For Protocol Amendment #8 to: NRG-GY012

NCI Protocol #: NRG-GY012
Local Protocol #: NRG-GY012

NCI Protocol Version Date: May 23, 2024

This amendment is being submitted in response to an RRA received by Dr. Helen Chen (helen.chen@nih.gov) received on May 9, 2024.

Section	Comment

7.3.4	• Added New Risk:
	  • Less Likely: Cardiac troponin T increased
	  • Rare but Serious: Endocrine disorders - Other (thyroiditis); Hypophysitis; Optic nerve disorder, Nervous system disorders - Other (non-infective encephalitis); Skin and subcutaneous tissue disorders - Other (pemphigoid)
	  • Also Reported on Durvalumab Trials But With Insufficient Evidence for Attribution: Acidosis; Adult respiratory distress syndrome; Alkaline phosphatase increased; Aspiration; Cardiac disorders - Other (valvular vegitation); Cardiac troponin I increased; Cholecystitis; Chronic kidney disease; Cognitive disturbance; Colonic obstruction; Colonic stenosis; Death NOS; Dry mouth; Dysphagia; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Encephalopathy; Esophagitis; Fall; Febrile neutropenia; Gastritis; General disorders and administration site conditions - Other (failure to thrive); General disorders and administration site conditions - Other (general physical health deterioration); Generalized muscle weakness; Hypocalcemia; Hypothermia; Ileal stenosis; Immune system disorders - Other (Giany cell arteritis syndrome); Injury, poisoning, and procedural complications - Other (radiation pneumonitis); Insomnia; Ischemia cerebrovascular; Laryngeal obstruction; Leukocytosis; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myocardial infarction; Neck edema; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (increase in tumor mass); Nervous system disorders - Other (hypoesthesia); Nervous system disorders - Other (neuropathy peripheral); Pain in extremity; Palpitations; Proteinuria; Pulmonary edema; Pulmonary fistula; Respiratory, thoracic and mediastinal disorders - Other (asphyxia); Respiratory, thoracic and mediastinal disorders - Other (fungal pneumonia; Phialemonium spp.); Respiratory, thoracic and mediastinal disorders - Other (granulomatous changes in the lung); Sinus bradycardia; Stroke; Sudden death NOS; Syncope;

	Thromboembolic event; Transient ischemic attacks; Ventricular arrhythmia; Ventricular tachycardia
	
	• Increase in Risk Attribution:
	  • Changed to Less Likely from Also Reported on Durvalumab Trials But With Insufficient Evidence for Attribution: Anemia; Back pain
	  • Changed to Rare but Serious from Also Reported on Durvalumab Trials But With Insufficient Evidence for Attribution: Platelet count decreased
	
	• Deleted Risk:
	  • Also Reported on Durvalumab Trials But With Insufficient Evidence for Attribution: Tumor inflammation; Small intestinal obstruction

ICD	Please see the ICD for additional changes.

Changes made in addition to RRA:

Section	Comment
Title Page	• NCI Version Date is now May 23, 2024 • The Data Manager has been updated to Brianna Williams • Amendment 8 and version date have been added to the Document History box
TOC	• Page numbers have been updated
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
8.2.1	• CTSU language has been updated to agree with current template language
12.1	• CTSU language has been updated to agree with current template language

NRG-GY012

(ClinicalTrials.gov NCT # 03660826)

A Randomized Phase II Study Comparing Single-Agent Olaparib, Single Agent Cediranib, and the Combinations of Cediranib/Olaparib, Olaparib/Durvalumab (MEDI4736), Cediranib/Durvalumab (MEDI4736), Olaparib/AZD5363 (Capivasertib) in Women with Recurrent, Persistent or Metastatic Endometrial Cancer. A Multi-Arm Trial for Women with Recurrent or Persistent Endometrial Cancer **(24-MAY-2021) (08-NOV-2021)**

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

Lead Organization: NRG / NRG Oncology

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

Coordinating Center:
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Protocol Agents (24-MAY-2021)

Agent	Supply	NSC #	IND #	IND Sponsor
Cediranib	CTEP	732208	[redacted]	DCTD, NCI
Olaparib	CTEP	747856	[redacted]	DCTD, NCI
Durvalumab (MEDI4736)	CTEP	778709		DCTD, NCI
AZD5363 (capivasertib)	CTEP	782347		DCTD, NCI

Participating Sites (27-APR-2022)

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

Document History

	Version/Update Date
Amendment 8	May 23, 2024
Amendment 7	July 26, 2023
Amendment 6	April 27, 2022
Amendment 5	November 8, 2021
Amendment 4	August 27, 2021
Amendment 3	May 24, 2021
Amendment 2	June 11, 2019
Amendment 1	January 15, 2019
Activation	August 27, 2018

Lead Organization: NRG / NRG Oncology (24-MAY-2021)(27-APR-2022)(26-JUL-2023)

CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the >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) or CTSURegHelp@coccg.org for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923 or ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. .

The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site (https://www.ctsu.org).

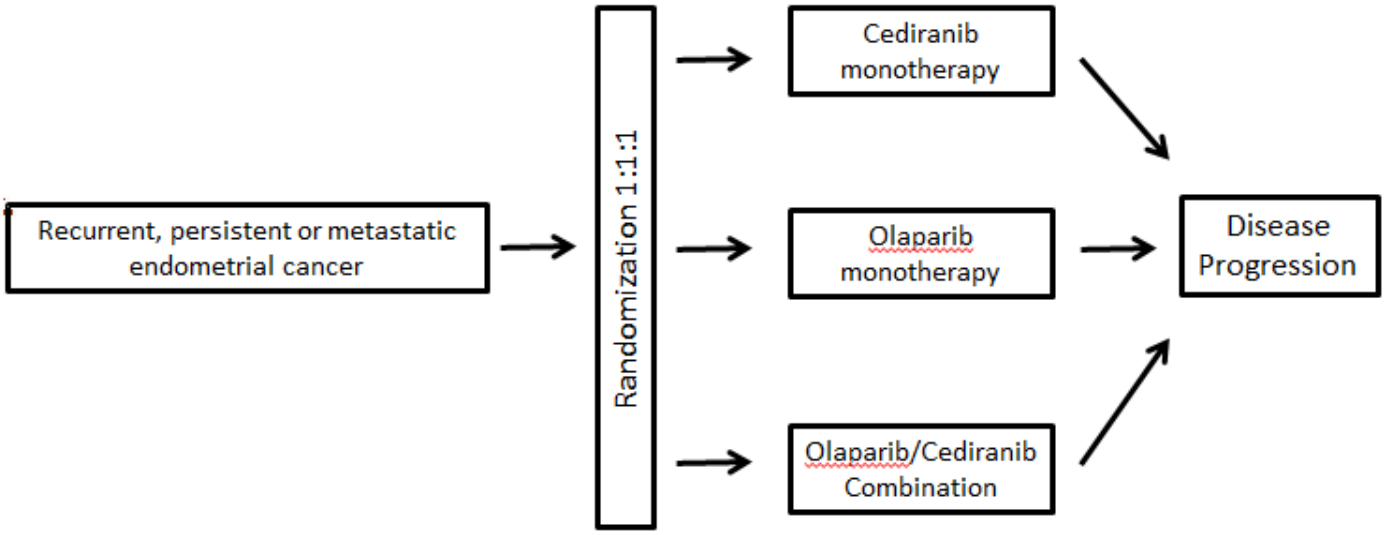
Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.

For clinical questions (i.e. patient eligibility or treatment-related) Contact the Study PI or 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.

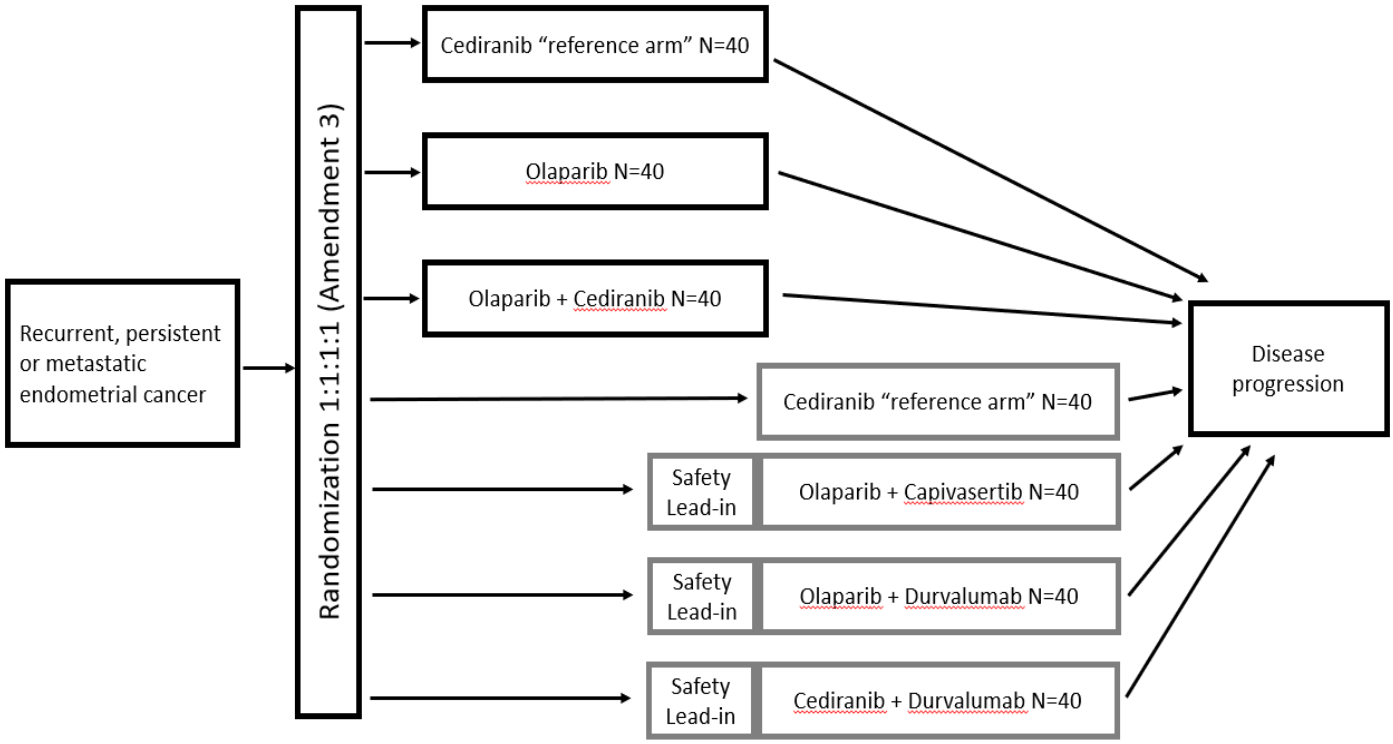
TABLE OF CONTENTS (24-MAY-2021)(27-APR-2022)(26-JUL-2023)(23-MAY-2024)

SCHEMA



Schema changes as of Amendment 3 **(24-MAY-2021)**:

Original schema **Subsequent schema (Amendment 3)**



1. OBJECTIVES

1.1 Primary Objective

To compare the efficacy of single-agent olaparib and the combination of olaparib and cediranib (and potentially other combination arms that may be added by subsequent amendment) versus single agent cediranib as measured by progression free survival (PFS), in patients with recurrent, persistent or metastatic endometrial cancer.

To compare the efficacy of the combination of olaparib and AZD5363 (capivasertib), and the combination of olaparib and durvalumab (MEDI4736), and the combination of cediranib and durvalumab (MEDI4736) versus single agent cediranib as measured by progression free survival (PFS), in patients with recurrent, persistent or metastatic endometrial cancer. **(24-MAY-2021)**

1.2 Secondary Objectives (24-MAY-2021)

1.2.1 To compare the efficacy of single-agent olaparib and the combination of olaparib and cediranib (and potentially other combination arms that may be added by subsequent amendment) versus single-agent cediranib as measured by overall survival (OS) in patients with recurrent, persistent or metastatic endometrial cancer.

To compare the efficacy of the combination of olaparib and AZD5363 (capivasertib), and the combination of olaparib and durvalumab (MEDI4736), and the combination of cediranib and durvalumab (MEDI4736) versus single agent cediranib as measured by overall survival (OS), in patients with recurrent, persistent or metastatic endometrial cancer.

1.2.2 To compare the efficacy of single-agent olaparib and the combination of olaparib and cediranib (and potentially other combination arms may be added by subsequent amendment versus single-agent cediranib as measured by response rate in patients with recurrent, persistent or metastatic endometrial cancer.

To compare the efficacy of the combination of olaparib and AZD5363 (capivasertib), and the combination of olaparib and durvalumab (MEDI4736), and the combination of cediranib and durvalumab (MEDI4736) versus single agent cediranib as measured by response rate in patients with recurrent, persistent or metastatic endometrial cancer.

1.2.3 To assess the safety and tolerability of single–agent cediranib, single-agent olaparib, and the combination of olaparib and cediranib (and potentially other combination arms may be added by subsequent amendment).

To assess the safety and tolerability of the combination of olaparib and AZD5363 (capivasertib), and the combination of olaparib and durvalumab (MEDI4736), and the combination of cediranib and durvalumab (MEDI4736).

Secondary objectives 1.2.4 and 1.2.5 apply to the first three treatment arms only: cediranib alone, olaparib alone, and the combination of olaparib and cediranib. Biomarkers for added treatment arms require either amendment or correlative science proposal submission and secured funding.

1.2.4 To assess if mutations in DNA Homologous Repair Genes (assayed prior to all treatment and prior to the study treatment) are predictive of response to olaparib alone or in combination with cediranib. (**Integrated Biomarker)**

1.2.5 To assess if markers of angiogenesis in serial plasma samples are associated with response to cediranib alone or in combination with olaparib. (**Integrated Biomarker**)

1.3 Exploratory Objectives

1.3.1 To compare the efficacy of the combination of olaparib and cediranib versus single agent olaparib as measured by PFS, response rate and OS, if and only if the combination is superior to the single-agent cediranib arm.

2. BACKGROUND

2.1 Endometrial Cancer (EC)

Endometrial cancer (EC) is the most common gynecologic malignancy in the developed world with 60,050 new cases and 10,470 deaths reported in the United States (US) in 2016 [Siegel, 2016]. Furthermore, with an aging population and rising rates of obesity, the incidence of EC will continue to rise. In the US, if current trends continue, there will be a doubling in the number of women diagnosed with EC by the year 2030 to 122,000 cases per year [Rahib, 2014]. Although the majority of EC are diagnosed when disease is limited to the uterus, up to 25% of cases will recur. For women with advanced or recurrent disease, therapeutic options are limited [Lheureux, 2014]. Frontline chemotherapy for recurrent or metastatic EC is platinum-based, with Protocol GOG-0209 confirming the non-inferiority of carboplatin/paclitaxel (TC) compared to the more toxic doxorubicin-based regimen (doxorubicin, cisplatin, paclitaxel, TAP), where median overall survival (OS) was 32 vs. 38 months for the TC vs. TAP arms [Miller, 2012]. The value of second line chemotherapy is disputed with response rates in the order of 20% and progression free survival (PFS) in the order of months (Lheureux et al., 2014). For low grade tumors, endocrine therapy may be an option, but OS duration remains limited.

The evaluation of a number of molecularly targeted agents in EC has demonstrated modest response rates with some evidence of prolonged disease stabilization Table 1 [Lheureux, 2014]. Currently, activity has been insufficient to result in approval of any targeted agent for use in EC.

STUDY	AGENT	Median PFS (months)
0229B	Thalidomide	1.7
0229C	Gefitinib	1.8
0229D	Lapatinib	1.8
0229E	Bevacizumab	4.3
0229F	Aflibercept	3.3
0229G	Bevacizumab and temsirolimus	5.6
0229H	Selumetinib	2.3
0229I	Brivanib	3.5
0229J	Cediranib	3.6
0229K	Nintedanib	3.3
0229L	Trebanib	2.0
0229N	dalantercept	2.1
0229	OVERALL	2.9

Table 1. A list of the results of the Protocol GOG-0229 series in recurrent or metastatic EC.

Furthermore, the EC patient population trends to the older patient age range and the rates of significant comorbidities including diabetes and obesity are high [Binder, 2016]. These factors need to be considered when developing therapeutic agents for women with EC as they can impact the ability of patients to tolerate treatment.

There is a significant unmet and increasing need for well tolerated therapeutic options in the metastatic and recurrent EC population.

2.2 DNA Repair as a Potential Therapeutic Target in Endometrial Cancer (EC)

The Cancer Genome Atlas (TCGA) identified genomic events that suggest that EC should be susceptible to DNA damaging agents and DNA repair inhibition, DNA-Ri [Kandoth, 2013]. Data from the TCGA and others suggest ARID1A mutations occur in approximately 40%, MSI 11% and PTEN loss in 55% of recurrent metastatic endometrioid EC [Mackay, 2010; Mhawech-Fauceglia, 2014]. ARID1A mutations are also observed in serous like EC in addition to high frequencies of non-silent p 53 mutations in up to 91% of cases [Kandoth, 2013] **Figure 1**. There are also reports suggesting there may be an increased risk for serous-like EC in women with germ line BRCA1 mutation [Shu, 2016].

