumab (MEDI4736) until patient is clinically stable. - If toxicity worsens, treat as Grade 3/4. - Durvalumab (MEDI4736) can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged steroid replacement can resume durvalumab (MEDI4736) on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**For Grade 2 (including symptomatic endocrinopathy):** − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. − For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). − Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. − Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] − For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated initiate hormone replacement as needed for management.
Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold	**For Grade 3 or 4:** − Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended.

		durvalumab (MEDI4736) until endocrinopathy symptom(s) are controlled. durvalumab (MEDI4736) can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged steroid replacement (e.g., adrenal insufficiency) can resume study drug(s) on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	− For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones).or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). − For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. − Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. − Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. − Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] .
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, **excluding** Myasthenia Gravis and Guillain-Barre	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity) General Guidance **For Any Grade:** − Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). − Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). − Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). − Perform symptomatic treatment with neurological consult as appropriate.		
	Grade 1	No dose modifications.	**For Grade 1:** − See "Any Grade" recommendations above.
	Grade 2	**For acute motor** neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. **For sensory** neuropathy/neuropathic pain, consider holding durvalumab (MEDI4736) until resolution to Grade ≤1. • If toxicity worsens,	**For Grade 2:** − Consider, as necessary, discussing with the Study Chair. − Obtain neurology consult. − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). − Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).

		treat as Grade 3 or 4. durvalumab (MEDI4736) can be resumed after improvement to Grade ≤1 and after completion of steroid taper.	
	Grade 3 or 4	**For Grade 3:** Hold durvalumab (MEDI4736) until resolution to Grade ≤1. Permanently discontinue durvalumab (MEDI4736) if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue durvalumab (MEDI4736)	**For Grade 3 or 4:** − Consider, as necessary, discussing with the Study Chair. − Obtain neurology consult. − Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). − Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as **Guillain-Barre and myasthenia gravis**)	**For Any Grade:** − The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. − Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, **it is essential to have a low threshold to obtain a neurological consult.** − Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. − It is important to consider that the use of **steroids as the primary treatment of Guillain-Barre is not typically considered effective.** Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.		
	Grade 1 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** − Consider, as necessary, discussing with the Study Chair. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult.
	Grade 2 (GB: moderate	Hold durvalumab (MEDI4736) until	**For Grade 2:** − Consider, as necessary, discussing with the Study

	symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	resolution to Grade ≤1. **Permanently discontinue** durvalumab (MEDI4736) if it does not resolve to Grade ≤1 within 30 days <u>or</u> if there are signs of respiratory insufficiency or autonomic instability.	Chair. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a neurology consult − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
	Grade 3 or 4 (Grade 3 GB: severe symptoms; limiting self-care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-	**For Grade 3:** Hold MEDI4736 (durvalumab0 until resolution to Grade ≤1. Permanently discontinue durvalumab (MEDI4736) if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue durvalumab.	**For Grade 3 or 4 (severe or life-threatening events):** − Consider, as necessary, discussing with Study Chair. − Recommend hospitalization. − Monitor symptoms and obtain neurological consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

	threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)		

Myocarditis	**General Guidance for Any Grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the Study Chair. − Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (*e.g.*, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − Initial workup should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory workup as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. − Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression, other medications, or infections) − **Discontinue durvalumab (MEDI4736) permanently if biopsy-proven immune-mediated myocarditis regardless of grade**		
	Grade 1 cardiac AE (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2	No dose modifications required unless clinical suspicion is high for myocarditis, in which case hold durvalumab (MEDI4736) during diagnostic workup. - If myocarditis is excluded, resume after complete resolution to Grade 0. - If myocarditis is diagnosed, permanently discontinue durvalumab MEDI4736)	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory workup as clinically indicated. - Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 cardiac AE or suspected myocarditis (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with	**For Grade 2:** - Hold durvalumab (MEDI4736) - If toxicity rapidly improves to Grade 0 and no evidence for myocarditis, then the decision to reinitiate MEDI4736 durvalumab (MEDI4736) is based upon	**For Grade 2-4:** − Monitor symptoms daily, hospitalize if myocarditis is suspected. − Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. − Supportive care (*e.g.*, oxygen).

	symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated *e.g.*, continuous IV therapy or mechanical hemodynamic support) * Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis	treating physician's clinical judgment and after completion of steroid taper. - If toxicity does not rapidly improve, permanently discontinue durvalumab (MEDI4736) - If myocarditis is diagnosed, permanently discontinue durvalumab (MEDI4736) regardless of timeline of recovery. - If Grade 3-4, permanently discontinue durvalumab (MEDI4736)	– If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/Polymyositis ("Poly/myositis")	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the Study Chair. – Initial workup should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory workup as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).		
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the Study Chair.
	Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living	Hold durvalumab (MEDI4736) until resolution to Grade ≤1. Permanently discontinue durvalumab (MEDI4736) if it	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology

	[ADLs])	does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional workup and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).[a]
	Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** Hold durvalumab (MEDI4736) until resolution to Grade ≤1. **Permanently discontinue** durvalumab (MEDI4736) if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** **Permanently discontinue** MEDI4736 (durvalumab).	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; hospitalization recommended. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the Study Chair. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If not improvement within 3-5 days after IV methylprednisolone at 2 to 4 mg/kg/day, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[a]ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow, MD.

[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

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

[1] Pneumonitis (ILD) investigation

If new or worsening pulmonary symptoms (*e.g.*, dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in this table will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters, etc.)

will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.
The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected including

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.), including auscultation for lung field will be assessed
- Saturation of peripheral oxygen (SpO2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    (i) ILD Markers (KL-6, SP-D) and β-D-glucan.
    (ii) Tumor markers: Particular tumor marker swhich are related to disease progression
    (iii) Additional clinical chemistry: CRP, LDH

6.3 Cediranib-related adverse events

Cediranib should be discontinued should any of the following AEs occur: GI perforation; arterial thromboembolic events; PRES (radiologically confirmed); severe or medically significant hemorrhage and severe persistent hypertension despite maximal anti-hypertensive treatment.

6.3.1 Hypertension

Only doses of cediranib will be modified for hypertension; olaparib or durvalumab (MEDI4736) doses will not be altered unless other toxicities are experienced.

Table 6.3.1 A: Hypertension Monitoring and Management

- See table for suggested antihypertensive medications by class (**Appendix IX**).
- Abbreviations: Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARB), selective beta blockers (BB), Calcium channel blockers (CCB)
- If patients require a delay of >2 weeks for management of hypertension, discontinuation of cediranib may be considered after discussion with the Study Chair.
- Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib
- Hypertension should be graded using the NCI CTCAE v5.0. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry. Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE criteria. Baseline grade of hypertension should also be recorded in the patient's record.
- **Note**: Stopping or reducing the dose of cediranib is expected to cause a decrease in BP. **The treating physician should monitor the patient for hypotension (also during the weekend when the patients do not take cediranib) and adjust the number and dose of antihypertensive medications accordingly. Please pressure cuffs with be provided for patients taking cediranib. See Section 9.7.4.**

Event	Definition	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
Grade	Asymptomatic transient (<24	Consider early initiation of BP medication for BP >	Continue standard BP	None

1	hrs) increase by >20 mmHg diastolic or to >140/90 mmHg if previously WNL	140/90 mmHg that is confirmed on a second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of HTN-related complications.	monitoring per treating MD and confirm resolution of BP to <140/90 mmHg within 36 hours.	
Grade 2	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to > 140/90 mmHg if previously WNL Monotherapy may be indicated	Initiate BP medication for first line treatment: • *Suggestion:* ACE inhibitor Escalate dose of medication until BP is controlled or at a maximum dose If BP is not controlled to < 140/90 mmHg with one "maximized" drug regimen, then add a second agent: **Study drug does not need to be held unless otherwise clinically necessary** *Consider cardiology or renal consult*	Increase frequency of monitoring (daily) until stabilized to BP <140/90 mmHg	Do not hold cediranib unless otherwise clinically necessary
Grade 3	Requiring more than one drug or more intensive therapy than previously.	Maximize 2 drug regimen • *Suggestions:* ACE inhibitor + BB or ACE inhibitor + CCB Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to < 140/90 mmHg with two drug regimen, then add a third agent. **Study Drug will not be held**	Increased frequency of monitoring until stabilized to BP <140/90 mmHg	Do not hold cediranib or other study drug unless BP is not decreased to less than 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen (e.g. headache). If BP is not controlled to less than 150/100 mmHg with maximal therapy or if

		during trial of two drug combinations. **Additional antihypertensive drugs, up to a total of 4, may be maximized for blood pressure control.** *Consider consult with a blood pressure management specialist if greater than 3 drugs are required for BP control.*		clinical symptoms worsen, then hold drug (up to 14 days) until maximum effect of the antihypertensive agents is achieved. If BP is reduced to Grade 1 within 14 days, cediranib may be resumed at prior dose.
Grade 4	If threatening consequences **OR** SBP ≥ 180mmHg **OR** DBP ≥ 110mmHg	Initiate treatment Hospitalize patient for ICU management, IV therapy as necessary 14 days are allowed to maximize the full effect of antihypertensive agents.	Intensive BP monitoring (hospitaliza-tion if necessary)	**Hold cediranib.** If BP is reduced to Grade 1 within 14 days, cediranib may be resumed at a reduced dose after discussion with the PI

Notes:

- While patients are receiving treatment with cediranib, the early initiation of antihypertensive treatment for grade 1 or 2 hypertension to minimize more severe or persistent hypertension is not considered a grade 3 adverse event.
- Decisions to hold or decrease the cediranib dose during treatment must be based on BP readings taken in the clinic by a medical professional.

6.3.2 Decreased Left Ventricular Ejection Fraction

Patients who have any of the following should undergo an echocardiogram or MUGA at baseline and every four cycles (16 weeks +/-1 week) while on study:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab or T-DM1
- A New York Heart Association classification of II controlled with treatment
- Prior central thoracic radiation therapy (RT), including RT to the heart
- History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)
- Prior history of impaired cardiac function

Only doses of cediranib will be modified for LVEF; olaparib or durvalumab (MEDI4736) doses will not be altered unless other toxicities are experienced. The decision to continue

or hold cediranib is based on the LVEF as it relates to the institution's lower limit of normal (LLN) and change in ejection fraction from screening (LVEF as measured at registration) according to the following table:

Table 6.3.2 A. Management and Monitoring of Decreased LVEF

Relationship of LVEF to Institution's LLN	LVEF Decrease < 10%	LVEF Decrease 10-15%	LVEF Decrease > 16%
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 1-2 cycles
1-5% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles
> 6% below LLN	Continue and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles	HOLD and repeat MUGA/ECHO within 1-2 cycles

6.3.3 Diarrhea **(27-AUG-2021)**

Diarrhea is often observed with cediranib. Diarrhea usually starts early (within the first 4 weeks of treatment), however, it can occur at any time during treatment. Management of diarrhea should start at the first sign of diarrhea. Loperamide and advice on how to manage diarrhea should be readily available to patients from the start of cediranib treatment so that they can be applied at first episode of diarrhea. Active and early management of diarrhea is recommended even with Grade 1 diarrhea. Management as follows:

Table 6.3.3 A: Management of Diarrhea

Toxicity	Management/Modifications
Initial grade 1 or 2 diarrhea:	Patients can take loperamide (per standard practice) and continue to take loperamide until patients are free from diarrhea for at least 12 hours. The dose of loperamide should not exceed 16mg in a 24-hour period. Patients should also be counseled to start a BRAT (bananas, rice, applesauce, toast) diet.
	Patients should be instructed to contact their study team if mild or moderate (NCI CTCAE Grade 1 or 2) diarrhea persists for over 48 hours despite treatment with loperamide and cediranib dose interruption. Cediranib may be restarted at the

	same dose once patients have been free from diarrhea for 12 hours after discussing with the study team.
For either persistent grade 2 diarrhea or grade 3 or 4 diarrhea *:	Follow 6.2.3.A

*Patients with persistent or severe diarrhea (NCI CTCAE Grade 3 or higher) may also require dose reduction or discontinuation of therapy with cediranib; follow guidance in Table 6.2.3. Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the Study Chair if evidence of clinical benefit.

6.3.4 Proteinuria

Although patients with ≥1+ proteinuria at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows:

Table 6.3.4 A: Management of Proteinuria

Proteinuria Value if following by U/A	Dose modification
Greater than 2+ on urine dipstick or U/A **AND** Creatinine ≤1.5x ULN	Continue study drugs at planned dose.
Greater than 2+ on urine dipstick or U/A AND Creatinine >1.5x ULN	Hold cediranib and evaluate possible prerenal causes such as dehydration or increased creainine.

6.3.5 Thyroid toxicities

The use of cediranib has been associated with elevations of the thyroid stimulating hormone (TSH) and patients should be managed as per the following table.

In all cases, study treatment should continue unless clinically contraindicated. Referral to an endocrinologist should also be considered if thyroid abnormalities occur.

Table 6.3.5 A: Monitoring and Management of Thyroid Toxicities

Result of TSH*, T4, and T3	Action
Increases of TSH with normal T4/T3:	Monitor
Increases in TSH with normal T4/T3 and adverse events suggestive of incipient hypothyroidism:	Consider replacement thyroxine.
Increase in TSH with reductions in T4 and T3:	Consider replacement thyroxine.

*Please consider requesting T3/T4 where TSH is elevated.

6.3.6 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

PRES has been uncommonly reported in clinical studies with cediranib. PRES is a neurological disorder which can present with headache, seizure, lethargy, confusion, blindness and other visual and neurologic disturbances, and can be fatal. Mild to severe hypertension may be present. In patients developing PRES, treatment of specific symptoms including control of BP is recommended. Confirmation of PRES requires brain imaging, preferably MRI. Cediranib should be discontinued following confirmation of PRES. The safety of reinitiating cediranib in patients previously experiencing PRES is not known.

Cediranib should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure. Cediranib should be discontinued upon diagnosis of RPLS.

6.3.7 Gastrointestinal perforation

GI perforation has been uncommonly reported in cediranib treated patients and may be fatal. Cediranib should be used with caution in patients at risk and permanently discontinued in patients who develop GI perforation.

6.3.8 Fistula

In patients treated with cediranib, fistula has been reported and reflected the location of the underling malignancy. In the ovarian cancer population, vaginal fistula has been uncommonly reported in cediranib treated patients. Cediranib should be used with caution in patients at risk of fistula and discontinuation of cediranib should be considered in patients who develop fistulae.

6.3.9 Arterial thromboembolism

Arterial thromboembolic events (including transient ischemic attack and ischemic stroke) have been reported in clinical studies with cediranib. Cediranib should be used with caution in patients who are at an increased risk of thrombotic events or who have a history of thrombotic events. Cediranib should be permanently discontinued in patients who develop an arterial thromboembolic event.

6.3.10 Venous thromboembolism

Venous thromboembolic events including pulmonary embolism and deep vein thrombosis have been commonly reported in patients treated with cediranib. Anticoagulant treatment should be started in accordance with clinical practice. Discontinuation of cediranib may be considered. Cediranib should be used with caution in patients at risk of venous thromboembolism.

6.3.11 Wound healing

Treatment with cediranib should be stopped at least 2 weeks prior to scheduled surgery. The decision to resume cediranib therapy after surgery should be based on clinical judgment of adequate wound healing. In patients who experience wound healing

complications during therapy, treatment with cediranib should be interrupted until the wound is fully healed. No formal studies of the effect of cediranib on wound healing have been conducted; however in the ICON6 pivotal study there was no evidence of an increase in wound healing complications in cediranib treated patients compared with placebo.

6.3.12 Fatigue

Fatigue is a common adverse drug reaction reported for both cediranib and olaparib. Fatigue experienced by patients taking cediranib may be rapid in onset. During clinic visits, patients fatigue levels should be discussed. Patients should seek medical advice early if Grade 2 fatigue develops (moderate fatigue causing difficulty performing some activities of daily living).

Care should be taken to ensure that the nutritional status of the patients is optimized and patients should be encouraged to drink plenty of fluids. Patients should be encouraged to manage fatigue by alternating periods of rest with light aerobic exercise, which may improve the symptoms in some cases.

Consideration should be given to other possible causes of fatigue (e.g., thyroid function, depression/insomnia and other concomitant medicinal products). Additionally, short interruption of cediranib dosing (initially 2-3 days-or longer-up to a maximum of 21 days) may help relieve fatigue. When symptoms improve cediranib should be restarted with the same dose or, if necessary, a dose reduction can be considered.

6.4 Olaparib-related AEs

AEs requiring olaparib to be discontinued:

- Bone marrow findings consistent with myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Severe persistent anemia
- Pneumonitis

6.4.1 AML/MDS

- Patients who have treatment held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery. If counts do not improve to CTCAE grade 1 or better despite drug cessation for 3 weeks, patients should be referred to a hematologist for further assessment.
- A bone marrow analysis should be considered per hematology assessment given there may be potential contributing factors for the development of MDS/AML, such as prior exposures to extensive chemotherapy with platinum agents or other DNA damaging agents.
- Patients who develop MDS/AML on treatment should be discontinued from olaparib treatment and managed appropriately.

6.4.2 Management of olparib-related new or worsening pulmonary symptoms

- If new or worsening pulmonary symptoms (e.g., dyspnea) or radiological

abnormalities occur in the absence of a clear diagnosis, an interruption in 1 or both investigational drugs dosing is recommended and further diagnostic workup (including a HRCT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then investigational drugs can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these need to be discussed with the Study Chair.

6.4.3 Management of nausea and vomiting

- Events of nausea and vomiting are known to be associated with olaparib treatment. In study D0810C00019 nausea was reported in 71% of the olaparib treated patients and 36% in the placebo treated patients and vomiting was reported in 34% of the olaparib treated patients and 14% in the placebo treated patients. These events are generally mild to moderate (CTCAE Grade 1 or 2) severity, intermittent and manageable on continued treatment. The first onset generally occurs in the first month of treatment for nausea and within the first 6 months of treatment for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.
- No routine prophylactic anti-emetic treatment is required at the start of treatment with the olaparib, however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines. Taking olaparib tablets with food may help alleviate symptoms of nausea and vomiting.
- As per international guidance on anti-emetic use in cancer patients (European Society for Medical Oncology [ESMO], NCCN), generally a single agent antiemetic should be considered e.g. dopamine receptor antagonist, antihistamines or dexamethasone.