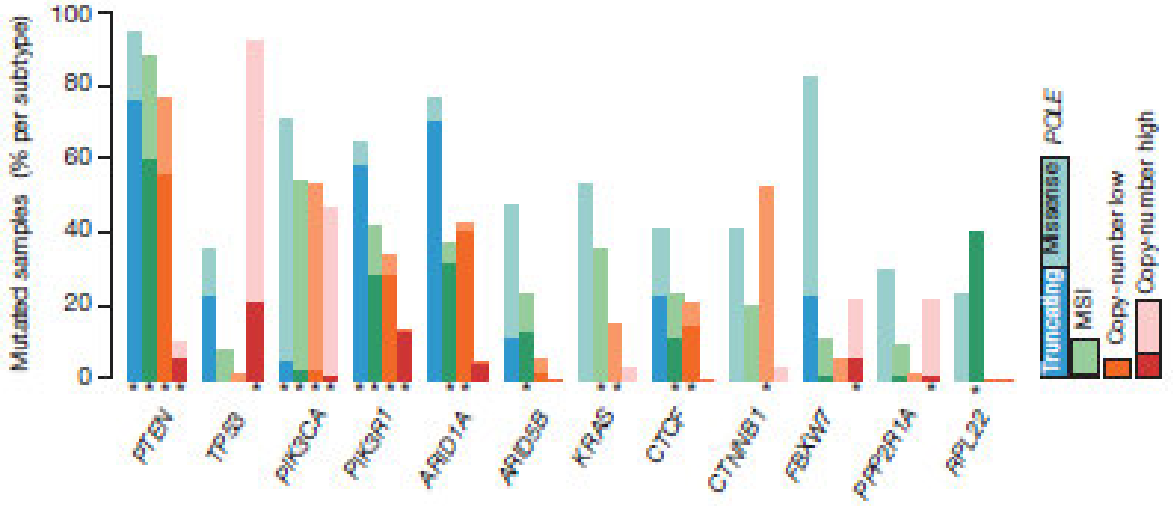


Figure 1: Frequent alteration in DNA repair genes seen in endometrial cancer. [5]

Additional genomic alterations that result in aberrations in the Homologous Recombination (HR) pathway are shown in **Figure 2**. In 137 patients with EC, a higher "HR deficiency (HRD) score" was associated with a worse prognosis [Hansen, 2016].

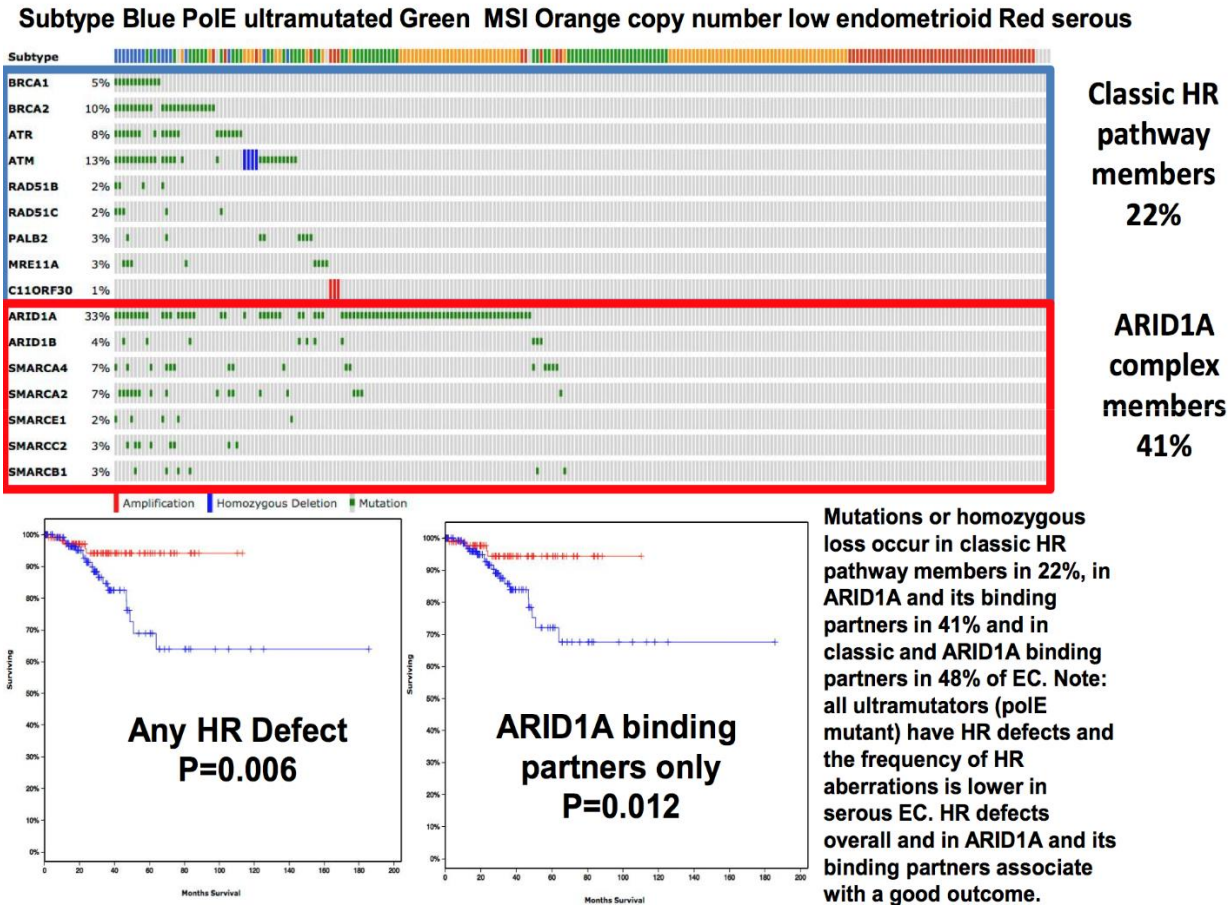


Figure 2: Genomic aberrations in HR pathway in EC (48%) exclusive of PTEN.

The incidence of molecular events in EC associated with DNA repair make targeting this an attractive therapeutic strategy to explore in this disease.

2.3 Olaparib and Endometrial cancer

Olaparib is an orally active poly (ADP-ribose) polymerase inhibitor (PARPi) that has demonstrated efficacy and tolerability in a number of solid tumor types including prostate, pancreatic, and epithelial ovarian cancer (EOC) [Audeh, 2010; Kaufman, 2015; Ledermann, 2014; Mateo, 2015]. Extensive data exist on the safety of this drug in Phase I, II and III trials, and it has FDA approval for the treatment of recurrent EOC [Ledermann, 2012; Pujade-Lauraine, 2017]. Investigators should be familiar with the current olaparib (AZD2281) Investigator Brochure (IB). Treatment is generally well tolerated with the main side effects being anemia, decreased appetite, dizziness, headache, dysgeusia, vomiting, diarrhea, nausea, dyspepsia, and fatigue. Health related quality of life remains high in patients despite long periods of treatment [Friedlander, 2017]. Preclinical data is published, suggesting efficacy for olaparib in EC [Dedes, 2010; Shen, 2015]. These include data suggesting response to olaparib in EC cell lines and mouse models [Hansen, 2016; Miyasaka, 2014]. Clonogenic assays show sensitivity to olaparib varies among EC cell lines, with SF50 values ranging from 8 nM to 2,500 nM. The high ratio (25%) of sensitive cells with SF50 values <100 nM support the investigation of olaparib in women with EC.

Dedes and colleagues documented increased PARP sensitivity in PTEN-deficient EC cell lines compared to cell lines with wild-type PTEN [Dedes, 2010], although subsequent data suggested response might be independent of PTEN status [Miyasaka, 2014]. ARID1A is recruited to DNA breaks through interaction with ATR and is required for normal G2/M checkpoint inhibition; ARID1A loss of function impairs ATR activation by DNA double-strand breaks (DSBs), associated with sensitization to PARP inhibition [Shen, 2015] **Figure 3.** Given the frequency of ARID1A mutation in EC, this suggests investigating olaparib would be a reasonable strategy. Hansen et al reported a significant reduction in tumor weight following olaparib treatment in EC tumor bearing mice. Reduced proliferation and increased apoptosis were observed in cell lines with both a high and lower HRD score although response was most marked in the model with the higher HRD score [Hansen, 2016].

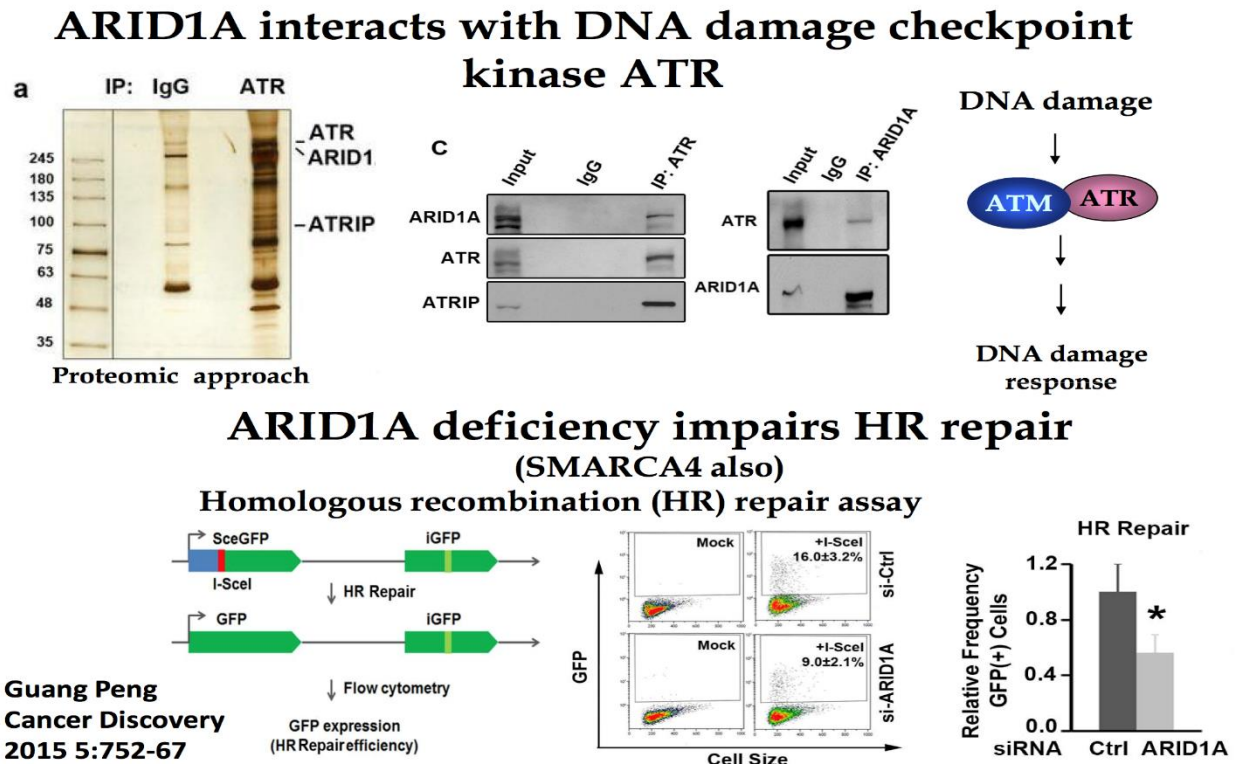


Figure 3: Demonstrating ARID1A deficiency and impairment of HR repair

2.4 Cediranib and Endometrial Cancer

Targeting angiogenesis has been extensively studied in EC [Lheureux, 2014]. A 48-patient phase II study in an unrestricted EC patient population evaluated cediranib, a tyrosine kinase inhibitor that targets vascular endothelial growth factor receptors (VEGFRs), platelet derived growth factor (PDGF) alpha and beta and fibroblast growth factor (FGF) receptor 1, in recurrent or metastatic EC has been completed. This study included all histological subtypes. A partial response was observed in 12.5% of patients and the six-month event free survival was 29%, meeting the protocol set efficacy objectives to warrant further investigation. Response was seen across histological subgroups although the number of serous patients was low (11 patients). Median PFS was 3.65 months with a median OS of 12.5 months. Table 1**,** illustrates this in the context of other agents investigated in the GOG-0229 series of phase II trials. Treatment was generally well tolerated with the most common grade 3 adverse events being: Hypertension (n=16), fatigue (10), and diarrhea (7) [Bender, 2015]. Cediranib is an oral agent, with an attractive mode of delivery compared to the intravenous route required for some other anti-angiogenic agents. Investigators should be familiar with the current cediranib (AZD2171) Investigator Brochure (IB). Single agent cediranib is included in this study to provide a comparator (reference arm) for the other study arms given the challenge of evaluating PFS against historical control. Furthermore, this study includes patients who may have received prior anti-angiogenic therapy, a population who would not have been included in prior phase II studies.

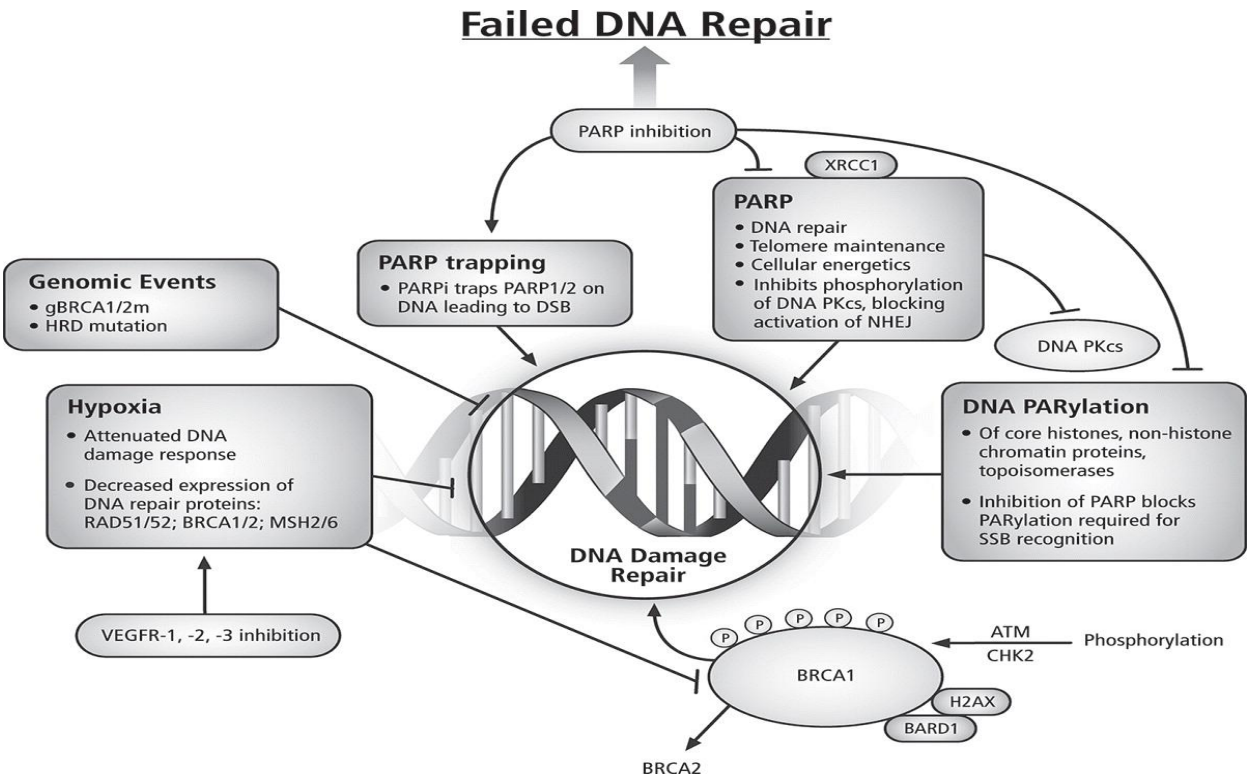


Figure 4: Augmenting DNA damage and repair: potential therapeutic directions [Ivy, 2016].