6.4.4 Management of renal impairment

- If subsequent to study entry and while still on study treatments, a patient's estimated creatinine clearance (CrCL) falls below the threshold for study inclusion (<50 mL/min), retesting should be performed promptly. A dose reduction of olaparib is recommended for patients who develop moderate renal impairment (calculated CrCL by Cockcroft-Gault equation of ≥31 mL/min and ≤50 mL/min) for any reason during the course of the study: the dose of olaparib should be reduced to 150 mg twice daily.
- Because the CrCL determination is only an estimate of renal function, in instances where the CrCL falls to between 31 mL/minutes and 50 mL/minutes, the Investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.
- Olaparib has not been studied in patients with severe renal impairment
- (CrCL ≤30 mL/minutes) or end-stage renal disease; if patients develop severe impairment or end stage disease is it recommended that olaparib be discontinued.

6.5 Management of durvalumab, Olaparib, or Cediranib for Surgery/Procedure

- At this time there is no recommendation for holding durvalumab (MEDI4736) in the event of surgery; decision to defer or hold treatment in the event of surgery is per discretion of the PI.

- Olaparib should be stopped two weeks prior to planned surgery or at least 1 day prior to planned procedures, *e.g.,* colonoscopy. After surgery or procedure, olaparib may be restarted when the wound has healed. For planned procedures, olaparib may be restarted next day.
- Because the AEs related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.
- Cediranib has the potential to affect wound healing. Cediranib should be stopped two weeks prior to elective surgery and restarted when the wound has healed. In the event of emergency surgery, cediranib should be stopped and appropriate precautions should be taken to minimize potential risks of bleeding and thrombosis associated with this class of agents.
- Cediranib should be discontinued at least 3 days prior to planned procedures, *e.g.,* colonoscopy and cediranib may be restarted 3 days after procedures or when the wound has healed.
- No stoppage of investigational drugs is required for any needle biopsy procedure.
- Olaparib and/or cediranib should be discontinued for a minimum of 3 days before a patient undergoes radiation treatment. Both drugs should be restarted within 2 weeks as long as any bone marrow toxicity has recovered.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents
The investigational agents administered in NRG-GY023 are durvalumab, olaparib, and cediranib which are being made available under an IND sponsored by CTEP. For patients receiving durvalumab, olaparib, or cediranib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.2.2 of the protocol.

Commercial Agents
The commercial agents in NRG-GY023 are paclitaxel, topotecan, and pegylated liposomal doxorubicin (PLD). For patients receiving paclitaxel, Topotecan, or pegylated liposomal doxorubicin determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.2.2.1 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 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

7.2.2 Definition of an Adverse Event (AE)

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

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

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

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for Study Agents

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MEDI4736 (durvalumab, NSC 778709)

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 2833 patients.* Below is the CAEPR for MEDI4736 (durvalumab).

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 2.4, April 17, 2019[1]

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (idiopathic thrombocytopenic purpura)[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Myocarditis[2]	

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes insipidus)	
		Endocrine disorders - Other (diabetes mellitus type 1)[2]	
	Hyperthyroidism[2]		
		Hypopituitarism[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Keratitis[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
		Gastrointestinal disorders -Other - (gastrointestinal perforation)[2,3]	
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (autoimmune hepatitis)[2]	
IMMUNE SYSTEM DISORDERS			
		Immune system disorders - Other (immune related adverse events)[2]	
		Immune system disorders - Other (sarcoidosis)	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 2)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		***Alanine aminotransferase increased[2] (Gr 2)***
	Aspartate aminotransferase increased[2]		***Aspartate aminotransferase increased[2] (Gr 2)***
	Creatinine increased		***Creatinine increased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		

Adverse Events with Possible Relationship to MEDI4736 (durvalumab) (CTCAE 5.0 Term) [n= 2833]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]	
	Myalgia		***Myalgia (Gr 2)***
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2,5]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (aseptic meningitis)[2]	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
	Dysuria		***Dysuria (Gr 2)***
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
Cough			***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Pneumonitis[2]		
	Respiratory, thoracic and mediastinal disorders - Other (dysphonia)		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		
	Pruritus		***Pruritus (Gr 2)***
	Rash[2,6]		***Rash[2,6] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (scleroderma)	
		Skin and subcutaneous tissue disorders - Other (severe dermatitis)[2,7]	
	Skin hypopigmentation		***Skin hypopigmentation (Gr 2)***

NOTE: Cardiomyopathy, and graft versus host disease, while not observed on clinical trials of durvalumab (MEDI4736) at this time, are known events with this class of agent (PD-L1 antagonist).

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

[2]Immune-mediated adverse reactions (irAEs) have been reported in patients receiving MEDI4736 (durvalumab). irAEs can involve any of the organs or systems in the body. Most irAEs were reversible and managed with interruptions of MEDI4736 (durvalumab), administration of corticosteroids and supportive care, however, these events can be serious and fatal.

[3]Gastrointestinal perforations have been observed only in patients receiving durvalumab (MEDI4736) in combination with tremelimumab (CP-675,206).

[4]Infections includes infection in the lungs, upper respiratory tract, dental and oral soft tissues and other organs under the INFECTIONS AND INFESTATIONS SOC. Infections generally are mild (Gr 1-2) but severe infections including sepsis, necrotizing fasciitis, and osteomyelitis have been reported.

[5]Guillain-Barre Syndrome has been reported in patients receiving durvalumab (MEDI4736) in combination with tremelimumab (CP-675,206) but can potentially occur after durvalumab (MEDI4736) monotherapy.

[6]Rash includes the terms: rash erythematous, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, erythema, and eczema.

[7]In rare cases, severe dermatitis has been reported to manifest as Stevens-Johnson syndrome, toxic epidermal necrolysis, or rashes complicated by dermal ulceration or necrotic, bullous, or hemorrhagic manifectations.

Adverse events reported on durvalumab (MEDI4736) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that durvalumab (MEDI4736) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Disseminated intravascular coagulation
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (coronary artery disease); Pericardial effusion; Pericardial tamponade; Restrictive cardiomyopathy; Right ventricular dysfunction; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired
EYE DISORDERS - Eye disorders - Other (choroidal effusion with shut down of ciliary body)
GASTROINTESTINAL DISORDERS - Ascites; Constipation; Dental caries; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Mucositis oral; Proctitis; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema trunk; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic hemorrhage
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (drug-induced liver injury); Serum sickness
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Wound complication
INVESTIGATIONS - Blood bilirubin increased; CPK increased; Electrocardiogram T wave abnormal; GGT increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Rhabdomyolysis
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (brain metastasis swelling); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lung cyst); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare, tumor inflammation); Treatment related secondary malignancy; Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Dizziness; Edema cerebral; Headache; Nervous system disorders - Other (axonal neuropathy); Nervous system disorders - Other (hemiparesis); Paresthesia; Seizure
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Hypoxia; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin
VASCULAR DISORDERS - Hypertension

Note: Durvalumab (MEDI4736) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Olaparib (AZD2281, NSC 747856)(25-JUL-2023)

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

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

Version 2.6 June 5, 2023[1]

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

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	
VASCULAR DISORDERS			
		Vascular disorders - Other (venous thromboembolism)	

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

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

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

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Enterocolitis; Esophageal stenosis; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other

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

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

7.5 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cediranib (AZD2171, NSC 732208)

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 1608 patients.* Below is the CAEPR for Cediranib (AZD2171).

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 2.15, November 7, 2018[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dysphagia		***Dysphagia (Gr 2)***
		Gastrointestinal fistula[2] ENREF_2	
		Gastrointestinal perforation[3] ENREF_3	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
		Pancreatitis	
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection[4] ENREF_4		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lymphocyte count decreased		
	Neutrophil count decreased		

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Platelet count decreased		
	Thyroid stimulating hormone increased		***Thyroid stimulating hormone increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
	Vascular disorders - Other (hemorrhage)[5]		

[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]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the

GASTROINTESTINAL DISORDERS SOC.

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

[5]Hemorrhage is a known consequence of VEGF/VEGFR signaling inhibition. The majority of hemorrhage events reported were mild; however, serious events, defined as symptomatic bleeding in a critical area or organ system (e.g., eye, gastrointestinal tract, genitourinary [GU] tract, respiratory tract, and nervous system) have been reported.

Adverse events reported on cediranib (AZD2171) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that cediranib (AZD2171) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

Note: Cediranib (AZD2171) 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.

7.6 Adverse Events for Commercial Study Agents

Refer to the package insert for detailed pharmacologic and safety information.

7.7 Expedited Reporting of Adverse Events (23-AUG-2022)

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://ctepcore.nci.nih.gov/ctepaers/security/login

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.

7.7.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.

- Supporting source documentation is requested by the IND Sponsor for this study (CTEP/DCTD) and NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-230-0159 and to NRG Regulatory Affairs at 215-854-0716.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as “an action not recommended” must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the “NOT recommended” assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.7.2 Expedited Reporting Requirements for Adverse Events

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2] (FOR ARMS II, III, and IV)

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="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

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

Effective Date: May 5, 2011

7.7.2.1 Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1,2] (FOR ARM I ONLY)

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.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

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 agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.7.3 Reporting to the Site IRB/REB

Investigators will report unanticipated problems to NCI CIRB according to the NCI CIRB SOPs.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be

provided.

7.7.4 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.

7.7.5 Pregnancy

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

8. REGISTRATION AND STUDY ENTRY PROCEDURES

Investigator and Research Associate Registration with CTEP (25-JUL-2023)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at

https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.
.

RCR utilizes five person registration types.

- Investigator (IVR) – MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) – advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (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)	✔	✔	✔		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;
- Selection as the treating, credit, or or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task 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.

Refer to the NCI RCR page on the CTEP website for additional information. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures (23-AUG-2022)(25-JUL-2023)

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.

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

IRB Approval:

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (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 (SSW) for Local Context 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 for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB

Signatory Institution(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements for Protocol NRG-GY023 Site Registration

Additional site 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);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US Sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

8.1.1 Downloading Site Registration Documents

Download the site registration forms from the NRG-GY023 page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org)
- Click on Protocols in the upper left of the screen
  - Enter the protocol # NRG-GY023 in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select NRG, and protocol # NRG-GY023.
- Click on *Documents, Protocol Related Documents*, *and* use the *Document Type* filter and select Site Registration to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section of the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and

describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

Submitting Regulatory Documents:

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

To access the Regulatory Submission Portal log in to the CTSU members' website go to the Regulatory section and select Regulatory Submission. **(27-AUG-2021)**

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org 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 site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

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

8.2 Patient Enrollment (23-AUG-2022)(25-JUL-2023)

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 Lead Protocol Organization (LPOs) registration/randomization systems or 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type; **(27-AUG-2021)**
- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and

- Have an approved site registration for a 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 Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please 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.

9. DRUG INFORMATION

9.1 Investigational Study Agent: Durvalumab (MEDI4736) (NSC# 778709)

9.1.1 Other Names: Imfinzi™

Classification: Anti-PD-L1 Mab

Molecular Weight: ~ 149 kDa

Mode of Action: Durvalumab (MEDI4736) inhibits binding of programmed cell death ligand 1 (PD-L1) to PD-1 and CD80. In-vitro studies demonstrate that durvalumab (MEDI4736) relieves PD-L1-mediated suppression of human T-cell activation. Durvalumab (MEDI4736) does not trigger antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity in cell-based functional assays.

9.1.2 Description: Durvalumab (MEDI4736) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody.

9.1.3 How Supplied: Durvalumab (MEDI4736) is supplied by AstraZeneca, and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Durvalumab (MEDI4736) injection is a clear to slightly opalescent, colorless to slightly yellow solution for intravenous use. Each vial contains 500 mg of durvalumab (MEDI4736) in 10 mL of solution. Each 1 mL of solution contains 50 mg of durvalumab (MEDI4736) and is

formulated in: L-histidine (2 mg), L-histidine hydrochloride monohydrate (2.7 mg), α,α-trehalose dihydrate (104 mg), polysorbate 80 (0.2 mg), and Water for Injection, USP.

9.1.4 Preparation: Durvalumab (MEDI4736) solution for infusion must be diluted prior to administration.To prepare the infusion solution add the dose volume of durvalumab (MEDI4736) to an infusion bag containing 0.9% Sodium Chloride Injection or Dextrose 5% in Water Injection, USP and mix by gentle inversion to ensure homogeneity of the dose in the bag. The final concentration must be between **1 mg/mL to 15 mg/mL**.

Infusion bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride.

9.1.5 Storage: Store intact vials between 2-8°C (36-46°F). Do not freeze. Protect from light by storing in the original box.

If a storage temperature excursion is identified, promptly return durvalumab (MEDI4736) to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.6 Stability: Refer to the package label for expiration.

Total in-use storage time from needle puncture of durvalumab (MEDI4736) vial to start of administration should not exceed 8 hours at room temperature or 24 hours at 2-8°C (36-46°F). Prior to the start of the infusion, ensure that the bag contents are at room temperature (approximately 25°C) to avoid an infusion reaction due to the administration of the solution at low temperatures.

9.1.7 Route of Administration: IV infusion

9.1.8 Method of Administration: Infuse over approximately 60 minutes using an infusion set containing a 0.22 or 0.2 µm in-line filter. No incompatibilities between durvalumab (MEDI4736) and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed. Flush the IV line with a volume of IV bag diluent equal to the priming volume of the infusion set used at the completion of infusion. Do not co-administer other drugs through the same infusion line.

9.1.9 Patient Care Implications: Refer to the protocol for information on evaluation and management of potential immune-related adverse events.

9.2 Olaparib (AZD2281) (NSC# 747856)

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

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

9.2.3 Classification: PARP inhibitor

9.2.4 CAS Registry Number: 763113-22-0

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

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

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

9.2.8 Description: crystalline solid

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

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

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

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

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

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

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

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

9.2.13 Potential Drug Interactions: *In vivo* data indicate that CYP3A4/5 is important for olaparib

metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

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

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

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

Patients who are taking warfarin may participate in this trial; however, it is recommended that international normalised ratio (INR) be monitored carefully at least once per week for the first month, then monthly if the INR is stable. Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with olaparib and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (e.g apixaban and rivaroxaban) if possible.

9.2.14 Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least one (1) month after the last dose of olaparib. It is not known whether olaparib is found in seminal fluid, so as a precaution, male study participants must use a condom during treatment and for three (3) months after the last dose and should avoid fathering a child or donating sperm during this same time period. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

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

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

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

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

9.3 Cediranib (NSC# 732208)

9.3.1 4-[(4-Fluoro-2-methyl-1H-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1- yl)propoxy] quinazoline maleate

9.3.2 **Other Names:** cediranib maleate, AZD2171 maleate

9.3.3 **Molecular Formula:** $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$ **M W:** 566.59 (maleate salt), 450.52 (free base)

9.3.4 **Approximate Solubility:** The aqueous solubility of cediranib (AZD2171) is 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.76 mg/mL for the maleate salt (distilled water, at 25°C).

9.3.5 **Mode of Action:** Cediranib (AZD2171) is a highly potent tyrosine kinase inhibitor of all three vascular endothelial growth factor receptors (VEGFR-1, -2 and -3). Inhibition of VEGF signaling leads to inhibition of angiogenesis, neovascular survival and vascular permeability. Pre-clinical tumor models show that cediranib (AZD2171) reduces micro-vessel density and metastasis, indicating that it limits tumor growth.

9.3.6 **How Supplied:** Astra-Zeneca supplies and CTEP, NCI, DCTD distributes cediranib (AZD2171). The agent is available as beige, round, biconvex, film-coated tablets containing 15 mg, and 20 mg of cediranib (AZD2171) free base. The 15 mg and 20 mg tablets are 7 mm and 8 mm in diameter, respectively. Each high-density polyethylene bottle contains 35 tablets.

In addition to the active pharmaceutical ingredient, tablet excipients include mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate with a film coat containing hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

9.3.7 **Storage:** Store intact bottles at controlled room temperature 20°C to 25°C (68 to 77°F).

If a storage temperature excursion is identified, promptly return cediranib (AZD2171) to room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.3.8 Stability: Stability studies are ongoing. Dispense cediranib (AZD2171) tablets in their original containers. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration.

9.3.9 Route and Method of Administration: Oral. Cediranib (AZD2171) tablets should be taken either one hour before or two hours after meals.

If the study sponsor determines appropriate, cediranib tablets may be administered as a dispersion in plain water. Liquids other than non-carbonated water should not be used and the tablets should not be crushed or ground. The following procedure is recommended by the manufacturer for patients who can swallow liquids:

Drop the appropriate dose of cediranib tablet/s into a glass containing 50-60 mL non-carbonated water. Stir the tablet/s until dispersed in the water, about 10 minutes (no crushing). Swallow the liquid immediately after dispersion is completed. Any residue in the glass is mixed with a half glass of water and swallowed.

9.3.10 Potential Drug Interactions: Cediranib (AZD2171) clearance is primarily mediated by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UPDGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that cediranib (AZD2171) is a substrate for P-glycoprotein (P-gp), but not breast cancer resistance protein (BCRP). Since clinically relevant induction or inhibition of FMO enzymes is uncommon**,** use caution in patients taking concomitant medications that are strong inhibitors (e.g. ketoconazole) or strong inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's Wort) of UPDGT1A4 or P-gp in particular. If chronic concomitant administration of strong inducers or inhibitors is unavoidable, consult the protocol document and/or the principal investigator before making any dose adjustments.

In vitro studies using hepatic cultures show that cediranib (AZD2171) did not inhibit CYP 1A2, 2A6, 2C8, 2C9, 2C19 and 2E1 and showed no induction of CYP 1A2, 2B6 and 3A4/5. It did weakly inhibit CYP 2D6 and 3A4/5, but this inhibition not expected to cause any clinically relevant drug interactions. The possibility that cediranib (AZD2171) may induce gastrointestinal CYP3A and UPDGT enzymes cannot be excluded; therefore the efficacy of hormonal contraceptives may be reduced. Advise women study participants to use an additional non-hormonal contraceptive method.