2.5 Combination of Olaparib and Cediranib

Pre-clinical studies have indicated that angiogenesis inhibitors combined with PARPi can have supra-additive effects in some cell types. In vivo anti-angiogenic effects have been observed with PARPi's and in PARP -1 knockout mice [Tentori, 2007]. In addition, down regulation of HR genes have been observed in hypoxic conditions (contextual synthetic lethality) with enhancement of PARPi sensitivity [Bindra, 2005]**, Figure 4.** Pre-clinically cediranib and olaparib have shown potential synergistic activity in decreasing tumor cell invasion and blood vessel growth. In a recent phase II study in women with platinum sensitive EOC the combination of the oral anti-angiogenic agent cediranib and olaparib exhibited greater efficacy than olaparib alone, and toxicity in this patient population was acceptable. In the subset of patients that were BRCA non-carrier/unknown the median PFS was 5.7 months with olaparib alone and 16.5 months with the combination (HR 0.32, 95% CI 0.14-0.74, p=0.008). Olaparib and cediranib were well tolerated. The most commonly reported grade 3 or 4 toxicities included fatigue 27%, hypertension 41% and diarrhea 23% [Liu, 2014].

Although direct pre-clinical data is lacking for EC for the combination of olaparib and cediranib, based on data in other tumor types, on pre-clinical models suggesting targeting DNA repair in EC is a valid therapeutic direction and on evidence of efficacy for single agent cediranib, investigating this combination in women with EC is warranted.

2.6 Future Combination Strategies

Augmenting DNA damage by targeting multiple parts of the DNA repair process is an attractive potential therapeutic strategy in EC. Whilst targeting angiogenesis in combination with PARP inhibition represents one approach other potential actionable opportunities exist Figure 4. Promising targets include ATM and ATR, and WEE1 and CHEK2 G2 checkpoint kinases [Ivy, 2017; Juvekar, 2012; Hu, 2016]. Other emerging strategies include combining PARP inhibition with anti-metabolic activity of agents such as the phosphor inositol 3 kinase inhibitors. The goal being to take advantage of clinical synthetic lethality resulting in selective tumor cell kill. As this protocol evolves and data on combination strategies targeting DNA repair mature consideration will be given to amending the protocol to allow inclusion of new study arm(s).

Sections 2.7-2.10 have been added as additional combinations of interest **(24-MAY-2021)**

2.7 AZD 5363 (Capivasertib) and Endometrial Cancer

More than 80% of endometrioid endometrial cancers have an aberration in *PTEN*, a tumor suppressor gene that encodes a pivotal phosphatase in the regulation of the PI3K-AKT-mTOR pathway [Korets SB… CCR 2011]. Loss of PTEN function leads to cellular proliferation via upregulation of the pathway [Dedes KJ et al Sci Trans Med 2010]. PTEN is also involved in maintaining genomic stability, and *PTEN* mutations lead to defects in homologous recombination (responsible for repairing double-strand DNA breaks).

AKT (also known as protein kinase B) is a key member of the PI3K pathway. Activation of AKT leads to cellular proliferation and survival through various downstream targets, including mTOR. Targeting AKT is an area of great interest for endometrial cancer secondary to the known molecular aberrations throughout this pathway. *In vitro* and *in vivo* studies of AKT inhibitors have demonstrated activity against both ovarian and endometrial cancer [Wu…Cho CCR 2011, Engel…Perifosine Eur J Obst Gyn Repro 2008]. The AKT inhibitor perifosine has demonstrated activity in phase I studies of solid tumors. Additionally, abbreviated versions of the planned clinical trials of the allosteric AKT inhibitor MK-2206 in women with operable breast cancer and another with platinum-resistant ovarian, primary peritoneal, or fallopian tube cancer were published [Kalinsky K Clin Transl Oncol 2018, Lee EK…Liu J Gyn Onc Reports 2020]. Unfortunately, both trials demonstrated higher than anticipated toxicity which resulted in premature termination. A phase II study of patients with *PIK3CA* mutated recurrent endometrial cancer did successfully complete its enrollment, but of note did have to to dose reduce during the study due to unacceptable toxicity [Myers AP Int J Cancer 2019].

AZD5363 (capivasertib) is a potent, orally bioavailable, selective inhibitor of the kinase activity of the serine/threonine kinase AKT/protein kinase B (PKB) that is being developed as a potential treatment for solid and hematological malignancies. Thus far, AZD5363 (capivasertib) appears to have good tolerability when administered in phase II combination trials of breast cancer patients [Turner NC Ann Oncol 2019, Jones RH

Lancet Oncol 2020, Schmid P JCO 2020].

2.8 Combination of Olaparib and AZD5363 (Capivasertib)

More than 80% of endometrioid EC have an aberration in *PTEN*, a tumor suppressor gene that encodes a pivotal phosphatase in the regulation of the PI3K-AKT-mTOR pathway [Korets 2011]. Loss of PTEN function leads to cellular proliferation via upregulation of the pathway [Dedes 2010]. PTEN is also involved in maintaining genomic stability and potentially in HRD as described above.

Targeting the effects of PTEN loss in EC by inhibiting PI3K or exploitation of inadequate DNA repair, is an attractive therapeutic strategy. To date, this has met with limited success as the majority of agents investigated in EC have inhibited the pathway downstream at the mTOR complex. However, the majority of mTOR inhibitors evaluated in EC selectively inhibit only one of the two mTOR complexes, potentially resulting in cell survival via feedback activation of AKT [O'Reilly 2006]. AKT is a serine/threonine kinase also known as protein kinase B and is a key member of the PI3K pathway. Activation of AKT leads to cellular proliferation and survival through various downstream targets, including mTOR. Targeting AKT is therefore of interest in EC. In vitro and in vivo studies of AKT inhibitors have demonstrated activity against both ovarian and endometrial cancer [Engel 2008, Wu 2011]. AZD5363 (capivasertib) is a potent, orally bioavailable, selective inhibitor of the kinase activity of AKT/protein kinase B (PKB). AZD5363 (capivasertib) has shown activity against AKT 1 mutated tumors as part of the NCI-MATCH clinical trial. It has also been combined with paclitaxel without impact on tolerability (although it did not enhance efficacy) in metastatic breast cancer [Cancer Discov 2019, Turner 2019].

A recent Phase I study of the combination of olaparib and AZD5363 (capivasertib) demonstrated that the combination was safe and well-tolerated at olaparib 300mg BID and AZD5363 (capivasertib) 400 mg 4 day on/3 off schedule. Furthermore, in the endometrial cancer cohort, a 50% response rate among 8 evaluable patients was observed. Importantly, response duration was durable lasting a median of 14 months [Westin 2017].

2.9 Combination of Olaparib and Durvalumab (MEDI4736)

The efficacy of immunotherapy in patients with MSI high EC is well documented based resulting in FDA approval for the PD-L1 inhibitor pembrolizumab [Marcus 2019]. Recently a novel mechanism of PARPi action was demonstrated by Shen et al. PARPi promoted accumulation of cytosolic DNA fragments because of unresolved DNA lesions [Shen 2019]. These free DNA fragments activated the DNA-sensing cGAS–STING pathway [Chen 2016] Activation of this pathway lead to stimulated production of type I IFNs to induce antitumor immunity [Shen 2019]. This process was independent of BRCA mutation status. These effects of PARPi were further enhanced by immune checkpoint blockade. Durvalumab (MEDI4736) is an FDA approved monoclonal antibody that blocks the interaction of PD-L1 with the PD-1 and CD80 molecules.

A recent phase 1 study of the combination of olaparib and durvalumab (MEDI4736) in advanced ovarian malignancy was both safe and effective [Lee 2017]. At full doses of olaparib and durvalumab (MEDI4736) the combination demonstrated a disease control rate of 83/% with at least stable disease of >=4mo. While this study did not include advanced endometrial cancer patients, the preclinical data suggest that this strategy would be effective in endometrial cancer patients.

2.10 Combination of Cediranib and Durvalumab (MEDI4736)

Angiogenesis and tumor neovascularization are critically linked to the functionality of the host's immune system [Tartour 2011]. Angiogenic-related effects, seen in solid tumors, interfere with a functional immune response through a variety of mechanisms. Production of vascular endothelial growth factor (VEGF), the hypoxic tumor microenvironment, and proteins secreted by the tumor all lead to impaired immune function [Fukumura 2018]. The production and presence of VEGF has a negative impact on immune response. Circulating VEGF leads to recruitment, proliferation, and increased activity of T regulatory cells [Wada 2009], tumor-associated macrophages [Maenhout 2014], and myeloid-derived suppressor cells [Huang 2007]; all of which contribute to an immunosuppressed state. The development and activation of cytotoxic T lymphocytes is directly inhibited by VEGF; decreased cytokine production by T-cells is observed as well as their ability to traffic to a solid tumor [Motz 2014,Voron 2015]. Similarly, dendritic cells lose their ability to mature and present antigens in the presence of VEGF [Gabrilovich 1998].

Tumor neovascularization, often the result of VEGF production, can be misleading, as the vascular supply to the tumor is typically poor leading to a hypoxic and acidotic microenvironment. Hypoxia and acidosis trigger activation of the PD-1/PD-L1 immune checkpoint pathway via T-regulatory cells, tumor-associated macrophages, dendritic cells, and endothelial cells [Barsoum 2014, Jain 2014]. The compromised function of the immune system and its various components, as seen during PD-1/PD-L1 activation, further enhances the tumor's ability to evade the host's immune system. Lastly, tumors secrete soluble mediators directly into the circulation subsequently inducing expression of immunosuppressive chemokines. Circulating VEGF, TGF-beta, and prostaglandin E2 inhibit the activity of antigen presenting cells and ultimately reduce the anticancer response of the effector T-cells [Huang 2013, Li 2006, Raman 2007].

A reasonable rationale exists for blocking both angiogenic and the immune checkpoint PD-1/PD-L1 pathways given their coordinated relationship and role in tumor growth. Preclinical data demonstrated a synergistic effect during the simultaneous blockade of PD-1/PD-L1 and VEGF pathways. Yasuda and colleagues treated a colorectal cancer murine model with an anti-VEGF receptor 2 monoclonal antibody and an anti-mouse PD-1 blocking monoclonal antibody to show after three weeks of treatment a greater decrease was seen in tumor size compared to the decrease seen by either antibody alone [Yasuda 2013]. Similar observations were made in a metastatic castration-resistant prostate cancer mouse model [Lu 2017].

The strategic combination of immune checkpoint inhibitors and antiangiogenic blockade

has been studied in a variety of solid tumors and highlights the observation that response rates are considerably greater for the combination therapy compared to single agents [Atkins 2018, Hodi 2014, McDermott 2018]. Recently the FDA approved the combination of lenvatinib and pembrolizumab for MSS endometrial cancer and uterine serous carcinoma [Makker 2019] Lee and colleagues examined the specific combination of cediranib and durvalumab (MEDI4736) in ovarian, cervical and uterine tumors [Lee 2017]. Their phase I study identified an optimal dosing regimen for each agent with acceptable toxicity.

The recommended phase II dose from Lee et al [Lee 2017] for the combination was durvalumab (MEDI4736) 1500mg IV every 4 weeks and cediranib 20mg 5 days on 2 days off. This dosing strategy prevented excess accumulation of cediranib based on PK studies and provided sufficient washout based on the data gathered from the phase 1 study. Increased toxicity was noted with two patients in the continuous cediranib dosing arm having significant events (1 pulmonary hypertension, 1 colitis). Based on these results, the intermittent dosing schedule is chosen for this study.

Rationale for 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 durvalumab (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 (**Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**, **Error! Reference source not found.**). 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 (**Error! Reference source not found.**). 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, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (MEDI4736) (equivalent to 20 mg/kg Q4W) is included in the current study.

2.11 Rationale for Trial Design (24-MAY-2021)

The incidence of endometrial cancer (EC) is rising. There is no effective second line therapy for EC and no new agents have been approved for the treatment of EC in the last two decades**.** Well tolerated, effective therapies are urgently required.

The TCGA (and others) identified genomic events across the spectrum of EC histologic sub types that suggest EC may be susceptible to DNA damaging agents. There is therefore a strong rationale for targeting DNA repair across the histo-pathologic spectrum of EC. The US National Cancer Institute (NCI) Gynecologic Cancer Steering Committee (GCSC) identified the integration of the emerging molecular and/or histologic stratification data into EC management as a top strategic priority in clinical trial planning and convened a group of experts. In January 2016, the resulting Clinical Trials Planning Meeting, identified DNA repair as an actionable opportunity in EC and this trial concept emerged from that process [MacKay, 2017 (in press)]. We hypothesize that genomic events in EC effecting maintenance of genomic stability will pre-dispose EC to sensitivity to drugs, and drug combination strategies that prevent DNA repair and/or inhibit cell cycle checkpoint stop decisions.

This study incorporates oral agents, an attractive option for patients, and to date both the single agents: cediranib, olaparib and their combination have demonstrated acceptable toxicity profiles in the patient populations where they have been explored. As this study matures data may become available on other potentially attractive combinations targeting DNA repair and consideration will be given to amending the protocol to include additional arms.

In order to accelerate the pace of discovery and explore a number of different strategies (underpinned by a strong scientific rationale) targeting DNA repair in a time and resource efficient manner this trial has been designed as a three-arm randomized phase II study with the potential to amend the study to include future arms containing drugs specific to the DNA damage repair pathway. There is no standard of care for the second line treatment of EC, response rates are known to be low and comparisons of PFS with historical controls can be challenging. This study has therefore been designed to compare 2 (with the potential to include more by amendment) experimental arms versus cediranib, which has been previously shown to have promising activity in GOG-0229J [Bender, 2015]. Women with recurrent, persistent, or metastatic EC who have previously received treatment with at least one prior line of platinum based chemotherapy will be randomized in a 1:1:1: fashion to receive either cediranib alone (reference arm) olaparib alone, or the combination of olaparib and cediranib, The combination of olaparib and cediranib will allow us to test the hypothesis that the addition of an anti-angiogenic agent to olaparib will induce context specific synthetic lethality resulting in synergistic anti-tumor activity and increased efficacy in women with EC compared to cediranib alone. The current new arms are added to test additional hypotheses, and to expand on the data provided from the first three arms (cediranib, olaparib and the combination).

The study is powered to allow comparison of each of the experimental arms with the cediranib arm for the primary endpoint of progression free survival. Cediranib remains the

comparison arm for the subsequent arms, interim analysis demonstrated that the olaparib alone arm did not meet the prespecified endpoint. There were no new safety signals seen in the initial 3 arms of GY012 The Data Monitoring Committee reviewed a planned futility analysis for the first 3 rams and concluded that the interim analysis results met the criterion for lack of sufficient activity for the olaparib alone arm relative to the reference arm (cediranib), while the cediranib/olaparib combination arm was sufficiently active to continue evaluation. The recommendation was to discontinue consideration of the olaparib alone arm and to maintain the combination and reference arms until definitive evaluation of the trial at completion. No further safety concerns were raised.

Under Amendment 3, a formal safety review for the three new treatment arms will be conducted, as these arms contain agents or combinations that have not been previously explored in this patient population. The safety review will occur after 36 patients have been accrued across all four arms, with a hard stop on accrual put in place by the NRG SDMC. It is expected that there will be approximately 8 patients per treatment arm, and at least six patients on each of the three new treatment arms will be treated with at least 1 cycle of treatment. Accrual will stay suspended until the formal safety review is completed.

Tissue collection incorporated as part of this trial for correlative studies will allow a greater understanding of the biology of DNA repair in this disease and we hypothesize will provide data leading to the development of potential predictive biomarker(s) in subsequent trials.

2.12 Translational Science Background

Given the hypothesis underpinning this trial is that genomic events in EC effecting maintenance of genomic stability will pre-dispose to sensitivity to drugs, and drug combination strategies that prevent DNA repair, translational studies are warranted. Integrated and exploratory correlative studies undertaken on tissue collected as part of this clinical trial will allow us to gain a greater understanding into molecular events underlying DNA repair in EC. In addition, these studies will provide an opportunity to identify potential predictive biomarkers for response for further investigation and validation in subsequent clinical trials.

Homologous Recombination Defect (HRD) Studies (Integrated Biomarker)

PARPi's as a class are selectively lethal to HRD cells. This synthetic lethality may occur as a result of impaired base excision repair (BER) although other mechanisms have been proposed including: PARP trapping at the replication fork, alterations in non-homologous end joining (NHEJ) and DNA repair protein recruitment. Although initially focused on germ line mutation in BRCA genes (which do occur in small numbers in serous EC) [Shu, 2016] correlative studies conducted as part of ovarian cancer clinical trials have demonstrated that a broader patient population with HRD defects may benefit from this approach. This included the use of gene panels using next-generation sequencing assays to identify relevant somatic mutations and investigation of genomic scaring assays [Stover, 2016]. In pre-clinical EC models a higher HRD score resulted in greater tumor

response to olaparib [Hansen, 2016]. Data from the TCGA suggest a high proportion of patients with EEC may have mutations in genes of HR pathways. Following on from the work in ovarian cancer, investigating HRD in EC and correlating this with response to olaparib alone and in combination is indicated in this trial. The exact sequencing to be done will be determined by funding and the most appropriate assay at the time the investigators seek approval for distribution/testing. Sequencing data will be correlated with response. Given the evidence in other tumor types for response to PARPi's occurring in cancers with HRD defects, and the availability of HRD panels, we are investigating HRD as an integrated biomarker.