In vitro studies show that cediranib (AZD2171) is a weak inhibitor of BCRP, P-gp, OATP1B1, OATP1B3, OCT2,MATE1, UGT isoforms 1A1, 1A4 and 2B7. Use caution in patients who are taking concomitant medications that are sensitive substrates although clinically relevant inhibition of any of these is considered unlikely. *In vivo* studies show that cediranib (AZD2171) could increase exposure of drugs like metformin by inhibiting renal tubular transporter MATE2-K, but this is thought to be infrequent and mild in severity. Cediranib is not an inhibitor of OAT1 or OAT3.

Cediranib (AZD2171) is approximately 95% bound to human plasma proteins, with

human serum albumin and α1-acid glycoprotein accounting for most of this binding. Use caution in patients taking concomitant medications with narrow therapeutic ranges that are also highly protein-bound.

Oral anticoagulants are not absolutely contraindicated during treatment with AZD2171 (cediranib); however, use cediranib (AZD2171) with caution and increase monitoring in patients while on study. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

9.3.11 Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing. For patients already enrolled onto the protocol, the manufacturer recommends holding cediranib (AZD2171) for 2 weeks prior to surgery and restarting when the surgical wound is healed. Protocol exclusion criteria should include patients who have had major thoracic or abdominal surgery within 2 weeks prior to start of study or patients with any surgical incision that is not fully healed.

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for at least 6 weeks after the last dose of cediranib (AZD2171). The efficacy of hormonal contraceptives may be reduced while receiving cediranib and an additional non-hormonal method should be considered. Men study participants should use a condom while receiving cediranib and for at least one week after the last dose. Refer to the protocol document for specific guidance.

9.4 Commercial Agent—Paclitaxel (NSC# 673089)

9.4.1 Formulation:
Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi-dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

9.4.2 Storage/Stability
Storage: Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

Stability: Commercially available paclitaxel will be labeled with an expiration date. All solutions of paclitaxel exhibit a slight haziness directly proportional to the concentration of drug and the time elapsed after preparation, although when prepared as described below, solutions of paclitaxel (0.3-1.2 mg/ml) are physically and chemically stable for 27 hours.

9.4.3 Preparation: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room

lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions. Patients who experience severe hypersensitivity reactions to paclitaxel may be re-challenged with the drug.

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

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.5 Commercial Agent: Topotecan (NSC# 609699)

9.5.1 Formulation:

Topotecan is a cell cycle specific inhibitor of the nuclear enzyme topoisomerase I. It has a mean half-life of approximately three hours. Topotecan's metabolism and clearance are complex but it is estimated that approximately 40% of the drug undergoes renal clearance.

9.5.2 Supplier/How Supplied:

Topotecan is commercially available and is supplied in a sterile form for intravenous use only.

- **Topotecan for Injection (lyophilized powder)** is available generically as a sterile, lyophilized, buffered, light yellow to greenish powder available in single use vials containing topotecan hydrochloride equivalent to 4 mg of topotecan as the free base, with mannitol 48 mg and tartaric acid 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the product pH. Available products do not contain an antimicrobial preservative; thus any unused product should be discarded within 24 hours of initial vial entry.
- **Topotecan Injection (solution)** is available generically in individually-packaged single-use vials containing a sterile, non-pyrogenic, clear, yellow to yellow-green solution of topotecan HCl equivalent to 4 mg of topotecan as the free-base at a concentration of 1 mg/mL.

9.5.3 Solution Preparation:

Topotecan for Injection (lyophilized powder) reconstitution:

- Reconstitute lyophilized topotecan HCl with 4 mL sterile Water for Injection, USP (SWFI), to produce a yellow to yellow-green solution with concentration equal to 1 mg/mL and a pH within the range, 2.5 – 3.5.
- Dilute an amount of drug appropriate for a patient's dose in 50 – 250 mL of either 0.9% Sodium Chloride Injection (0.9%NS) or 5% Dextrose Injection (D5W), USP.

Topotecan Injection (solution) reconstitution:

- Each milliliter of solution contains topotecan hydrochloride equivalent to 1 mg of topotecan (free base), with 5 mg tartaric acid, NF, and SWFI. Hydrochloric acid and/or sodium hydroxide may be added to adjust product pH within the range 2.6 – 3.2.
- Dilute an amount of Topotecan Injection (1 mg/mL) appropriate for a patient's dose in a minimum volume of 50 mL of either 0.9% Sodium Chloride Injection (0.9%NS) or 5% Dextrose Injection (D5W), USP.

9.5.4 Storage/Stability:

Topotecan for Injection (lyophilized powder) storage and stability:

- Store intact vials protected from light in the original cartons at controlled room temperature between 20° – 25°C (68° – 77°F).
- After reconstitution with SWFI, vials should be used immediately.
- After dilution with 0.9% NS or D5W, solutions prepared with Topotecan Injection are stable for at least 24 hours when stored at 20° – 25°C under ambient lighting conditions.

Topotecan Injection (solution) storage and stability:

- Store intact vials under refrigeration at 2° – 8°C (35.6° – 46.4°F) and protected from light in the original packaging carton.
- After dilution with 0.9% NS or D5W, solutions prepared with Topotecan Injection are stable for 24 hours when stored at 20° – 25°C (68° – 77°F) under ambient lighting.

9.5.5 Adverse effects:

- Hematologic: thrombocytopenia, leukopenia, anemia, neutropenia
- Gastrointestinal: nausea and vomiting, mucositis, diarrhea
- Skin: rash
- Other: alopecia, fever, flu-like symptoms

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.6 Commercial Agent: Pegylated Lipomosal Doxorubicin (PLD)

Pegylated liposomal doxorubicin (PLD) is commercially available. All commercially available sources are allowed including:

- Generic PLD (http://www.caraco.com/outserts/Doxorubicin%20HClLip.pdf)
- Lipodox ® (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203263lbl.pdf)
- Doxil ® (http://www.doxil.com/assets/DOXIL_PI_Booklet.pdf)

Refer to the PLD package insert (Doxil, Lipodox™) for the most complete and current information on the following:

9.6.1 Formulation:
PLD (doxorubicin HCl liposome injection) is supplied as a sterile, translucent, red liposomal dispersion in 5 mL (Lipodox only), 10 mL, or 30 mL glass, single-use vials. Each vial contains doxorubicin HCl at a concentration of 2 mg/mL.

9.6.2 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.

9.6.3 Preparation:
PLD doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. 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.
- Do not use in-line filter.

9.6.4 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.

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

9.6.6 Supplier: Commercially available from Ortho Biotech Products, LP Raritan, NJ (DOXIL) and Caraco Pharmaceutical Laboratories Ltd, Detroit, MI (Lipodox).

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

Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

9.7 Agent Ordering and Agent Accountability

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

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

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

9.7.1 Investigator Brochure Availability

The current versions of the durvalumab, olaparib, and cediranib IB(s) 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.

9.7.2 Agent Accountability

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

Store and maintain separate NCI Investigational Agent Accountability Records for each study participant and ordering investigator on this protocol.

9.7.3 PMB Useful Links and Contacts

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

9.7.4 Blood Pressure Cuffs

A patient who is randomized to Arm II, II or IV will be given a blood pressure cuff. Blood pressure cuffs that are supplied for this study, are only to be used for this study.

9.7.4.1 Supply and Distribution: Blood pressure cuffs will be supplied and distributed by VWR. Each kit contains a blood pressure monitor (which includes standard size cuff), an adaptor and a large size cuff. Kits will be shipped in the original manufacturer's packaging.

9.7.4.2 Ordering Instructions: No starter supplies are available. Sites are permitted to order a maximum of 10 Blood Pressure kits at a time for enrolled patients in cediranib-containing arms (Arms II, III, and IV). To obtain the kits, please complete the "Shipment Authorization Form" and email to Lisa Rutter at lisa.rutter@vwr.com and also include Lucy Andrews (lucy.andrews@vwr.com) and Stacey Brackley (stacey.brackley@vwr.com). The form is available on the CTSU website. Please allow 72 hours to process and ship orders. If request is received at 4:30pm UK time, processing time will be 3 days beginning the following day.

10. PATHOLOGY/BIOSPECIMEN

10.1 Central Pathology Review Guidelines

Not applicable

10.2 Biospecimen Selection for Integral Biomarker Testing
Not applicable

10.3 Biospecimen Selection for Integrated Biomarker testing
Not applicable

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

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

Required Biospecimen (Biospecimen Code)	Collection Time Point	Sites Ship To
FFPE TUMOR TISSUE ***(Submit one of the following – Listed in order of preference)***		
FFPE Recurrent Primary or Recurrent Metastatic Tumor (FRP01 or FRM01)[1] Block must be submitted[2]	Prior to study treatment	NRG Oncology BB-Columbus within 8 weeks of registration[3]
FFPE Persistent Primary or Persistent Metastatic Tumor (FPP01 or FPM01)[1] Block must be submitted[2]		
FFPE Primary or Metastatic Tumor (FP01 or FM01)[1] Block must be submitted[2]	Prior to all treatment	
BLOOD BIOSPECIMENS		
Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)	Prior to study treatment	NRG Oncology BB-Columbus the day collected[3]

1 A copy of the corresponding pathology report must be shipped with all tissue biospecimens sent to the NRG BB-Columbus.
2 Only blocks will be accepted. Please provide Appendix XII to your pathologist.
3 NRG Oncology BB-Columbus / Protocol NRG-GY023, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

10.4.2 Optional Biospecimen Submissions
Not applicable

10.5 Biospecimen Selection for Exploratory Biomarker Testing
Biomarker 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.

10.5.1 PD-L1 and Tumor Infiltrating Lymphocyte Immunohistochemistry
Upon approval, the NRG Biospecimen Bank-Columbus will fresh-cut unstained sections of FFPE tumor for distribution to TBD for PD-L1 and tumor infiltrating lymphocyte (TIL) immunohistochemistry (IHC).

10.5.2 Homologous Recombination Deficiency

Upon approval, DNA extracted from whole blood and formalin-fixed, paraffin-embedded (FFPE) tumor will be batch shipped by the NRG BB-Columbus to Dr. Elizabeth Swisher for BROCA-HR testing.

Special Note Regarding Genetic Testing: Given the potential clinical implications conferred by detecting a germline mutation in one of these proven cancer genes, the following disclosure procedure articulated by the American College of Medical Genetics and Genomics will be followed.

1. For each subject with a clinically actionable result from BROCA sequencing, the testing laboratory will contact the NRG study PI at the enrolling institution to notify them that a research test result of potential clinical importance has been identified in one of their study participants. Please include the mutation in the genetic counselor's report and place a copy of the report in the research record.
2. The PI at the enrolling institution will be responsible for contacting the study participant to inform them that study-related research has uncovered genetic information that might affect their clinical care. Each participant can then:
    a. Elect not to receive the information, which will be retained by the enrolling physician in the event that the participant changes their mind at a later date.
    b. Elect to receive the information, in which case pre-test counseling should be provided prior to clinical testing of a freshly drawn blood sample. After being counseled, the patient may (i) decide not to undergo clinical testing for the mutation identified under research, or (ii) decide to undergo clinical testing, in which case a new blood sample will be collected at the enrolling site and shipped directly to the CLIA-approved laboratory for mutation confirmation at no cost to the patient. The clinical genetic test result will be returned to the clinicians involved in counseling and managing this aspect of the patient's care and it will be their responsibility to disclose the results to the patient.

10.6 Banking Biospecimens for Future Research

Biomarker 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.

Details regarding the banking and use of biospecimens for future research can be found in Appendix X.

11. SPECIAL STUDIES (NON-TISSUE)

Not Applicable

12. ASSESSMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

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

guideline (version 1.1). [Eur J Ca 45:228-247, 2009] 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.

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 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.

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.

12.2 Response Criteria

Determination of response should take into consideration all target (See 12.2.1) and non-target lesions (See 12.2.2).

12.2.1 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).

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.

12.2.2 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).

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).

12.2.3 Evaluation of Best Overall Response

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

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

Target Lesions	Non-Target Lesions	New Lesions*	Time Point Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD**	Yes or No	PD
Any	Any	Yes	PD

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

** 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	New Lesions*	Time Point Response
CR	No	CR
CR	No	Non-CR/non-PD*
Non-CR/non-PD	No	Non-CR/non-PD*
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	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

12.2.4 Best Overall Confirmed Response

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. Therefore, for GY023, confirmation of response is not required.

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.

12.3 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.

12.4 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. Patients who are alive without documentation at the time of analysis will censored on the date of last tumor assessment. Disease progression will be defined using RECIST v1.1 criteria (Section 12.2), as determined by the treating physician.

12.5 Overall Survival

Overall Survival (OS) is defined as the duration of time from study entry to date of death from any cause. A subject who has not died will be censored on the date that they were last known to be alive.

13. DATA AND RECORDS

13.1 Data Submission/Data Reporting (23-AUG-2022)(25-JUL-2023)

Medidata Rave is the 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:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or RAVE SLA role must have at a minimum an Associate (A) registration type.

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

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory Application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in

the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right-corner of the iMedidata screen. 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 eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; 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 replace the eLearning link under under the study name.

Site staff who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application 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 or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting. **Sites must initiate all AEs for this study in Medidata Rave.**

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period is used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational agent/intervention are collected using the Late Adverse event form.

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

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

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

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form (i.e., checking the

box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited reports in CTEP-AERS.

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

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

- Study specific documents: *Protocols > Documents> Protocol Related Documents>Adverse Event Reporting*; *and*
- Additional resources: Resources > *CTSU Operations Information> User Guides & Help Topics*.

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

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

Data Quality Portal

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

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

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data vis direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice

a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

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 for information about expedited and routine reporting.

DMU Light Monitoring

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.htm).

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

This is as a 4-arm randomized phase II study to assess whether the experimental arms provide superior efficacy relative to the standard of care (SOC). The design includes an interim futility when about 60% information is available in any pair of the SOC arm and one of the experimental arms. The four treatment arms are defined in Section 5.1. **(23-AUG-2022)**

The randomization procedure will assign each experimental arm to 2 patients, for every 1 patient randomized to the SOC arm. The randomization procedure tends to balance the

treatment allocation within patient-level stratification factors. The randomization will be stratified by:

1) Any prior immune checkpoint inhibitor (Yes/No)
2) Any prior PARP inhibitor (Yes/No)

A web-based enrollment procedure will be used to register patients onto the study. Immediately after a subject has been successfully enrolled, one of the study regimens will be randomly assigned (for this study the date of enrollment is equivalent to the date of randomization). The study treatments will be sequentially drawn from pre-allocated blocks of randomly permuted treatments, which are created for each stratum. The treatment assignments will be revealed to institutions and patients after registration is complete.

14.2 Study Endpoints

Primary Endpoint: Progression Free Survival (PFS), as defined in Section 12.4. The following censoring rules will also be applied:

1) Patients who are alive without documentation of disease progression at the time of analysis will censored on the date of last tumor assessment.
2) Patients who initiate a non-protocol anticancer therapy will be censored on the date of her last assessment prior to beginning that therapy
3) Patients who have no post-enrollment assessments will be censored 1 day after enrollment

Secondary Endpoints

1) Objective Response Rate (ORR), quantified as the binomial proportion of patients with measurable disease at enrollment who have a Best Overall Response of CR or PR, as defined in Section 12.2
2) Duration of Response is defined in Section 12.3
3) Overall Survival, as defined in Section 12.5
4) Safety data will be summarized for all treated subjects. All adverse events, including severe adverse events (SAEs) and treatment-related adverse events, will be categorized and graded for severity according to NCI CTCAE v 5.0.

14.3 Primary Objectives Study Design

The primary objective is to assess whether of the experimental regimens provide superior efficacy (PFS) relative to the standard of care. The specific hypotheses are described below.

14.3.1 Primary Hypothesis and Endpoints

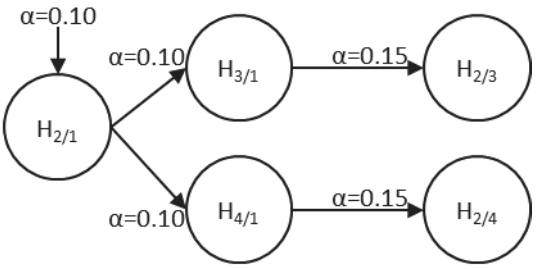
The null and alternative hypotheses for comparing the PFS hazards of treatment arms (i,j) are:

$$H0_{i/j}: \Delta_{i,j} = \frac{\lambda_i}{\lambda_j} \geq 1.0 \text{ vs } HA_{i/j}: \Delta_{i,j} < 1.0$$

where (λ_i, λ_j) are the PFS hazards in arms (i,j) respectively, and $\Delta_{i/j}$ is the corresponding hazard ratio. All hypotheses are assessed with one-sided log-rank tests.

14.3.2 How Primary Endpoints Will Be Analyzed

The null hypotheses are rejected for the superiority of arm(i) over arm(j). The following diagram shows the hypothesis testing strategy.



Arm	Treatment
1	SOC non-platinum chemo (reference)
2	Durvalumab+Olaparib+Cedirinib
3	Durvalumab+Cedirinib
4	Olaparib+Cedirinib

The first gatekeeping hypothesis compares the triplet arm(2) to the SOC arm(1), rejecting at α level =0.10. If this test fails to reject, formal testing of the other hypotheses will stop. If this test rejects, the doublet arms (3) and (4) are separately compared to the SOC arm(1), each test rejecting at α level =0.10. The triplet arm (2) will then be compared to the doublet arms(3,4) that demonstrate superiority over the SOC arm(1), with each test rejecting at α level =0.15. If found to be superior to either doublet, the triplet arm will be considered interesting for future research. If one test fails to reject, arms demonstrating superiority on previous tests in the hierarchy will be considered interesting for future research.

The primary analyses will be based on a stratified logrank test, including all patients enrolled onto the study regardless of compliance to their assigned study regimen. Patients will be grouped by their randomized treatment for intention-to-treat analyses (ITT). Treatment hazard ratios and 90% confidence intervals will be estimated using a proportional hazards model specified with a main-effect for the randomized treatment assignment (experimental ref: SOC) and stratified by the randomization stratification factors.