Markers of Angiogenesis (Integrated Biomarker)

Plasma Angiome
In further work assessing potential biomarkers related to response to antiangiogenic therapy in endometrial cancer, NRG/GOG published data from study GOG-0229E that linked response to bevacizumab to high VEGFA expression in tumors and plasma in a similar cohort of patients [Aghajanian, 2011]. Hence, as for bevacizumab, we intend to further evaluate the predictability of tumor (exploratory) *and* plasma (integrated) angiogenic biomarkers to identify the patients most likely to respond to cediranib.

To date, the effort to identify candidate predictive blood-based markers for anti-angiogenic inhibitors has been challenging for many reasons. These include biological complexity, limitations of available reagents, limited sample collection in most trials, and a lack of randomization, which is needed to deal with the potential confounding of prognostic and predictive markers. Many of these barriers have now been overcome. Compared to tissue-based biomarkers, blood-based biomarkers have the significant advantages of low cost, universal applicability, and the ability to be followed over the course of a patient's treatment. By focusing on soluble factors of known biological relevance, further scientific, diagnostic, and therapeutic efforts are greatly facilitated.

The application of multiplex ELISA approaches in clinical samples is rapidly evolving, having only recently shown positive results. The design of the Duke multiplex panel array to interrogate diverse biologies related to angiogenesis is novel. Many of the analytes in the multiplex array were developed and optimized for performance in plasma and serum samples from cancer patients. The Duke plasma angiome approach utilizes the Searchlight™ platform from Aushon BioSystems Inc., and the panel has been developed in tandem with the team at Aushon for over 7 years to develop multiple new assays and optimize the performance of the specific panel design.

Plasma-based marker identification			
Soluble Angiogenic Factors		**Matrix-Derived Factors**	**Markers of Vascular Activation and Inflammation**
ANG-2	PDGF-BB	sEndoglin	CRP
bFGF	PlGF	Osteopontin	ICAM-1
HGF	VEGF-A	TGFb1	IL-6
IGFBP1	VEGF-D	TGFb2	IL-8
IGFBP2	sVEGFR1	TGFbRIII	PAI-1 Active
IGFBP3	sVEGFR2	TIMP1	PAI-1 Total
PDGF-AA	sVEGFR3	TSP2	SDF-1
			VCAM-1

This approach is technically robust and readily adaptable to clinical practice. Because this data will be derived from patients, even preliminary data may significantly improve our understanding of how angiogenesis and tumor growth factors are regulated in cancer patients. Promising findings can be followed up in future clinical studies and in preclinical models. Because the Duke angiome lab serves as the core lab for multiplex ELISA analyses within the NCTN Group, Alliance, the current endometrial cancer profiling can be compared to the profiles seen in other disease site studies (including NRG Oncology ovarian studies, GY004 and GY005), helping to optimize future profiling approaches and provide the disease specific context needed for clinically meaningful companion diagnostics. Given the results of this prior work and the work of others, we anticipate being able to identify and validate or refute candidate markers of benefit that are specific for anti-angiogenic agents.

2.13 Inclusion of Women and Minorities

NRG and NRG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire population treated by participating institutions.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center-Pittsburgh Office: 412-624-2666.

3.1 Eligibility Criteria

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

Patients must have recurrent or persistent endometrial carcinoma, which is refractory to curative therapy or established treatments. Histologic confirmation of the original

primary tumor is required.

Patients with the following histologic epithelial cell types are eligible: Endometrioid adenocarcinoma, serous adenocarcinoma, undifferentiated carcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.). NOTE: Clear cell and carcinosarcoma histology is excluded.

3.1.2 Patients must have measurable disease as defined by RECIST 1.1 or non-measurable (detectable) disease.

3.1.2.1 Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI (See section 14). Patients with measurable disease must have at least one "target lesion" to be used to assess response on this protocol as defined by RECIST version 1.1 (Section 14). Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented, or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.1.2.2 Non-measurable (detectable) disease in a patient is defined in this protocol as one who does not have measurable disease but has at least one of the following conditions:

- Ascites and/or pleural effusion attributed to tumor.
- Solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 (see Section 14) definitions for target lesions.

3.1.3 Patients must have signed an approved informed consent and authorization permitting release of personal health information.

3.1.4 Prior Therapy:

3.1.4.1 Patients must have had one prior chemotherapeutic regimen for management of endometrial carcinoma. Initial treatment may include chemotherapy, chemotherapy and radiation therapy, and/or consolidation/maintenance therapy. Chemotherapy administered in conjunction with primary radiation as a radio-sensitizer WILL be counted as a systemic chemotherapy regimen.

3.1.4.2 Patients are allowed to receive, but are not required to receive, one additional cytotoxic regimen for management of recurrent or persistent disease according to the following definition: Cytotoxic regimens include any agent that targets the genetic and/or mitotic apparatus of dividing cells, resulting in dose-limiting toxicity to the bone marrow and/or gastrointestinal mucosa. Note: Patients on this non-cytotoxic study are allowed to receive one additional cytotoxic chemotherapy regimen for management of recurrent or persistent disease, as defined above. However, due to the novel nature of biologic compounds, patients are encouraged to enroll on second-line non-cytotoxic studies prior to receiving additional cytotoxic therapy.

3.1.4.3 Patients may have received non cytotoxic therapy including immunotherapy (1 prior line in either upfront or recurrent setting) but excluding cediranib, olaparib, AZD5363 (capivasertib), durvalumab (MEDI4736), or the combination of lenvatinib and pembrolizumab for the management of recurrent or persistent disease. Prior hormonal therapy is allowed. Hormonal therapy for grade 1 endometrial cancers with low volume or indolent disease is encouraged. **(24-MAY-2021)**

3.1.4.4 Bevacizumab, or one course of single-agent immune-checkpoint therapy, excluding durvalumab (MEDI4736), is permitted prior to enrollment on this trial. **(24-MAY-2021)**

3.1.4.5 Body weight >30 kg **(24-MAY-2021)**

3.1.5 Age ≥ 18.

3.1.6 The trial is open to females only (including women with an intact uterus with uterine cancer). Fertile females of childbearing potential need to agree to use adequate contraceptive measures from 2 weeks prior to the study and until 1 month after study treatment discontinuation and have a negative serum or urine pregnancy test within 3 days prior to the start of study treatment.

3.1.7 Patients must have an ECOG Performance Status of 0, 1 or 2 (Karnofsky ≥ 60%) within 7 days prior to registration. Patients should have no deterioration over the previous two weeks. **(24-MAY-2021)**

3.1.8 Patients must have adequate organ and marrow function measured within 28 days prior to administration of study drug including:

3.1.8.1 Hemoglobin (Hgb) ≥ 10 g/dL with no blood transfusion in the past 28 days

3.1.8.2 Platelet count ≥ 100 x 10^9/L

3.1.8.3 ANC ≥ 1.5 x 10^9/L

3.1.8.4 Patients must have creatinine clearance estimated of ≥51 mL/min using the Cockcroft Gault equation or based on a 24-hour urine test:
Estimated creatinine clearance =

$$\frac{(140\text{-age [years]}) \times \text{weight (kg)} (\times F)^{a}}{\text{serum creatinine (mg/dL)} \times 72}$$

[a] where F=0.85 for females and F=1 for males **(24-MAY-2021)**

3.1.8.5 Serum bilirubin ≤ 1.5 X ULN.

3.1.8.6 Aspartate aminotransferase (AST)/Alanine aminotransferase (ALT) ≤ 3 x ULN **(24-MAY-2021)(27-APR-2022)**

3.1.8.7 Urinalysis (dipstick) <= 1+ proteinuria OR Urine protein creatinine ratio (UPCR) <1. **(27-APR-2022)**

3.1.9 Patients must be able to swallow and retain oral medications and without gastrointestinal illnesses that would preclude absorption of cediranib, olaparib, or AZD5363 (capivasertib). **(24-MAY-2021)**

3.1.10 Patients must have adequately controlled blood pressure (BP), with a BP no greater than 140 mmHg (systolic) and 90 mmHg (diastolic) for eligibility. Patients must have a BP of ≤ 140/90 mmHg taken in the clinic setting by a medical professional within 2 weeks prior to starting study. Patients with hypertension may be managed with up to a maximum of three antihypertensive medications. It is strongly recommended that patients who are on three antihypertensive medications be followed by a cardiologist or blood pressure specialist for management of blood pressure while on protocol.

Note: Patients must be willing and able to check and record daily blood pressure readings.

3.1.11 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.1.12 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction.

3.1.13 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 IPs. 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 Patients must have a life expectancy of greater than 16 weeks.

3.1.15 Patients with a previous diagnosis of immune or inflammatory colitis or chronic diarrhea > 1 month without immune or inflammatory colitis are eligible with adequately controlled colitis (no diarrhea greater than grade 1 for at least 28 days) and in the absence of symptoms related to colonic dysfunction. Patients who required steroids

for prior immune related colitis are not eligible. **(24-MAY-2021)**

3.1.16 Females of child-bearing potential should use two forms of highly reliable methods of contraception from the time of screening until 4 weeks after discontinuing study treatment.

Acceptable methods of contraception include:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine system.
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
- Male partner sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
- True abstinence (ie, not engaging in sexual activity for the total duration of study treatment and the treatment washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control).
- Bilateral tubal occlusion or salpingectomy

Acceptable Non-hormonal birth control methods include:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; this must continue for the total duration of the trial and for at least 1 month after the last dose of study drug <<for 3 months after last dose *for male patients*>>. [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- IUD PLUS male condom. Provided coils are copper-banded.

Acceptable hormonal methods:

- Normal and low dose combined oral pills PLUS male condom.
- Cerazette (desogestrel) PLUS male condom. Cerazette is currently the only highly efficacious progesterone-based pill.
- Hormonal shot or injection (eg., Depo-Provera) PLUS male condom.
- Etonogestrel implants (e.g., Implanon, Norplant) PLUS male condom.
- Norelgestromin/EE transdermal system PLUS male condom
- Intrauterine system [IUS] device (e.g., levonorgestrel releasing IUS -Mirena®) PLUS male condom.
- Intravaginal device (e.g., EE and etonogestrel) PLUS male condom.
  (24-MAY-2021)

3.2 Ineligibility Criteria

Patients with any of the following conditions are NOT eligible for this study. **(24-MAY-2021)**

3.2.1 Prior enrollment into a clinical trial including cediranib or olaparib. Note: prior bevacizumab is not an exclusion criterion.

3.2.1.1 Prior enrollment into a clinical trial including cediranib, olaparib, AZD5363 (capivasertib), durvalumab (MEDI4736), or the combination of lenvatinib and pembrolizumab. Note: Prior bevacizumab or single-agent immune checkpoint blockade, excluding durvalumab (MEDI4736), is not an exclusion criterion. **(24-MAY-2021)**

3.2.2 Prior chemotherapy, endocrine therapy, radiotherapy, or investigational agents within 4 weeks.

3.2.3 More than one prior line of treatment with immune checkpoint blockade therapy. **(24-MAY-2021)**

3.2.3 Current signs/symptoms of bowel obstruction and/or signs/symptoms of bowel obstruction within the preceding 3 months.

3.2.4 History of gastrointestinal perforation. Patients with a history of abdominal fistula will be considered eligible if the fistula was surgically repaired or has healed, there has been no evidence of fistula for at least 6 months, and patient is deemed to be at low risk of recurrent fistula.

3.2.5 Uncontrolled intercurrent illness including, but not limited to known ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 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 (e.g. ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatments is 2 weeks for strong inhibitors, and at least 1 week for moderate inhibitors. See Appendix IV**. (24-MAY-2021)**

3.2.7 Concomitant use of potent inhibitors or inducers of CYP3A4 within 2 weeks before the start of study treatment (3 weeks for St John's wort), or sensitive substrates of CYP3A4, CYP2C9 and/or CYP2D6 with a narrow therapeutic window within 1 week before the start of study treatment. Concomitant use of drugs known to prolong the QT interval within 5 half-lives of the first dose of study treatment. **(24-MAY-2021)**

3.2.8 Pregnant women are excluded from this study because cediranib and olaparib are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with cediranib and olaparib, breastfeeding should be discontinued if the mother is treated with cediranib or olaparib. These potential risks may also apply to other agents used in this study. For women of childbearing capacity, a negative pregnancy test is required.

3.2.9 Known HIV-positive individuals are ineligible because of the potential for pharmacokinetic interactions between many anti-HIV drugs and cediranib, olaparib, and/or AZD5363 (capivasertib). In addition, these individuals are at increased risk of lethal infections when treated with marrow-suppressive therapy. **(24-MAY-2021)**

3.2.10 Known active Hepatitis B or Hepatitis C infection on antiviral treatment

3.2.11 Prior history of stroke or transient ischemic attack within the last 6 months.

3.2.12 Left ventricular ejection fraction (LVEF) < lower limit of normal (LLN) per institutional guidelines, or <55%, if threshold for normal not otherwise specified by institutional guidelines, for patients with the following risk factors:

- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior central thoracic RT, including exposure of heart to therapeutic doses of ionizing RT
- History of myocardial infarction within 6-12 months prior to start of IPs
- Prior history of other significant impaired cardiac function

3.2.13 Patients with any of the following:

- History of myocardial infarction within 6 months prior to starting treatment
- Unstable angina
- Resting electrocardiogram (ECG) with clinically significant abnormal findings or with QTc > 470 msec on 2 or more time points within a 24-hour period or family history of long QT syndrome
- New York Heart Association functional classification of II, III or IV.

3.2.14 Prior history of hypertensive crisis or hypertensive encephalopathy.

3.2.15 Major surgical procedure within 4 weeks prior to starting treatment; patients must have recovered from any effects of any major surgery and surgical wound should have healed prior to starting treatment. **(24-MAY-2021)**

3.2.16 History of intra-abdominal abscess within 3 months prior to starting treatment.

3.2.17 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.

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

3.2.19 Whole blood transfusions in the last 120 days prior to entry to the study (packed red blood cells and platelet transfusions are acceptable.

3.2.20 Patients with myelodysplastic syndrome (MDS)/treatment-related acute myeloid leukemia (t-AML) or with features suggestive of MDS/AML.

3.2.21 Central nervous system metastases:

- Symptomatic uncontrolled brain metastases requiring corticosteroid treatment.
- History of spinal cord compression unless after definitive treatment the patient has clinically stable disease (SD) for at least 28 days prior to starting IPs.

In the absence of these features and in an asymptomatic patient a scan to confirm the absence of brain metastases is not required.

3.2.22 Other malignancy within the last 5 years except for:

- Curatively treated basal cell or squamous cell carcinoma of skin; in situ cancer of the cervix, ductal carcinoma in situ of the breast or stage 1, grade 1 endometrial carcinoma.
- Curatively treated other solid tumors including lymphomas (without bone marrow involvement) with no evidence of disease for ≥5 years prior to start of IPs.

3.2.24 Persisting ≥Grade 2 CTCAE toxicity (except alopecia and Grade 2 peripheral neuropathy) from previous anti-cancer treatment(s).

3.2.24 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib, olaparib, AZD5363 (capivasertib), or durvalumab (MEDI4736). **(24-MAY-2021)**

3.2.25 Pneumonitis or moderate-severe pre-existing pulmonary disease. **(24-MAY-2021)**

3.2.26 Patients who have a diagnosis of immunodeficiency or are receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days of enrollment.

- Premedication with steroids for CT scan contrast is allowed.
- Inhaled or topical corticosteroids are allowed.
- The use of mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- The use of physiologic doses of corticosteroids may be approved after consultation with the study chair. **(24-MAY-2021)**

3.2.27 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. This includes, but is not limited to, patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome because of the risk of recurrence or exacerbation of disease. **(24-MAY-2021)**

3.2.28 Patients with vitiligo, endocrine deficiencies including type I diabetes mellitus, thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. **(24-MAY-2021)**

3.2.29 Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible. **(24-MAY-2021)**

3.2.30. Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice). **(24-MAY-2021)**

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

4.1 Pre-treatment Assessments (24-MAY-2021)(27-APR-2022)

The following observations and tests 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 should begin within 14 days of registration.

Assessments	Prior to Registration	Prior to Cycle 1 Day 1 Treatment
Informed Consent	A	
Medical History	A	
Physical Examination	A	C
Concomitant Medications	B	D
Performance Status	A	C
Toxicity Assessment	B	C
Vital Signs (Blood Pressure, Heart Rate, Temperature, and Pulse Oxygen Saturation)	A	D
Weight	A	C
CBC/Differential/Platelets	B	B
Chemistries: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, total protein[J]	B	B
TSH	B	B
Urinalysis[I]	B	B
Urine protein: creatinine ratio[I]	B	B
Electrocardiogram	A	A
Pregnancy Test (if childbearing potential exists)	A	E[F]
Radiographic Tumor Measurement[G]	A	A
Echo or MUGA[H]	A	

Assessments prior to registration must meet eligibility criteria. Patients do not need to re-meet eligibility criteria on Cycle 1 Day 1 in order to be treated.