The final analysis will be done when at least 18 PFS events are observed in the SOC Arm (which is the expected number to occur with 47 events total for each $H_{i/1}$ comparison when the hazard ratio is $\Delta_{i/1} = 0.50$. If warranted, the triplet arm(2) comparisons to doublet arms(3,4) that are superior to the SOC will be done at this time.

A proportional hazards model will be used to estimate the treatment hazard ratios and corresponding confidence interval, after adjusting for the patients' stratification values. Time to event endpoints will be presented by Kaplan Meier methods. Product-limit methods will be used to estimate the cumulative distribution of PFS duration for each of the study treatments.

14.3.3 Sample Size and Power Calculations:

Total accrual of at least 164 patients is expected. When accrual matures, 23 patients are expected in the SOC arm, and 47 in each experimental arm.

For experimental arm comparisons to the SOC arm ($\Delta_{i/1}$ i ϵ {2,3,4}) with one-sided α=0.10, a total of 47 PFS events has power=0.80 to detect a hazard ratio of $\Delta_{i/1}$ = 0.50.

The design parameters are based on the following piecewise-hazard assumptions for the SOC arm, obtained from control arm of the AURELIA trial[48].

Months from Enrollment	Proportion Alive and Progression Free
0	100
1.5	90
3.4	50
6.0	20
15 and beyond	1.0

If the PFS times are exponentially distributed, and the median PFS is 3.4 months in the SOC arm, a hazard ratio of $\Delta_{i/1}$ =0.50 corresponds to a median PFS of 6.8 months in the experimental arm. The relationship between power and the minimum detectable hazard ratio (HR) is shown in the table below. If the true $\Delta_{i/1}$ is 0.60, the power decreases to 0.61.

HR	Power
0.50	0.80
0.55	0.71
0.60	0.61

14.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study

on an “as needed” basis.

Consent withdrawals are individually reviewed and approved by the study data manager as part of routine data curation processes. Withdrawas and other reasons for discontinuation are summarized and monitored in all routine DMC reporting. If discontinations are frequent enough to potentially jeoprodize the primary objectives, an appropriate course of action will be determined by a blinded, ad hoc committee with representation from the study chair, NRG clinical and statistical leadership, and the sponsor. If deemed necessary by this group, a drafted protocol amendment will be developed and presented to the DMC for input on patient safety.

The design includes an interim futility analysis to occur when a total of 28 PFS events (60% information) are observed in any pair of arm(1) and one of the experimental arms. This is expected to occur approximately 11 months after starting accrual. If the HR ($\Delta_{i/1}$ i ϵ {2,3,4}) estimate is >0.87, consideration will be given to dropping arm (i) for futility. The SOC arm(1) will not be dropped unless all experimental arms demonstrate futility. The probability of futility for an experimental arm is 0.66 under the null hypothesis, and 0.09 under the alternative hypothesis (i.e., 0.09 of the 0.20 beta is spent at the interim analysis). The interim analysis results will be examined by the NRG Oncology Data Monitoring Committee. The decision to terminate accrual to an arm may include consideration of toxicities, treatment compliance, and progression-free survival and other endpoints, and results from external studies.

If the study is still accruing patients, accrual will not be suspended for the interim analysis.

14.5 Accrual/Study Duration Considerations

With an accrual rate of 10 eligible patients per month (1.3 patients per month for the SOC arm, 2.9 for each experimental arm), a sample size of 164 patients will accrue over 16.4 months. At this time, 23 patients are expected in the SOC arm, and 47 in each experimental arm. A follow-up period of 1.0 month should provide the needed number of events. Total study duration is estimated to be 17.4 months.

14.6 Gender/Ethnicity/Race Distribution

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	2	0	0	0	2
Asian	10	0	0	0	10
Native Hawaiian or Other Pacific Islander	1	0	0	0	1

Black or African American	10	0	0	0	10
White	132	0	6	0	138
More Than One Race	0	0	3	0	3
Total	155	0	9	0	164

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

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APPENDIX I-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 II – 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.

APPENDIX III-GENERAL THERAPY GUIDELINES

- 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).

- For weekly regimens, it will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window," for example; "Day 8 chemotherapy" can be delivered on Day 7, Day 8, or Day 9 and "Day 15 chemotherapy" can be given on Day 14, Day 15, or Day 16.

- Chemotherapy doses can be "rounded" according to institutional standards without being considered a protocol violation (most institutions use a rule of approximately +/- 5% of the calculated dose).

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

APPENDIX IV-CTEP COLLABORATIVE AGREEMENTS LANGUAGE

The agent supplied by CTEP, DCTD, NCI used in this protocol is 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:

   E-mail: 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 V-DURVALUMAB (MEDI4736) CLINCAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: NRG-GY023

Study Drug(S): MEDI4736 (durvalumab)

For more information:
1-800-4-CANCER
cancer.gov
clinicaltrials.gov

APPENDIX VI- CEDIRANIB PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #:**	
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	Cediranib (AZD2171)

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

These are the things that your healthcare providers need to know:
Cediranib (AZD2171) interacts with certain enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

	Explanation
CYP isoenzymes	The enzymes in question are CYP 3A4, 2D6, flavin-containing monooxygenase (FMO) and UGT1A4. Cediranib (AZD2171) is metabolized by FMO1, FMO3 and UGT1A4 and may be affected by other drugs that strongly inhibit or induce these enzymes. Cediranib (AZD2171) weakly inhibits CYP 2D6 and 3A4 and may increase levels of affected substrates. Cediranib (AZD2171) may induce gastrointestinal CYP3A and UGT enzymes, therefore potentially reducing the effectiveness of hormonal contraceptives. Cediranib (AZD2171) is 95% protein bound (human serum albumin and alpha-1-acid glycoprotein) and may displace other highly protein-bound drugs. Use caution in patients taking concomitant medications with narrow therapeutic ranges.
Protein transporters	The transport proteins in question are P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Cediranib (AZD2171) requires P-gp to move in and out of cells. Cediranib (AZD2171) inhibits P-gp, BCRP and MATE2-K which may affect the clearance of other drugs that are dependent on these transport proteins.

These are the things that you need to know:
The study drug cediranib, may interact with other drugs which can cause side effects. For this

reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib (AZD2171) inhibits enzymes "CYP 2D6 and 3A4, transport proteins P-gp, BCRP and MATE2-K and is highly protein-bound." These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Cediranib (AZD2171) may potentially reduce the effectiveness of hormonal contraceptives. Please check with your study provider about using contraception while on study treatment.
- Patients receiving Cediranib (AZD2171) are at increased risk of bleeding. If you are receiving anticoagulation therapy, you will be monitored more frequently.
- Make sure your doctor knows to avoid certain prescription medications.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

EMERGENCY INFORMATION	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE
		DRUG INTERACTIONS	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** Cediranib interacts with: CYP 3A4, 2D6, FMO and UGT1A4 which are needed to clear cediranib from the body; transport proteins P-gp, needed to move cediranib in and out of cells; and P-gp, BCRP and MATE2-K needed to clear other drugs from the body. Cediranib must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):** Cediranib (AZD2171)	**Use caution and avoid the following drugs if possible:** ***Hormonal contraceptives*** NIH NATIONAL CANCER INSTITUTE	Your healthcare providers should be aware of any medicines that are "strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib (AZD2171) inhibits enzymes "CYP 2D6 and 3A4, transport protein, P-gp. BCRP and MATE2-K and is highly protein-bound." **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. Version DEC/2019	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

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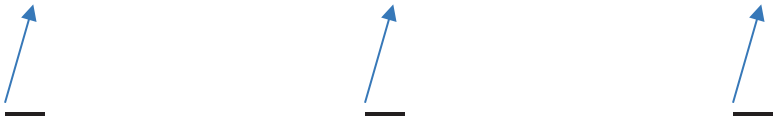

APPENDIX VII- OLAPARIB PATIENT CLINICAL TRIAL WALLET CARD

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #: NRG-GY023

Study Drug(S): olaparib

For more information:
1-800-4-CANCER
cancer.gov
clinicaltrials.gov

APPENDIX VIII-ARM 2 CEDIRANIB AND OLAPARIB PATIENT DRUG DIARY (23-AUG-2022)

Today's Date _____ Cycle # _____
Patient Name _____ Patient Study ID _____

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

CEDIRANIB
Take ____ (number) _____ mg tablets once a day.
Take on an empty stomach 1 hour before taking the morning dose of olaparib.

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

Day	Date	15mg	20mg	AM	Day	Date	100mg	150mg	AM	PM
1	*1/1/2021*	*2*	*0*	*7:00*	*1*	*1/1/2021*	*2*	*0*	*8:00*	*8:00*
1					1					
2					2					
3					3					
4					4					
5					5					
6					6					
7					7					
8					8					
9					9					
10					10					
11					11					
12					12					
13					13					
14					14					
15					15					
16					16					
17					17					
18					18					
19					19					
20					20					
21					21					
22					22					
23					23					
24					24					
25					25					
26					26					
27					27					
28					28					

Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date _____

APPENDIX IX-ARM 3 CEDIRANIB PATIENT DRUG DIARY (23-AUG-2022)

Today's Date _____ Cycle # _____
Patient Name _____ Patient Study ID _____

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

CEDIRANIB

Take __(number) ____mg and __(number) ____ mg tablets once daily. Take on an empty stomach.

Day	Date	15mg	20mg	AM
1	*1/1/2021*	*2*	*0*	*7:00*
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
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14				
15				
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24				
25				
26				
27				
28				

Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date_____

APPENDIX X-ARM 4 CEDIRANIB AND OLAPARIB PATIENT DRUG DIARY (23-AUG-2022)

Today's Date _____ Cycle # _____
Patient Name _____ Patient Study ID _____

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

CEDIRANIB
Take ____ (number) _____ mg tablets once a day.
Take on an empty stomach 1 hour before taking the morning dose of olaparib.

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

Day	Date	15mg	20mg	AM	Day	Date	100mg	150mg	AM	PM
1	*1/1/2021*	*2*	*0*	*7:00*	*1*	*1/1/2021*	*2*	*0*	*8:00*	*8:00*
1					1					
2					2					
3					3					
4					4					
5					5					
6					6					
7					7					
8					8					
9					9					
10					10					
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20					20					
21					21					
22					22					
23					23					
24					24					
25					25					
26					26					
27					27					
28					28					

Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date _____

APPENDIX XI- PATIENT BLOOD PRESSURE DIARY

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

Instructions to the Patient:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, normal blood pressure is 120/80).
2. Record the date, then record your blood pressure twice each day using a home blood pressure monitor.
   - Each morning while you are resting (not while you are active: dressing, making breakfast, etc.)
   - Each evening at bedtime or while you are relaxing during the evening
3. If you take your blood pressure at other times, record the numbers and time under "Other Readings."
4. If your systolic pressure is greater than 140 **OR** your diastolic blood pressure is greater than 90, please contact your local doctor's office at _____ for instructions.
5. Please bring this form to every clinic visit or appointment.

Day	Date	AM Readings	PM Readings	Other Readings (include time)	Day	Date	AM Readings	PM Readings	Other Readings (include time)
1		/	/		15		/	/	
2		/	/		16		/	/	
3		/	/		17		/	/	
4		/	/		18		/	/	
5		/	/		19		/	/	
6		/	/		20		/	/	
7		/	/		21		/	/	
8		/	/		22		/	/	
9		/	/		23		/	/	
10		/	/		24		/	/	
11		/	/		25		/	/	
12		/	/		26		/	/	
13		/	/		27		/	/	
14		/	/		28		/	/	

Patient's Signature: _____ Date: _____

Physician's office will complete this section:

Date of this clinic visit _____

Physician/Nurse's Signature _____ Date _____

APPENDIX XII- ORAL ANTIHYPERTENSIVE MEDICATIONS.

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with cediranib through CYP450. Agent classes are listed in order of preference in the absence of any other compelling indication, such as impaired renal function, proteinuria, etc. Note that each agent's dosing should be maximized before being replaced or adding another agent class.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	Yes (CYP450 unknown)
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	**Yes, but not CYP450**
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 and 2C9 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**
Selective	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate

β Blockers (BB)	**atenolol**	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	CYP 3A4 substrate
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	Yes, but not CYP450
Diuretics	Hydralazine	10 mg four times daily	25 mg four times daily	50 mg four times daily	no
	Hydrochlorothiazide	12.5 mg AM daily	25 mg AM daily	50 mg AM daily	no
	Furosemide	20 mg daily	20 mg twice daily	40 mg twice daily	no
Nitrates	Isosorbide dinitrate ER	40 mg daily	40 mg twice daily	80 mg twice daily	CYP 3A4 substrate
	Isosorbide mononitrate ER	30 mg AM daily	60 mg AM daily	90 mg AM daily	CYP 3A4 substrate
Dihydropyridine Calcium-Channel Blockers (DHP CCB)	nifedipine XL	30 mg daily	60 mg daily	90 mg daily	CYP 3A4 substrate
	amlodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate

APPENDIX XIII– TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES (23-AUG-2022)

1. Obtaining a Bank ID for Translational Science Biospecimens

An NRG Bank ID is automatically assigned once the biospecimen consent questions are completed in Rave. the biospecimen consent questions ae located on the Specimen Consent. The NRG Bank ID will appear at the top of the biospecimen transmittal forms located in the Translational Research Folder in Rave.

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

Please contact Support if you need assistance (Email: support@nrgoncology.org). Do not contact the NRG Biospecimen Bank, as the bank is not responsible for NRG Bank ID assignment.

2. Requesting Translational Science Biospecimen Kits

Biospecimen kits are not provided for this study.

3. FFPE Tissue Shipped to the NRG BB-Columbus

Only one block may be submitted per tissue type. All tissue biospecimens sent to the NRG BB-Columbus must be shipped with a copy of the corresponding pathology report. Redact personally identifiable information, including name, medical record/account numbers, etc. Do not redact the surgical pathology ID number, block number, or collection date. A completed copy of the Pathology Materials Verification Form (Appendix XI) should be provided to your Pathology Department when FFPE materials are requested and must be completed by the person providing the FFPE materials.

3.1 FFPE Biospecimen Requirement

3.1.1 Tumor Tissue Type

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

- **Recurrent (FRP01) or persistent (FPP01) primary and recurrent (FRM01) or persistent (FPM01) metastatic** tumor should be collected prior to the study treatment and is the preferred tumor type.
- **Primary (FP01)** or **metastatic (FM01)** tumor should be collected prior to all treatment.

3.1.2 FFPE Type

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

3.1.3 Labeling FFPE Biospecimens

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

REQUIRED FFPE BIOSPECIMEN LABELING
Bank ID (N # # # # # # # # #)*
NRG ID (X X # # # -GY023- # # # # #)
Biospecimen Code (see section 10)
Collection Date (mm/dd/yyyy)
Surgical Pathology Accession Number
Block Number

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

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

3.1.4 Completing Form TR for FFPE Biospecimens (23-AUG-2022)

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

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

Labeling Whole Blood

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

REQUIRED WHOLE BLOOD BIOSPECIMEN LABELING
Bank ID (N # # # # # # # # #)*
NRG ID (X X # # # -GY023- # # # # #)
Biospecimen Code (WB01)
Collection Date (mm/dd/yyyy)

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

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

4.1 Whole Blood

4.1.1 Collection Time Points

Whole blood should be collected prior to study treatment as per Section 10.4.1.

4.1.2 Collecting Whole Blood

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

collected. If the specimen absolutely cannot be shipped the day it is collected, please contact the NRG BB-Columbus.

5. Submitting Biospecimen Transmittal Forms

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

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

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

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

Retain a printout of the completed form for your records.

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

6. Shipping Translational Science Biospecimens

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

  NRG BB-Columbus / Protocol NRG-GY023
  Nationwide Children's Hospital
  700 Children's Dr, WA1340
  Columbus, OH 43205
  Phone: 614-722-2865
  FAX: 614-722-2897
  Email: BPCBank@nationwidechildrens.org

6.1 FFPE Tissue Shipped to the NRG BB-Columbus

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

Do not ship FFPE tissue for Saturday delivery.

6.2 Whole Blood Shipped to the NRG BB-Columbus

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

6.2.1 Whole Blood Collected in EDTA Tubes

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

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

6.2.1.1 Shipping Whole Blood in EDTA Tubes

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

7. Banking Translational Science Biospecimens for Future Research

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

Note: 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 the Specimen Consent form. At the time of biospecimen selection for project distribution, the most recent consent information will be used.

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

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

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

APPENDIX XIV-BIOSPECIMEN BANK-COLUMBUS PATHOLOGY MATERIALS VERIFICATION FORM

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

REQUIRED FFPE MATERIALS

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

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

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

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

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

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

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

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

Tissue Type: □ Recurrent Primary (FRP01) □ Recurrent Metastatic (FRM01)
□ Persistent Primary (FPP01) □ Persistent Metastatic (FPM01)
□ Primary (FP01) □ Metastatic (FM01)

Site: □ Ovary □ Other, specify _____

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

_____ _____
Name of person preparing materials Date

APPENDIX XV– LETTER TO PATHOLOGISTS

Dear Pathologist,

Your site is a participant in **NRG GY023**, "A randomized phase II trial of triplet therapy (PD-L1 inhibitor, durvalumab, in combination with olaparib and cediranib) compared to olaparib and cediranib or durvalumab (MEDI4736) and cediranib or standard of care chemotherapy in woman with platinum-resistant recurrent epithelial ovarian cancer, primary peritoneal or fallopian cancer who have received prior bevacizumab."

This study includes exploratory biomarker testing, including PD-L1 and tumor infiltrating lymphocyte immunohistochemistry that requires all slides used must be *fresh cut*.

Given the biospecimen requirements for this biomarker testing, **NRG GY023 requires all sites submit FFPE blocks only (i.e., unstained slides will not be accepted).** Blocks may be submitted on a permanent or temporary basis.

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

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

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

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

Sincerely,

Jung-Min Lee, MD
Heather A Lankes, PhD, MPH