A: ≤ 28 days
B: ≤ 14 days
C: ≤ 7 days
D: Day of treatment
E: ≤ 3 days
F: The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of hCG. Two pregnancy tests on blood or urine samples will be performed for pre-menopausal women of childbearing potential one within 28 days prior to the start of study treatment and the other on Day 1 of the study prior to commencing treatment. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated.
G: Radiographic tumor measurements should be obtained via imaging of at least the chest, abdomen, and pelvis at baseline. See RECIST 1.1 for allowable imaging modalities used to assess disease at baseline and subsequent assessments. Contrast CT is the preferred modality.
H: Patients who have undergone prior treatment with anthracyclines, trastuzumab, prior central thoracic RT or have

a history of myocardial infarction within 6-12 months or other significant impaired cardiac function only.
I: Urinalysis (dipstick) <= 1+ proteinuria OR Urine protein creatinine ratio (UPCR) ≤1
J: All glucose samples should be done under fasting conditions. Fasting is defined as no caloric intake for ≥4 hours before sampling.

4.2 Assessments During Treatment (24-MAY-2021)(27-APR-2022)

The following observations and tests 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. Please refer to Section 10 for Specimen Requirements.

Assessments	Prior to Day 1 of Each Cycle	Cycle 1 & 2, Day 15 (+/-3 days)	After completion or stopping of therapy[A]	Timed (Treatment Cycle Independent)
History and Physical	D		G	
Vital Signs (Blood Pressure, Heart Rate, Temperature and Pulse Oxygen Saturation)	E			
Performance Status	D			
Toxicity Assessment	D	X	G	
CBC/Differential/Platelets	F		G	
Concomitant Medications[J]	D	X	G	
Chemistries: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin, total protein[K, N]	F		G	
Pregnancy Test (if childbearing potential exists)	F			
TSH[B]	F			
Urinalysis or Urine protein creatinine ratio (UPCR)[L]	F			
Electrocardiogram	C			
Home blood pressure assessment	Please see footnote H			
Radiographic tumor measurement				I
Bone Marrow or Blood Cytogenetics				M
Echo or MUGA	C			

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

should clarify with the patient if withdrawal of consent is for treatment or for treatment and follow up.

B: For patients on cedirinib and/or durvalumab containing arms, obtain TSH prior to every other cycle (e.g., C3, C5, etc.). Additional assessment of thyroid function should be performed as clinically indicated.

C: If clinically indicated.

D: ≤ 1 day of treatment

E: Day of treatment/assessment

F: ≤ 3 days of treatment

G: 30 days post End of Treatment (+/- 7 days)

H: 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 Arm 1 and 3 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.

I: Every 8 weeks (+/- 7 days) from cycle 1, day 1 (regardless of delays and/or changes in treatment schedule) for the first year; then every 12 weeks (+/- 7 days) thereafter until disease progression is confirmed; also repeat at any other time if clinically indicated based on symptoms or physical signs suggestive of new or progressive disease. An Excel tool is available on the CTSU website to calculate dates of re-imaging. Utilize **same** imaging modality as for pre-cycle 1 baseline assessment.

J: Because of a potential for interaction of cediranib and olaparib and AZD5363 (capivasertib) 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 V for a list of these medications.

K: In case a subject shows an AST or ALT ≥3xULN or total bilirubin ≥ 2xULN please refer to Appendix IX 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions

L: For patients on cedirinib containing arm, obtain urinalysis (dipstick) OR Urine protein creatinine ratio (UPCR) prior to every other cycle (e.g., prior to C3, C5, etc.)

M: Bone marrow or blood cytogenetic analysis may be performed according to standard hematological practice for patients with prolonged hematological toxicities as defined in Section 6. Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to carry out the tests on a blood sample. If findings are consistent with MDS/AML, study drug should be discontinued, and a full description of findings should be submitted with an SAE report by the investigator to AstraZeneca Patient Safety for documentation on the Patient Safety database. Presence or absence of blood cytogenetic abnormalities and flow cytometry will be documented on the clinical database."

N: For patients on Capivasertib containing arm, glucose samples should be done under fasting conditions. Fasting is defined as no caloric intake for ≥4 hours before sampling.

X: Phone, telehealth, or in person.

4.3 Assessments After Treatment (27-APR-2022)

The following observations and tests 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 patient withdraws from study participation. Please note: Each entry refers to the corresponding footnote at the end of the table.

Assessments	Timed
Vital Status	A
Toxicity Assessment	B
Radiographic tumor measurement	C

A: Every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected for the 5-year follow-up period or until study termination.
B: 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.
C: In the case that protocol-directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under Assessments During Treatment (until disease progression documented by RECIST 1.1 or until patient initiates a subsequent cancer therapy). The study team should clarify with the patient if withdrawal of consent is for treatment or for treatment and follow up.

Definition of Disease

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

5. TREATMENT PLAN/REGIMEN DESCRIPTION (24-MAY-2021)

All eligible patients will be randomized to one of three arms in a 1:1:1 basis.

5.1 Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy (Amendments 1-2)

- ARM 1: Cediranib 30 mg orally once daily. One cycle will be considered 28 days. Two dose reductions allowable. See section 6
- ARM 2: Olaparib 300mg in tablet formulation orally twice daily. One cycle will be considered 28 days. Two dose reductions allowable. See Section 6
- ARM 3: Olaparib 200mg in tablet formulation orally twice daily. Cediranib 30 mg orally once daily. One cycle will be considered 28 days. Two dose reductions allowable for each drug dependent on toxicity(s) observed. See section 6.

Accrual under Amendments 1 and 2 completed in June 2019. Patients accruing under Amendment 3 and following will be randomized 1:1:1:1 to the following treatment arms.

Subsequent Chemotherapy/Hormonal Therapy/Other Agent-Based Therapy

- **ARM 1 (Reference arm):** Cediranib 30 mg orally once daily. One cycle will be considered 28 days. Two dose reductions allowable.

- **ARM 2 (Existing study arm completed accrual**): Olaparib 300 mg in tablet formulation orally twice daily. One cycle will be considered 28 days. Two dose reductions allowable.
- **ARM 3 (Existing study arm completed accrual**): Olaparib 200 mg in tablet formulation orally twice daily. Cediranib 30 mg orally once daily. One cycle will be considered 28 days. Two dose reductions allowable for each drug dependent on toxicity(s) observed.
- **ARM 4**: Olaparib 300 mg in tablet formulation orally twice daily. AZD5363 (capivasertib) 400 mg orally twice daily taken 4 days on and then 3 days off each week. One cycle will be considered 28 days. Two dose reductions allowable for each drug dependent on toxicity(s) observed.
- **ARM 5:** Olaparib 300mg in tablet formation orally twice daily. Durvalumab (MEDI4736) is administered at a dose of 1500 mg as an IV infusion over approximately 60 minutes (± 5 minutes) every 4 weeks. 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 Once cycle will be considered 28 days. Two dose reductions allowable for olaparib dependent on toxicity(s) observed.
- **ARM 6:** Cediranib 20mg orally once daily 5 days on 2 days off each week. durvalumab (MEDI4736) is administered at a dose of 1500 mg as an IV infusion over approximately 60 minutes (± 5 minutes) every 4 weeks. 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. One cycle will be considered 28 days. One dose reduction will be allowable for cediranib dependent on toxicity(s) observed.

First radiological assessment of response will be at 8 weeks, then every 8 weeks thereafter for the first year; then every 12 weeks thereafter until disease progression is confirmed. Radiological assessment will also be repeated at any other time if clinically indicated based on symptoms or physical signs suggestive of new or progressive disease. Patients demonstrating clinical or radiological progression of disease or toxicity prohibiting ongoing participation in study will be taken off study. Patients showing evidence of objective response or stabilization of disease subsequent to treatment will continue on study unless they become ineligible for alternative reasons. Modified RECIST 1.1 criteria will be used to determine on going eligibility.

Patients removed from study due to PD will be seen at 1 month and followed for overall survival. Patients removed due to clinical progression will be followed with attempts to confirm radiological progression.

Toxicity evaluation and grading will be per Common Toxicity Criteria for Adverse

Events (CTCAE v 5.0). Dose modifications will be allowed for adverse events likely related to the study drugs. The time a drug is held should not exceed 21 days' treatment, patients in whom toxicity has not resolved, despite maximal support, to grade 1 or better will be removed from study.

The dose of cediranib and the morning dose of olaparib (Arm 3) can be taken at the same time and can be taken with or without food, at least 2 hours after a meal and 1 hour before the next meal in a similar way each morning. Twice daily doses should be taken 12 hours apart in a similar way each day.

Where possible, all doses of AZD5363 (capivasertib) should be taken at approximately the same time each day, 12 hours apart in a fasted state (water to drink only) from at least 2 hours prior to the dose to at least 1-hour post-dose. If vomiting occurs, a replacement dose should not be taken, and the patient should take their allotted dose at the next scheduled time. Should a patient miss a scheduled dose, the patient will be allowed to take the dose up to a maximum of 2 hours after the scheduled dose time, with a fasting state being maintained. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time. If a patient needs to take the dose earlier for whatever reason, the patient can take the dose up to 2 hours earlier than the scheduled dose time. The patient should make every reasonable effort to take the AZD5363 (capivasertib) tablet(s) on time. AZD4363 (capivasertib) and olaparib can be taken at the same time. AZD5363 (capivasertib) should be taken at least 2 hours after a meal and 1 hour before the next meal.

For those patients participating, olaparib will be dispensed on Day 1 and every 28 day thereafter until the patient completes the study, withdraws from the study or closure of the study.

Patients will be administered olaparib orally twice daily at 300 mgs bid continually. 150 mg olaparib tablets should be taken at the same time each day, approximately 12 hours apart with one glass of water. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved or divided. Olaparib tablets can be taken with or without food.

If vomiting occurs shortly after the tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose for whatever reason (e.g., as a result of forgetting to take the tablets or vomiting), the patient should take their next allotted dose at the next scheduled time. **(27-APR-2022)**

5.2 General Concomitant Medication and Supportive Care Guidelines (24-MAY-2021)

5.2.1 Permitted Supportive/Ancillary Care and Concomitant Medications
All supportive therapy for optimal medical care will be given during the study protocol and documented on each site's source documents as concomitant medication.

- Anticonvulsants
- Antiemetics
- Analgesics
- Nutritional supplementation

- Over the counter and complementary/alternative medications are strictly prohibited due to the risk of drug interaction.

- **Anticoagulant Therapy**

  Non-vitamin K antagonist oral anticoagulants (NOACs), subcutaneous heparin and low molecular weight heparin may be given concomitantly with study treatments and INR monitoring is not required. If NOACs are used, it is preferable to avoid CYP3A substrates (e.g., apixaban and rivaroxaban) if possible.

- **Anti-emetics/Anti-diarrheals**
  If a patient develops nausea, vomiting and or diarrhea, then these symptoms should be reported as AEs (see Section 6) and appropriate treatment of the event given.

- **Palliative radiotherapy**
  Palliative radiotherapy may be used for the treatment of pain at the site of bony metastases that were present at baseline, provided the investigator does not feel that these are indicative of clinical disease progression during the study period. Study treatment should be discontinued for a minimum of 3 days before a patient undergoes therapeutic palliative radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

- **Administration of other anti-cancer agents**
  Patients must not receive any other concurrent anti-cancer therapy, including investigational agents, while on study treatment. Patients may continue the use of bisphosphonates or denosumab for bone disease and corticosteroids for the symptomatic control of brain metastases provided the dose is stable before and during the study and they were started at least 4 weeks prior to beginning study treatment.

- **Corticosteroids**
  Patients must not be receiving chronic administration of corticosteroids for the treatment of autoimmune disease or other medical disorders.
    - Premedication with steroids for CT scan contrast is allowed.
    - Inhaled or topical corticosteroids are allowed.
    - The use of mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
    - The use of physiologic doses of corticosteroids may be approved after consultation with the study chair

5.2.2 Prohibited Therapies and Drugs to be Avoided or Used with Caution **(24-MAY-2021)**
CYP3A4 inhibitors and inducers are prohibited during the study. The following tables list CYP3A4 inducers and inhibitors. Investigators should consult a frequently updated drug

information reference for a list of strong inducers and inhibitors.

CYP3A4 Inducers (prohibited)

Armodafenil[1]	Mitotane	Primidone[1]
Barbituates[2]	Modafenil[2]	Rifabutin
Bosentan[1]	Nafcillin[1]	Rifampin
Carbamazepine	Nevirapine	Rifampicin
Dexamethasone[1]	Oxcarbazepine	Rifapentine[1]
Enzalutamide	Pentobarbital[1]	St. Johns Wort[2]
Efavirenz	Phenobarbital	Troglitazone[3]
Fosphenytoin[1]	Phenytoin	
Glucocorticoids[2] (see note)	Pioglitazone[2]	

Note: topical steroids are permitted. Systemic steroids may be acceptable after discussion with overall PI.

1. Cited in Cytochrome P450) Enzymes: Substrates, inhibitors and inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012:1810-1818
2. Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011.
3. Weak Inhibitor per Lacy et al. May be used with caution.

   Note: Drugs without superscript are included in both Lacy and Flockhart references.

CYP3A4 Inhibitors (prohibited or used with caution)

Strong inhibitors (prohibited)	**Moderate Inhibitors (use with caution, avoid if possible)**	**Weak Inhibitors (use with caution, avoid if possible**
Amprenaivr[1]	Amiodarone[1]	Chloramphenicol[2]
Atazanavir[1]	Aprepitant	Ciprofloxacin[2]
Boceprevir	Cimetidine[1]	Diethyldithiocarbamate[2]
Clarithromycin	Clotrimatazole[1]	Fluvoxamine[2]
Conivaptan[1]	Cyclosporine[1]	Gestodene[2]
Cobicistat	Desipramine[1]Diltiazem	Mibefradil[2]
Delavirdine[1]	Doxycycline[1]	Mifepristone
Elvitegravir	Efavirenz[1]	Norfluoxetine[2]
Fosamprenavir[1]	Erythromycin	Star Fruit[2]
Fospropofol[1]	Fluconazole	Troleandomycin[2]
Imatinib[1]	Fosaprepitant[1]	
Indinavir	Grapefruit juice	
Isoniazid[1]	Halperidol[1]	
Itraconozole	Lidocaine[1]	
Ketoconazole	Metronidazole[1]	
Lopinavir	Norfloxacin[1]	
Miconazole[1]	Sertaline[1]	
Nefazodone	Tetracycline[1]	
Nelfinavir	Verapamil	
Nicardipine[1]		
Posaconazole[1]		

Propofol[1] Quinidine[1] Ritonavir Saquinavir[1] Telithromycin Tipranivir Telaprevir Troleandomycin Voriconazole		

1. Cited in Cytochrome P450) Enzymes: Substrates, inhibitors and inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012:1810-1818
2. Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011.
Note: Drugs without superscript are included in both Lacy and Flockhart references.

5.2.3 CYP3A4, CYP2D6 or CYP2C9 and MATE1 and/or OCT2 transporter substrates whose exposure may be increased by AZD5363 (capivasertib) and should either be avoided or used with caution.

CYP3A4, CYP2D6 or CYP2C9 substrates (prohibited or used with caution)

Medication	Recommendation	Rationale
Alfentanil Atorvastatin Carbamazepine Cerivastatin Cyclosporin Diergotamine Ergotamine Fentanyl Lovastatin Simvastatin Sirolimus Tacrolimus	Prohibited one week prior to AZD5363 (capivasertib) administration and for one week following discontinuation of AZD5363 (capivasertib)	CYP3A4 substrates, whose exposure may be increased by AZD5363 (capivasertib)
Amitriptyline Atomoxetine Desipramine Doxepin Metoprolol Nefazodone Nebivolol Perphenazine Tolterodine Trimipramine Tropisetron	Prohibited one week prior to AZD5363 (capivasertib) administration and for one week following discontinuation of AZD5363 (capivasertib).	CYP2D6 substrates, whose exposure may be increased by AZD5363 (capivasertib).
Haloperidol Tramadol	Prohibited one week prior to AZD5363 (capivasertib)	Combined CYP3A4 and CYP2D6 substrates,

	administration and for one week following discontinuation of AZD5363 (capivasertib).	whose exposure may be increased by AZD5363 (capivasertib).
Alprazolam Domperidone Erythromycin Felodipine Isradipine Midazolam Methylprednisolone Nifedipine Pimozide Quinidine Sertraline Tamoxifen Trazodone Triazolam	May be used with caution.	CYP3A4 substrates, whose exposure may be increased by AZD5363 (capivasertib).
Fluoxetine Paroxetine Venlafaxine	May be used with caution[a].	CYP2D6 substrates, whose exposure may be increased by AZD5363 (capivasertib).
Warfarin	May be used with caution[a].	CYP2C9 substrate, whose exposure may be increased by AZD5363 (capivasertib).
Dofetilide	May be used with caution[a].	MATE1 and OCT2 substrate with a narrow therapeutic window whose exposure may be increased by AZD5363 (capivasertib).
Metformin	May be used with caution[a].	MATE1 and OCT2 substrate whose exposure may be increased by AZD5363 (capivasertib).
Procainamide	May be used with caution[a].	OCT2 substrate with a narrow therapeutic window whose exposure may be increased by AZD5363 (capivasertib).

a. Drugs are permitted but caution should be exercised and patients monitored closely for possible drug interactions. Please refer to full prescribing information for all drugs prior to co-administration with AZD5363 (capivasertib).

Grapefruit juice
It is prohibited to consume grapefruit juice while on olaparib therapy.

Medications that may NOT be administered
No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (Hormone replacement therapy (HRT) is acceptable), radiotherapy, biological therapy or other novel agent) is to be permitted while the patient is receiving study medication. Live virus and live bacterial vaccines should not be administered whilst the patient is receiving study medication and during the 30 day follow up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib are unknown.

5.3 Duration of Therapy

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

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s), as described in Section 6
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT (24-MAY-2021)

6.1 Potential dose modifications for each arm and drug are shown in Table 6.1.

Table 6.1: Dose Modifications for Each Arm

Arm	Initial Dose	1 level reduction	2 level reduction
Arm 1 - Cediranib	30 mg daily	20 mg daily	15 mg daily
Arm 2 - Olaparib	300 mg BID	200 mg BID	150 mg BID
Arm 3 - Olaparib	200 mg BID	150 mg BID	100 mg BID
Arm 3 - Cediranib	30 mg daily	20 mg daily	15 mg daily
Arm 4 - Olaparib	300 mg BID	200 mg BID	150 mg BID
Arm 4 – AZD5363 (capivasertib)	400 mg BID 4 days on 3 days off	320 mg BID 4 days on 3 days off	200 mg BID 4 days on 3 days off
Arm 5 - Olaparib	300 mg BID	200 mg BID	150 mg BID
Arm 5 – Durvalumab (MEDI4736)	1500 mg every 28 days	No dose modifications*	
Arm 6 - Cediranib	20 mg 5 days on 2 days off	15 mg 5 days on 2 days off	
Arm 6- Durvalumab	1500 mg every 28	No dose modifications*	

(MEDI4736)	days	

Durvalumab (MEDI4736) is administered at a dose of 1500 mg every 4 weeks. 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.

6.2 Holding Study Medications

For 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.

Dose modifications will be allowed for adverse events likely related to the study drugs, **see Section 6**. The time a drug is held should not exceed 14 days. Patients in whom toxicity has not resolved, despite maximal support, to grade 1 or better will be removed from study.

Both study treatments in the combination arms (Arms 5, 6, and 7) (olaparib/AZD5363 (capivasertib) or olaparib/durvalumab (MEDI4736) or cediranib/durvalumab (MEDI4736) **should be discontinued at the same time if the AE may be attributable to either agent**. Patients are allowed to remain on monotherapy within an arm (ARM 5,6,7) with cediranib, olaparib; AZD5363 (capivasertib) or durvalumab (MEDI4736) only if the AE is strongly attributable to one or the other agent.

Patients experiencing ongoing clinical benefit who develop a toxicity requiring permanent discontinuation of an investigational product (IP) may be allowed to continue on the unrelated drug if in the opinion of the treating investigator the risk benefit remains favorable and only after discussion with the Principal Investigator.

Once a patient discontinues any arm of the study (both agents if dual therapy), other treatment options are at the discretion of the investigator.

6.3 Dose Modifications for Hematologic Events, Neutropenia or Thrombocytopenia

Dose modifications related on these arms should be managed per **Table 6.3**:

Table 6.3: Dose Modifications for Hematologic Events (neutropenia or thrombocytopenia)

	Action
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.
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE Grade ≤1 for a maximum of 2 weeks. Upon

ANC<1.0 G/L or Platelet count <50 G/L	recovery, olaparib dose should be reduced by one dose level. If repeat CTCAE grade 3-4 occurrence, further dose reduce one or both IPs.

Abbreviations: ANC absolute neutrophil count; CTCAE common terminology criteria for adverse events; IP investigational product

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 2 weeks, patients should be referred to a hematologist for further assessment. A bone marrow analysis should be considered per hematology assessment.

6.3.1 Use of Hematopoietic Agents

Use erythropoietin-stimulating agents per standard of care National Comprehensive Cancer Network (NCCN) and/or institutional guidelines, iron supplements, and/or transfusions as clinically indicated for management of anemia. Prescribing information for the erythropoiesis stimulating agents (including Aranesp, Epogen and Procrit) highlight that there is a potential risk of shortening the time to tumor progression or disease-free survival. Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended. They do not alleviate fatigue or increase energy. They should not be used in patients with uncontrolled hypertension. The package inserts should be consulted.

If a patient develops febrile neutropenia, IPs should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours of the last dose of olaparib unless absolutely necessary.

6.3.2 Management of Anemia Related to Olaparib Arms 4 and 5

Common treatable causes of anemia (e.g., iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. Any subsequently required dose interruptions, related to development of anemia, or coexistent with newly developed neutropenia, and/or thrombocytopenia, will require olaparib dose reductions to 150 mg twice daily as a first step and to 100 mg twice daily as a second step.

If Hgb drops to < 8 g/dL despite the dose reduction or more than one blood transfusion is required to recover Hgb levels with no alternative explanation for the anemia, olaparib should be permanently discontinued.

Platelet transfusions, if indicated, should be done according to local hospital guidelines.

Exclude immune related toxicities as a cause of anemia e.g., colitis in Arm 6 (See Section 6.7)

Table 6.3.2: Management of Anemia Arm 1 (Cediranib)		
	Action	**Cediranib dose**
Hgb <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 Hgb **<10 but ≥8** g/dL, dose interrupt until Hgb ≥10 g/dL for maximum of 2 weeks and upon recovery dose reduce dose level -1 as a first step and to **dose level -2** as a second step.	No change
Hgb < 8 g/dL	Give appropriate supportive treatment and investigate causality. Interrupt olaparib until improved Hgb ≥ 10 g/dL. Upon recovery dose reduce olaparib to **150 mg bd**.	No change

Abbreviations: bd twice daily; Hgb hemoglobin

6.3.3 Management of prolonged hematological toxicities while on study treatment

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 IPs due to CTCAE Grade ≥3 neutropenia (ANC <1 x 10^9/L)
- ≥2 week interruption/delay in 1 or both IPs 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 2 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 IPs should be discontinued if blood counts do not recover to CTCAE Grade ≤1 within 2 weeks of dose interruption.

6.4 Non-Hematologic Toxicity

The management of general adverse events not otherwise specified in the following sections should be as per Table 6.2 below. Management of specific toxicities, including hypertension, diarrhea, proteinuria, decrease in LVEF, thyroid toxicities, RPLS and specific immune related toxicities to durvalumab (MEDI4736) are outlined in below specific subsections and not per Table 6.2.

Table 6.4: General Management of Non-Hematologic Toxicity

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Any ≥ grade 3 non-hematologic (excluding grade 3 fatigue or easily correctable asymptomatic grade 3 laboratory abnormalities)	Hold 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. [2] Recurrence of Grade 3 or 4 toxicity requires dose reduction of study drug (s)
Any grade 2 non-hematologic AE or grade 3 fatigue related to cediranib or olaparib 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.[2] Patients whose toxicity has not resolved after 14 days will be removed from study.
Grade 3 or 4 non-hematologic AE related to cediranib or olaparib that does not resolve to grade 0-2 within 21 days despite maximum supportive care after treating patient at the lowest reduced dose level.[3]	Remove patient from protocol-specified treatment.

[1]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 continued to receive the 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.

6.5 Hypertension Related to Cediranib Arms 1 and 6

All patients should check their BP twice daily for at least the first 8 weeks after starting cediranib, or, if antihypertensive 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, BP monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib dose interruption for 2 weeks.

Patient BP will also be measured during routine study visits to ensure that BP guidelines are being correctly followed. Increase in BP should be treated promptly with standard antihypertensive therapy, ensuring that the maximum recommended dose and number of antihypertensive medicinal products is reached before considering cediranib dose adjustment.

Table 6.5: Hypertension Monitoring and Management

- See Appendix IV for suggested antihypertensive medications by class.
- Abbreviations: Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARB), selective beta blockers (BB), Dihydropyridine calcium channel blockers (DHP-CCP)
- Only doses of cediranib will be modified for hypertension; olaparib, durvalumab (MEDI4736) doses will not be reduced unless other toxicities are experienced.
- If patients require a delay of >3 weeks for management of hypertension, discontinuation of cediranib or protocol therapy may be considered after discussion with the Study Chair. In case of persistent or severe hypertension, despite the optimal use of antihypertensive medicinal products and cediranib dose reduction, cediranib should be permanently discontinued.
- 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 v5.0 criteria. Baseline grade of hypertension should also be recorded in the patient's record.
- Note: Stopping or reduce the dose of cediranib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.

Event	Definition	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to ≥	Consider early initiation of BP medication for BP > 140/90 mmHg that is confirmed on a	Continue standard BP monitoring per treating MD and confirm resolution of BP	None

	140/90 mmHg if previously WNL	second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of HTN-related complications.	to <140/90 mmHg within 24 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. *Suggestions:* ACE-inhibitor or Calcium Channel Blocker Escalate dose of medication in step-wise fashion 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 renal consult*	Increase frequency of monitoring 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 + Calcium Channel Blocker Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not hold cediranib 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

		controlled to < 140/90 mmHg with two drug regimen, then add a third agent. **Study Drug will not be held during trial of two drug combinations. Additional anti-hypertensive 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.*		than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then hold cediranib (up to 14 days) until maximum effect of the anti-hypertensive agents is achieved. If BP is reduced to less than 140/90 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 anti-hypertensive agents.	Intensive BP monitoring (hospitalization if necessary)	**Hold cediranib.** If BP is reduced to less than 140/90 within 14 days, cediranib may be resumed at a reduced dose after discussion with the Study PI and/or sponsor.

6.5.1 Diarrhea (24-MAY-2021)

Diarrhea may be observed with cediranib or AZD5363 (capivasertib) or durvalumab (MEDI4736). **Note Diarrhea occurring in patients on study Arms 5 and 6, containing durvalumab (MEDI4736), see Section 6.7.**

Patients should be instructed to promptly contact investigators if they develop diarrhea due to any cause

6.5.1.1 Management of Diarrhea in Patients Receiving Cediranib Alone

(For patients receiving cediranib in in combination with durvalumab (MEDI4736), see Section 6.7)

For cediranib, diarrhea usually starts early (within the first 4 weeks of treatment), however, it can occur at any time during treatment. Investigators are recommended to prescribe anti-diarrheal treatment at the first visit so that patients can start treatment at the first sign of diarrhea, should it occur 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.

Table 6.5.1.1: Management of Diarrhea Secondary to Cediranib Alone

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.
	If diarrhea persists despite 24 hours of loperamide treatment, hold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhea for 12 hours. Patients should be instructed to contact their study physician if diarrhea persists for over 48 hours despite treatment with loperamide and cediranib dose interruption
For either persistent grade 2 diarrhea or grade 3 or 4 diarrhea:	Patients with persistent or severe diarrhea (CTCATE Grade 3 or higher) may also require dose reduction or discontinuation of therapy with cediranib Follow 6.2.

6.5.1.2 Management of Diarrhea in Patients Receiving AZD5363 (capivasertib), Arm 4

Alternative etiologies should be ruled out prior initiating the dose modifications. Investigators are recommended to prescribe anti-diarrheal treatment at the first visit so that patients can start treatment at the first sign of diarrhea, should it occur. Loperamide is the preferred anti-diarrhoea agent for the management of diarrhea. Dose modifications for AZD5363 (capivasertib)-related diarrhea are provided in the table below.

Table 6.5.1.2: Dose Modifications for AZD5363 (capivasertib)-related Diarrhea	
NCI CTCAE v5 Toxicity Grade	**Action**
Grade 1	Maintain same AZD5363 (capivasertib) dose. Anti-diarrheal treatment (e.g., loperamide) should be initiated at first report of diarrhea. Maximize the supportive care (e.g., dietary modifications, appropriate hydration therapy and electrolyte supplements as clinically indicated).
Grade 2	Interrupt AZD5363 (capivasertib) dose (up to 21 days) until recovery to ≤ Grade 1 and resume dosing at same dose level. Anti-diarrheal treatment (eg loperamide) should be initiated at first report of diarrhea. Maximize the supportive care (e.g., dietary modifications, appropriate hydration therapy and electrolyte supplements as clinically indicated). Consider secondary prophylaxis with anti-motility agents such as loperamide
Grade ≥3	Interrupt AZD5363 (capivasertib) dose (up to 21 days) and institute appropriate anti-diarrhoeal treatment
• Improves to Grade ≤1 within 21 days	• Resume dosing at same dose or one reduced dose level as clinically appropriate maintaining treatment for toxicity as necessary and/or start secondary phophylaxis

6.5.2 Fatigue

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). See Section 6.6 for patients receiving durvalumab (MEDI4736) in Arms 5 and 6. Additionally, short interruption for dosing (initially 2-3 days-or longer-up to a maximum of 14 days) may

help relieve fatigue. When symptoms improve for olaparib and cediranib should be restarted with the same dose or, if necessary, a dose reduction can be considered.

6.5.3 Proteinuria (patients on cediranib alone) Arm 1

For patients receiving cediranib in combination with durvalumab (MEDI4736) see Section 6.7.

Although patients with ≥1+ proteinuria or UPC > 1.0 at entry are ineligible, increases in proteinuria may occur during treatment and should be managed as follows:

Table 6.5.3: Management of Proteinuria

Proteinuria Value if following by U/A	Monitoring	Dose modification
Greater than 2+ on urine dipstick or U/A **AND** Creatinine ≤1.5x ULN	Perform UPC.	Continue study drugs at planned dose and see below.
Greater than 2+ on urine dipstick or U/A **AND** Creatinine >1.5x ULN	Perform UPC.	**HOLD cediranib** until results of UPC are known, and see below
Based on results of the UPC†:		
UPC ≤ 1.0	Continue monitoring prior to each cycle as per previous.	Continue study drugs at planned dose.
UPC > 1.0 and ≤ 3.5 **AND** Creatinine ≤1.5x ULN	Perform UPC prior to each cycle.	Continue study drugs at planned dose.
UPC > 3.5 **OR** Creatinine >1.5x ULN	Perform UPC prior to each cycle.	**Hold cediranib** for up to 14 days and repeat UPC and Creatinine assessment. If UPC resolves to <3.5 and Creatinine to ≤1.5x ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist.
†If UPC is <1.0 and creatinine >1.5x ULN, AE management should be followed as per Table 6.2.2.2.3A		

6.5.4 Thyroid Toxicities (cediranib arm alone, Arm 1)

For patients receiving durvalumab (MEDI4736) combinations (including with cediranib) Arms 5 and 6, see Section 6.7.

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. **(24-MAY-2021)**

Table 6.5.4: 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 FT4and adverse events suggestive of incipient hypothyroidism:	Consider replacement thyroxine.
Increase in TSH with reductions in FT4 :	Consider replacement thyroxine.

6.5.5 Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior reversible encephalopathy syndrome (PRES) has been uncommonly reported in clinical studies with cediranib ARM 1 and 6. 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.

6.5.6 Decrease in LVEF

Patients randomized to cediranib containing arms (ARMS 1 and 6) who have any of the following should undergo an echocardiogram or MUGA at baseline (ECGs should be performed at baseline and prior to each cycle if clinically indicated) and every four cycles (16 weeks) while on study:

a. Prior treatment with anthracyclines
b. Prior treatment with trastuzumab
c. Prior central thoracic radiation therapy (RT), including RT to the heart
d. History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarction within 6 months are excluded from the study)

The decision to continue or hold cediranib/olaparib 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 6.5.6: Management and Monitoring of Decreased LVEF			
Relationship of LVEF to Institution's LLN at baseline	**LVEF Decrease < 10%**	**LVEF Decrease 10-15%**	**LVEF Decrease ≥ 15%**
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 4-8 weeks
1-5% below LLN	Continue and repeat MUGA/ECHO within 4-8 weeks	Continue and repeat MUGA/ECHO within 4-8 weeks	HOLD and repeat MUGA/ECHO within 3 weeks
>6% below LLN	Continue and repeat MUGA/ECHO within 4-8 weeks	HOLD and repeat MUGA/ECHO within 3 weeks **(24-MAY-2021)**	HOLD and repeat MUGA/ECHO within 3 weeks

6.5.7 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. GI perforation is also reported in relation to colitis in patients receiving durvalumab (MEDI4736). See Section 6.

6.5.8 Fistula

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

6.5.9 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.

6.5.10 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.

6.5.11 MDS/AML

Patients who develop Myelodysplastic Syndrome /Acute Myeloid Leukemia on treatment should be discontinued from olaparib treatment and managed appropriately.

6.5.12 Pulmonary Symptoms (General)

For specific recommendations in patients receiving durvalumab (MEDI4736) combinations (ARMS 5 and 6), see Section 6.7.

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 IPs dosing is recommended and further diagnostic workup) should be performed to exclude pneumonitis.

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

6.5.13 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 treatment with the study; 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.

6.5.14 Renal Impairment (olaparib and cediranib)

Patients with mild and moderate renal impairment discontinued cediranib more often due to adverse events, particularly when cediranib was co-administered with chemotherapy. Population PK analysis showed that no adjustment of cediranib dose is required in this population as cediranib is minimally renally cleared; however, cediranib clearance may be decreased in patients with low body weight. In the ICON6 pivotal study, patients with mild or moderate impairment had lower median body weight compared with patients with normal renal function. Caution should be exercised in patients with mild and moderate renal impairment and a cediranib dose adjustment should be considered in case of signs of toxicity. **(24-MAY-2021)**

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 bd.

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. For information on use of cediranib in patients with renal impairment, please see **to** Section 6.5.3.

6.5.15 Wound Healing (24-MAY-2021) (Cedarinib Arms 1 and 6)

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.

6.5.16 Elderly (24-MAY-2021) (Cediranib Arms 1 and 6)

There is a limited amount of safety data available for cediranib use in patients aged 75 years and older. Based on a population PK analysis, the clearance of cediranib decreased with age, however, no dose adjustment is needed given the small impact on exposure or variability. Caution should be taken when treating patients who are aged 75 years or older with cediranib. In case of toxicity dose pause or dose reduction may be considered.

6.5.17Weight decreased (24-MAY-2021) (Cediranib Arms 1 and 6)

In the ICON6 study, weight decreased was very commonly reported in cediranib treated patients. Weight loss (≥7%) in cediranib-treated patients was associated with higher incidence of decreased appetite, vomiting and stomatitis, although these events were also commonly reported in patients who did not lose weight.

6.6 AZD5363 (capivasertib) Specific Toxicities (Arm 4)

Dose Modifications due to general AZD5363 (capivasertib)-related toxicities
Treatment with AZD5363 (capivasertib) should be temporarily interrupted for any

intolerable adverse event regardless of grade or for any adverse events ≥Grade 3 that occurs despite optimal supportive care, are not attributable to the disease under investigation, where the Investigator considers the AE of concern to be specifically associated with AZD5363 (capivasertib). Dose modification guidelines for AZD5363 (capivasertib)-related toxicities are shown in Table 3 below. Appropriate and optimal treatment of the toxicity is assumed prior to considering dose modifications. The study physician may be consulted prior to discontinuation of study drug due to toxicities. Please see Section 6.6.1-6.6.3 for the management of AZD5363 (capivasertib) specific toxicities including hyperglycemia, maculo-papular rash and other skin reactions, and diarrhea.

AZD5363 (capivasertib) administration adjustments based on toxicity grading:

Grade 1	If clinically significant or intolerable, hold dosing of AZD5363 (capivasertib). If resolves to baseline or clinically tolerable within 21 days of onset, resume dosing at same dose or one reduced dose level as clinically appropriate. If does not resolve within 21 days of onset, discontinue study drug and observed until resolution.
Grade 2	If clinically significant or intolerable, hold dosing. If resolves to baseline or clinically tolerable within 21 days of onset, resume dosing at same dose or one reduced dose level as clinically appropriate. If does not resolve within 21 days of onset, discontinue study drug and observe patient until resolution.
≥ Grade 3	Hold dosing of AZD5363 (capivasertib). If ≥3 for ≤ 21 days and resolves to ≤ grade 2 or baseline within 21 days of onset, resume dosing at same dose or one reduced dose level as clinically appropriate. If does not resolve within 21 days of onset, discontinue study drug and observe patient until resolution.

6.6.1. Hyperglycemia related to AZD5363 (capivasertib) (24-MAY-2021)

Hyperglycemia may be seen with AZD5363 (capivasertib). These are general recommendations, therefore, due consideration should be given to baseline values and fasting condition (and time since food if applicable) when interpreting glucose results. In diabetic patients, it may be beneficial to rule out concomitant aetiologies that could be associated with hyperglycaemia (e.g. infections, dehydration, vascular events, glucocorticoids).

Patients should be made aware of symptoms of hyperglycaemia (eg, polydipsia and polyuria).

Dose modification guidelines for AZD5363 (capivasertib)-related hyperglycemia are

shown in Table 6.2.16.1. In addition, for all grades, patients may receive education on lifestyle changes (eg, a diabetic diet) and consider beginning home glucose monitoring (eg, fasting self-blood glucose monitoring [SBGM] once-daily) at the discretion of the investigator. If glucose home monitoring is instituted, the AZD5363 (capivasertib) treatment decision should be based on the morning fasting glucose value obtained prior to the dose of AZD5363 (capivasertib).

It is recommended that approaches to the management of AZD5363 (capivasertib)-induced hyperglycaemia include advice from an endocrinologist where appropriate (eg, diabetic patients). Metformin is currently the preferred oral antidiabetic recommended for the management of hyperglycaemia occurring in patients participating in studies of AZD5363 (capivasertib) (see below for further guidance). If a second agent is required, consideration should be given to the intermittent schedule of AZD5363 (capivasertib) and the pattern of glucose changes (eg. sulphonylureas should be avoided due to their risk of hypoglycaemia secondary to their mechanism of action).

Table 6.6.1: Dose Modifications for AZD5363 (capivasertib)-related Hyperglycemia*

NCI CTCAE v5 Toxicity Grade	**Action**
Grade 1	Maintain same AZD5363 (capivasertib) dose level.
Grade 2	Asymptomatic: • Maintain same AZD5363 (capivasertib) dose level. • Treatment as per local guidelines, consider the use of oral antidiabetic (e.g., metformin) on AZD5363 (capivasertib) dosing days [see further guidance on choice of antidiabetic agents on text above and below the table] Symptomatic: Appropriate clinical management as per local guidelines. • Interrupt AZD5363 (capivasertib) until resolution of symptoms and fasting blood glucose is ≤ 160 mg/dL or ≤8.9 mmol/L (treatment can be interrupt up to 21 days) • Restart at same dose level maintaining appropriate antidiabetic treatment (eg addition of/higher dose of oral metformin) • Consider consult with endocrinologist

Table 6.6.1: Dose Modifications for AZD5363 (capivasertib)-related Hyperglycemia*	
NCI CTCAE v5 Toxicity Grade	**Action**
Grade 3	Hold AZD5363 (capivasertib) up to 21 days, until resolution of symptoms. Consult with endocrinologist. • If fasting blood glucose decreases to ≤ 160 mg/dL or ≤ 8.9 mmol/L within 21 days and under appropriate anti-diabetic treatment, resume AZD5363 (capivasertib) at 1 lower dose level. If fasting blood glucose does not decrease to ≤ 160 mg/dL or ≤ 8.9 mmol/L within 21 days following appropriate antidiabetic treatment, permanently discontinue AZD5363 (capivasertib)
Grade 4	Appropriate clinical management of hyperglycemia per local guidelines. Consider consult with the diabetologist. Consider permanent cessation of AZD5363 (capivasertib)

*Patients may receive education on lifestyle changes (eg, a diabetic diet) and consider beginning home glucose monitoring (eg, fasting self-blood glucose monitoring [SBGM] once daily) at the discretion of the investigator. If glucose home monitoring is instituted, the AZD5363 (capivasertib)/placebo treatment decision should be based on the morning fasting glucose value obtained prior to the dose of AZD5363 (capivasertib)/placebo.

NCI CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

SBGM, self-blood glucose monitoring

6.6.1.1 Use of metformin

Metformin is currently the preferred oral antidiabetic recommended for the management of hyperglycaemia occurring in patients participating in studies of AZD5363 (capivasertib). Investigators should exercise caution in the dosing and management of patients receiving the metformin/AZD5363 (capivasertib) combination and must be vigilant for signs of renal impairment and metformin toxicity, such as lactic acidosis and hypoglycaemia, namely: lethargy, hypotension, poor urine output, drowsiness, irritation, tachypnoea, sweating, diarrhoea, and vomiting.

Due to the potential interaction of metformin and AZD5363 (capivasertib) (cause by inhibition of renal transporters [eg. OCT2] involved in the excretion of metformin), when taking both AZD5363 (capivasertib) and metformin concurrently, patients should attend

the clinic for monitoring of serum creatinine at least once per week for the first 3 weeks after initiation of metformin, then every 3 weeks thereafter.

Metformin should only be given on the days when AZD5363 (capivasertib) is also administered (the half-life of AZD5363 (capivasertib) is approximately 7-15 hours) and should be withdrawn when treatment with AZD5363 (capivasertib) is withdrawn, unless otherwise clinically indicated. Consider withholding of metformin on the days patients are due to have imaging with contrast (in order to reduce the already low risk of lactic acidosis.

6.6.2 Maculo-papular rash related to AZD5363 (capivasertib)

Dose modifications for AZD5363 (capivasertib)-related maculo-papular rash, which is the most frequent skin toxicity observed in patients treated with AZD5363 (capivasertib), are provided in Table 6.2.17.2 below. However, these management guidelines can be used for other skin toxicities at the discretion of the investigator and/or following consultation with the dermatologist.

Table 6.6.2: Dose Modifications for AZD5363 (capivasertib)-related Maculo-papular Rash

NCI CTCAE v5 Toxicity Grade	Action
Grade 1 or 2	Continue dosing at current dose and initiate dermatological treatment: • Topical steroid of moderate strength BD • Non-sedating oral antihistamines
Grade ≥3 or clinically intolerable	Withhold dosing for up to 28 days and initiate dermatological treatment (topical steroid of moderate strength and non-sedating oral antihistamines) with oral steroid for a short course (e.g. up to 2 weeks). Consultation with dermatologist is advised

Table 6.6.2: Dose Modifications for AZD5363 (capivasertib)-related Maculo-papular Rash	
NCI CTCAE v5 Toxicity Grade	**Action**
• Improves to Grade ≤ 1 and tolerable within 28 days from onset	• Continue dermatological treatment* and restart dosing at same dose
• Improves to Grade 2 and tolerable within 28 days from onset	• Continue dermatological treatment* and restart dosing at reduced dose (1 dose level reduction)
• Does not improve to Grade 2 and tolerable within 28 days from onset	• Continue dermatological treatment* and discontinue AZD5363 (capivasertib)
Recurrence of Grade ≥3, or Grade 4 (e.g., severe bullous, blistering or exfoliating skin conditions), or any % BSA associated with extensive superinfection, with IV antibiotics indicated; life-threatening consequences)	Discontinue AZD5363 (capivasertib)

* In patients with persistent rash or previous occurrence of grade 3 consider secondary prophylaxis by continuing topical steroids and/or non-sedating oral antihistamines.

6.6.3 Hypersensitivity reactions to AZD5363 (capivasertib) (24-MAY-2021)

In the case of hypersensitivity reactions, AZD5363 (capivasertib) should be discontinued and symptomatic/supportive therapy should be initiated (including with antihistamines and/or steroids) as considered appropriate by the investigator/treating physician. Drug rechallenge is not recommended; any subsequent consideration on rechallenge with AZD5363 (capivasertib) at the same or a lower dose, with its potential for recurrence of such or more severe events should be carefully considered against the potential benefits to the individual patient from continuation of AZD5363 (capivasertib) therapy. Further management should follow local guidelines on management of hypersensitivity reactions.

6.7 Management of toxicities related to durvalumab (MEDI4736) Arms 5 and 6

Guidelines for the management and dosing modifications for immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab (MEDI4736) in combination with olaparib ARM5 and cediranib Arm 6 are provided in

the subsections below as follows:

- General guidelines for toxicity management and dosing modifications (Table 6.1).
- Toxicity management and dosing modifications guidelines for specific immune-related adverse events (irAEs)/immune-mediated AEs (imAEs) and other irAEs/imAEs not specified (Table 6.7 A).
- Toxicity management and dosing modifications guidelines for Infusion-related reactions (Table 6.7 B).
- Toxicity management and dosing modifications guidelines for non-immune-mediated AEs (Table 6.7 C).

Because immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. In case of doubt, the Investigator should consult with the Study Physician.

Table 6.7 A: General Guidelines for Toxicity Management and Dosing Modifications for Durvalumab (MEDI4736) and Cediranib

General Considerations Regarding Immune-Mediated Reactions

- Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). **In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated.**
- Institute medical management promptly, including specialty consultation as appropriate. In general:
  - **Withhold** study drug/study regimen for severe (Grade 3) imAEs.
  - **Permanently discontinue** study drug/study regimen for
    - life-threatening (Grade 4) imAEs,
    - recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or
    - an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.
- Based on the severity of the imAE,durvalumab (MEDI4736) should be withheld and corticosteroids administered. Upon improvement to Grade ≤1, **corticosteroid should be tapered over ≥28 days.** More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant 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.
- Because immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. In case of doubt, the Investigator should consult with the Study Physician.

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

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	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. – Consider Pulmonary and Infectious disease consult.		
	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.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	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 decision to retreat will be based upon treating physician's discretion and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (*e.g.*, prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – 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 2 to 3 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 IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). 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, 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	Permanently discontinue study drug (s) .	**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 provide Supportive care (e.g., oxygen) – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg IV once,

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	indicated [*e.g.*, tracheostomy or intubation])		may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider) 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.** – **Permanently discontinue study drug for any grade of intestinal perforation.** – 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, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.		
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (*e.g.*, American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	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 study MEDI4736 (durvalumab) 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. **Permanently discontinue study drug for any grade of intestinal perforation.**	**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 2 to 3 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 1 to 2 mg/kg/day. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg IV once (may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider).[a] **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
			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, urgent intervention indicated)	Grade 3 Permanently discontinue study drug (s) n 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. Grade 4 Permanently discontinue study drug/study regimen. **Permanently discontinue study drug for any grade of intestinal perforation.**	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 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 2 days of IV methylprednisolone 1 to 2 mg/kg/day or equivalent, promptly start further immunosuppressives (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – 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]
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 if 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	• Hold study drug/study regimen dose until	**For Grade 2:** – Regular and frequent checking of LFTs (*e.g.*, every 1

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3.0-5.0×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)	resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤1, resume study drug/study regimen after completion of steroid taper. • Permanently discontinue study drug (s) for any case meeting Hy's law criteria (AST and/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]	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 (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 1 to 2 mg/kg/day. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of IV methylprednisolone, promptly start further immunosuppressives (*i.e.*, mycophenolate mofetil at 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult).[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; and/or TB >10xULN if baseline normal, >10.0×baseline if baseline	For transaminases elevations ≤8 × ULN, or total bilirubin elevations ≤5 × ULN: • Hold durvalumab until resolution to Grade ≤1 or baseline. • Resume study drug(s) if LFT elevations resolve to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • **Permanently discontinue** study drug(s) if no resolution within 14 days **Permanently discontinue** durvalumab for: • Transaminases elevation >8 × ULN or total bilirubin >5 × ULN. • Grade 4 event • Any case meeting Hy's law criteria (AST or ALT >3 × ULN + bilirubin >2 × ULN	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (*i.e.*, mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). 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]

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	abnormal)	without initial findings of cholestasis (*i.e.*, elevated alkaline P04) and in the absence of any alternative cause).[b]	
Nephritis or renal dysfunction (elevated serum creatinine)	**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 (and cediranib or olaparib) 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, consider additional workup. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs			
Adverse Events	**Grade of the Event** (NCI CTCAE v 5.0)	**Dose Modifications**	**Toxicity Management**
			– 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 study drug s.	**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, consider additional workup and prompt treatment with an immunosuppressive in consultation with a nephrologist. – 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).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** General Guidance **For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **Hold study drug if Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), or other severe cutaneous adverse reaction (SCAR) is suspected.** – **Permanently discontinue study drugs if SJS, TEN or SCAR is confirmed.**		
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (*e.g.*, diphenhydramine or hydroxyzine) and topical therapy (*e.g.*, emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold durvalumab 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. – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 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 week or recurs
	Grade 3 or 4	**Grade 3:** Hold durvalumab until	**For Grade 3 or 4:** – Consult dermatology.

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
		resolution to Grade ≤1 or baseline. If no improvement within 30 days, permanently discontinue study drug(s). **Grade 4 (or life-threatening):** Permanently discontinue study drug	– 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) – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study. – 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 two subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2	**For Grade 2 (including symptomatic endocrinopathy):**

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs			
Adverse Events	**Grade of the Event** (NCI CTCAE v 5.0)	**Dose Modifications**	**Toxicity Management**
		endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold durvalumab until patient is clinically stable. - If toxicity worsens, treat as Grade 3/4. - Study drug(s) can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged steroid replacement 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.	– 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. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis**. – 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 durvalumab until endocrinopathy symptom(s) are controlled. Study drug/study regimen 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	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine workup, except those with isolated hypothyroidism or Type 1 diabetes mellitus, and as guided by an endocrinologist, promptly 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

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
		is controlled. 2. The patient is clinically stable as per investigator's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	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]
Amylase/ Lipase Increased	**For Any Grade:** – 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. – Assess for signs/symptoms of pancreatitis. – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT). – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase. – If evidence of pancreatitis, manage according to pancreatitis recommendations.		
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**For Any Grade:** – Consider gastroenterology referral.		
	Grade 1	No dose modifications.	- IV hydration - Manage as per amylase/lipase increased (asymptomatic)
	Grade 2	Hold durvalumab (MEDI4736) dose until resolution to Grade ≤1.	- Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - IV hydration
	Grade 3 or 4	Permanently discontinue durvalumab (MEDI4736).	- Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - IV hydration
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, **excluding** Myasthenia	**Any Grade** 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. – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**		

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs			
Adverse Events	**Grade of the Event** (NCI CTCAE v 5.0)	**Dose Modifications**	**Toxicity Management**
Gravis and Guillain-Barré)	**Grade 1**	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (*e.g.* loss of deep tendon reflexes or paresthesia)
	Grade 2	**For acute motor** neuropathies or neurotoxicity, hold study drug (s) dose until resolution to Grade ≤1. **For sensory** neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. **Permanently discontinue** durvalumab (MEDI4736) if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. If toxicity worsens, treat as Grade 3 or 4. Study drug(s) can be resumed after improvement to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – 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 2 to 3 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 or other immunosuppressant depending on the specific imAE).
	Grade 3 or 4	Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days.	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (*e.g.*, IV IG or other immunosuppressant depending on the specific imAE). – Once stable, gradually taper steroids over ≥28 days.

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
Peripheral neuromotor syndromes (such as Guillain-Barré 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 physician. – 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 symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	Hold study drug/study regimen dose until resolution to Grade ≤1. **Permanently discontinue** study drugs if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (*e.g.*, gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs			
Adverse Events	**Grade of the Event** (NCI CTCAE v 5.0)	**Dose Modifications**	**Toxicity Management**
			○ 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. ○ 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:* ○ It is important to consider here 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 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-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drugs 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 study drugs .	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. – *MYASTHENIA GRAVIS:* ○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. ○ 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:* ○ It is important to consider here 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.

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
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 physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (*e.g.*, pulmonary embolism, congestive heart failure, malignant pericardial effusion). A cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial workup should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory workup as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression, other medications, or infections). – **Discontinue drug permanently if biopsy-proven immune-mediated myocarditis regardless of grade.**		
	Grade 1 (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 during diagnostic workup. - If myocarditis is excluded, resume after complete resolution to Grade 0. - **If myocarditis is diagnosed, permanently discontinue durvalumab**	**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 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-	**For Grade 2:** - Hold durvalumab - If toxicity rapidly improves to Grade 0 and no evidence for myocarditis, then the decision to reinitiate study drug/study regimen is based upon treating physician's clinical judgment and after completion of steroid taper. - If toxicity does not rapidly improve, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (*e.g.*, oxygen). – If no improvement within 2 to 3 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 IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. **Infliximab is contraindicated for patients who have heart failure.** – Once the patient is improving, gradually taper steroids

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
	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.	- If cardiac symptoms/signs are **Grade 3-4,** permanently discontinue durvalumab/ tremelimumab. **If myocarditis is diagnosed, permanently discontinue durvalumab regardless of grade** -	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 physician. – Initial workup should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory workup as indicated, including a number of possible rheumatological/antibody tests (*i.e.*, consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, disease progression, other medications, or infections).		
	Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider neurology consult. – Consider, as necessary, discussing with the study physician.
	Grade 2 (moderate pain	Hold study drug/study regimen dose until	**For Grade 2:** – Monitor symptoms daily and consider

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs			
Adverse Events	**Grade of the Event** (NCI CTCAE v 5.0)	**Dose Modifications**	**Toxicity Management**
	associated with weakness; pain limiting instrumental activities of daily living [ADLs])	resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	hospitalization. – Obtain neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from neurology consultant. – If clinical course is *not* rapidly progressive, start systemic steroids (*e.g.*, prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up 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 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). 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]
	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 study drug/study regimen dose until resolution to Grade ≤1. **Permanently discontinue** study drugs 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** study drugs	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; hospitalization recommended. – Obtain neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from neurology consultant. – If not improvement within 2 to 3 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 IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). 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.

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
			– 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]
Other immune-mediated reactions	General Guidance **For Any Grade:** – Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g., immune thrombocytopenia, hemolytic anemia, uveitis, vasculitis). – The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section. – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections).		
	Grade 1	No dose modifications.	- Monitor as clinically indicated.
	Grade 2	- Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. - 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. - Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
	Grade 3	- Hold study drug/study regimen.	- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)
	Grade 4	- Permanently discontinue study drug/study regimen	- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO) -

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

Table 6.7 A: Durvalumab (MEDI4736) (ARMS 5 and 6) Dose Delays and Toxicity Management for imAEs

Adverse Events	Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management

[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.

Table 6.7 B: Durvalumab (MEDI4736) Dose delay and Toxicity Management for Infusion-Related Reactions

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

Table 6.7 C: Durvalumab (MEDI4736) Dose Delay and Toxicity Management for Non–Immune-Mediated Reactions		
Severity Grade of the Event (NCI CTCAE version 5.0)	**Dose Modifications**	**Toxicity Management**
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (*i.e.*, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Per institutional standard.
Grade 1	No dose modifications.	Per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."

6.8 Adverse events of special interest (AESI) for durvalumab (MEDI4736) (24-MAY-2021)

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to:

- Pericarditis
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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

Further information on these risks (e.g., presenting symptoms) can be found in the current version of the durvalumab (MEDI4736) Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally

related to the study drug/study regimen by the reporting investigator.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agents administered in NRG-GY012, cediranib and olaparib are being made available under an IND sponsored by CTEP. For cediranib and olaparib, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4 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 CTEP Study Agents

7.3.1 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]	
		Gastrointestinal perforation[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]		
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)***

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%)**	
	Lymphocyte count decreased		
	Neutrophil count decreased		
	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 Lethargy		***Headache (Gr 3)***
		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.

7.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Olaparib (AZD2281, NSC 747856)(27-AUG-2021)(26-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			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 3449]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
	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)***
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.

7.3.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for AZD5363 (Capivasertib) (NSC 782347) (24-MAY-2021) (08-NOV-2021)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 300 patients*. Below is the CAEPR for AZD5363 (capivasertib).

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

Version 2.5, October 18, 2021[1]

Adverse Events with Possible Relationship to AZD5363 (capivasertib) (CTCAE 5.0 Term) [n= 300]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral[2]		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
METABOLISM AND NUTRITION DISORDERS			
Anorexia			
Hyperglycemia			***Hyperglycemia (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
		Erythema multiforme	
	Pruritus		
Skin and subcutaneous tissue disorders - Other (rash)[3]			***Skin and subcutaneous tissue disorders - Other (rash)[3] (Gr 2)***

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

[2]Mucositis oral may include aphthous ulcer, aphthous stomatitis, mouth ulceration.

[3] Rash may include rash erythematous, rash maculo-papular, and rash papular.

Adverse events reported on AZD5363 trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that AZD5363 caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia
GASTROINTESTINAL DISORDERS - Abdominal pain; Constipation
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Fatigue; Fever

INVESTIGATIONS - Creatinine increased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain
NERVOUS SYSTEM DISORDERS - Dizziness; Headache
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough

Note: AZD5363 (capivasertib) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.3.4 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Durvalumab (MEDI4736), NSC 778709) (24-MAY-2021)(23-MAY-2024)

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 3006 patients.* Below is the CAEPR for Durvalumab (MEDI4736).

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

Version 2.5, February 29,2024[1]

Adverse Events with Possible Relationship to Durvalumab (MEDI4736) (CTCAE 5.0 Term) [n= 3006]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (idiopathic thrombocytopenic purpura)[2]	
		Thrombotic thrombocytopenic purpura[2]	
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes insipidus)	
		Endocrine disorders - Other (diabetes mellitus type 1)[2]	
		Endocrine disorders - Other (thyroiditis)	
	Hyperthyroidism[2]		
		Hypophysitis	
		Hypopituitarism[2]	

Adverse Events with Possible Relationship to Durvalumab (MEDI4736) (CTCAE 5.0 Term) [n= 3006]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypothyroidism[2]		
EYE DISORDERS			
		Keratitis[2]	
		Optic nerve disorder	
		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)***
	Cardiac troponin T increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
		Platelet count decreased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthritis[2]		
	Back pain		***Back pain (Gr 2)***
		Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]	
	Myalgia		***Myalgia (Gr 2)***
		Myositis[2]	

Adverse Events with Possible Relationship to Durvalumab (MEDI4736) (CTCAE 5.0 Term) [n= 3006]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2,5]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (aseptic meningitis)[2]	
		Nervous system disorders - Other (non-infective encephalitis)	
		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 (pemphigoid)	
		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 Durvalumab (MEDI4736). irAEs can involve any of the organs or systems in the body. Most irAEs were reversible and managed with interruptions of Durvalumab (MEDI4736), 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 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 - Disseminated intravascular coagulation; Febrile neutropenia; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (coronary artery disease); Cardiac disorders - Other (valvular vegitation); Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Restrictive cardiomyopathy; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Ventricular arrhythmia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired
EYE DISORDERS - Eye disorders - Other (choroidal effusion with shut down of ciliary body)
GASTROINTESTINAL DISORDERS - Ascites; Colonic obstruction; Colonic stenosis; Constipation; Dental caries; Dry mouth; Dysphagia; Esophagitis; Gastritis; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Ileal stenosis; Mucositis oral; Proctitis; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema trunk; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (failure to thrive); Hypothermia; Neck edema; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic hemorrhage
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (drug-induced liver injury); Immune system disorders - Other (Giany cell arteritis syndrome); Serum sickness
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning, and procedural complications - Other (radiation pneumonitis); Wound complication
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; GGT increased; Lipase increased; Lymphocyte count decreased; Neutrophil count decreased; Serum amylase increased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypermagnesemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Pain in extremity; 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 (increase in tumor mass); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (lung cyst); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare); Treatment related secondary malignancy; Tumor hemorrhage; Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dizziness; Edema cerebral; Encephalopathy; Headache; Ischemia cerebrovascular; Nervous system disorders - Other (axonal neuropathy); Nervous system disorders - Other (hemiparesis); Nervous system disorders - Other (hypoesthesia); Nervous system disorders - Other (neuropathy peripheral); Paresthesia; Seizure; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Confusion; Insomnia

RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Aspiration; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal obstruction; Pleural effusion; Pneumothorax; Pulmonary edema; Pulmonary fistula; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (asphyxia); Respiratory, thoracic and mediastinal disorders - Other (granulomatous changes in the lung); Respiratory, thoracic and mediastinal disorders - Other (fungal pneumonia; Phialemonium spp.)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Bullous dermatitis; Dry skin
VASCULAR DISORDERS - Hypertension; Thromboembolic event

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 Expedited Reporting of Adverse Events (27-APR-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 https://ctepcore.nci.nih.gov/ctepaers/security/login.

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP by telephone at 301-897-7497 and the Biostatistical/Data Management Center by phone, (number to be provided). An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.4.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS24-hour notification must be followed by a complete report within 3 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to CTEP at 301-230-0159 and the 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.

7.4.2 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]

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 CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 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; 3 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

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

7.4.3 Reporting to the Site IRB/REB

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

7.4.4 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.

7.4.5 Reporting to the Pharmaceutical Company: As the IND Sponsor, CTEP/DCTD will assume the responsibility of forwarding CTEP-AERS reports to the pharmaceutical collaborator as needed.

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES (24-MAY-2021)(26-JUL-2023)(23-MAY-2024)

Investigator and Research Associate Registration with CTEP

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) credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems. 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
CTEP-IAM Account with ID.me credentials			✓	✓	✓	✓	✓
FDA Form 1572 • Practice sites, IRBs, and labs	✓		✓				
Financial Disclosure Form	✓		✓		✓		
NCI Biosketch (education, training, employment, certification, licensure, ABMS certification, GCP Training, personal statement, memberships, honors, publications, research support)	✓		✓		✓		
GCP Training Certified (mandatory file upload)	✓		✓		✓		
Agent Shipment Form (if applicable)	✓						
CV (optional file upload)	✓		✓		✓		
Annual Re-registration ✓	✓	✓	✓		✓		

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 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 or treating 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 (27-APR-2022)(26-JUL-2023)(23-MAY-2024)

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 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 through 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 (CTSURegPref@ctsu.coccg.org) or by calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

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 to be completed:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval 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 FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

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
- Compliance with all applicable protocol-specific requirements (PSRs).

Additional Requirements for sites in Canada:

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines [per section 6.2.5 of ICH E6(R2)]. This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result essential documents must be retained for 25 years following the completion of the trial at the participating site (25 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by the sponsor, NRG Oncology, that documents no longer need to be retained [per C.05.012 (4) of the FDR]. In addition, upon request by the auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access [per section 4.9.7 of ICH]. Prior to clinical trial commencement, sites in Canada must also complete and submit via the Regulatory Submission portal on the CTSU website:

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Investigator Brochure Signature Page
- Delegation of Tasks (DTL) Log

The following items are collected By NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log

Record Retention: The sponsor, NRG Oncology, shall maintain records identified in *Health Canada guidelines Part C, Division 5, section C.05.012* for a period of 25 years.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted 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 number in the search field at the top of the protocol tree; or
  - Click on the By Lead Organization folder to expand, then select NRG, and protocol number NRG-GY012.

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.)

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*.

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 Your Site's Registration Status:

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

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

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

8.2 Patient Enrollment (26-JUL-2023)(23-MAY-2024)

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

8.2.1 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 an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the Institutional Review Board (IRB) number used on the site's IRB approval on their Form Food and Drug Administration (FDA 1572) in Registration and Credential Repository (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). **(27-APR-2022)**

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

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

9. DRUG INFORMATION

9.1 Cediranib (AZD2171, NSC 732208) (24-MAY-2021)

9.1.1 Chemical Name: 4-[(4-Fluoro-2-methyl-1H-indol-5-yl) oxy]-6-methoxy-7-(3-pyrrolidin 1- ylpropoxy) quinazoline maleate

9.1.2 Other Names: AZD2171 maleate

9.1.3 CAS Registry Number: 288383-20-0 (for the free base)

9.1.4 Molecular Formula: $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$

9.1.5 Molecular Weight: 566.59 as maleate salt (450.52 as free base)

9.1.6 Approximate Solubility: The aqueous solubility of AZD2171 is 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.9 mg/mL for the maleate salt (distilled water, pH 4.4 at 25°C).

9.1.7 Mode of Action: AZD2171 is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity, which inhibits VEGF-dependent angiogenesis, neovascular survival and vascular permeability.

9.1.8 How Supplied: Astra-Zeneca supplies and CTEP, NCI, DCTD distributes AZD2171. The agent is available as beige film-coated tablets containing 15 mg, and 20 mg of 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.

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.

9.1.9 Storage: Store intact bottles at controlled room temperature [20°C-25°C, (68-77°F)] and protect from light and moisture.

9.1.10 Stability: Stability studies are ongoing. Dispense 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.

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.

9.1.11 Route of Administration: Oral. AZD2171 tablets should be taken either one hour before or two hours after meals.

9.1.12 Potential Drug Interactions:
AZD2171 (cediranib) is primarily metabolized by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that AZD2171 (cediranib) is a substrate for P-glycoprotein (Pgp), 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 UGT1A4 or Pgp 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 UGT 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, Pgp, OATP1B1, OATP1B3, OCT2 and MATE1. Use caution in patients who are taking concomitant medications that are sensitive substrates of these transporters since there is a low potential for drug-drug interactions. 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.

AZD2171 (cediranib) 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 AZD2171 (cediranib) with caution and increase monitoring in patients while on study. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

9.1.13 Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing; therefore, it is recommended that AZD2171 is stopped two weeks prior to elective surgery and restarted when the surgical wound has healed. Patients should be excluded from participating in clinical studies with AZD2171 if they have had recent (at least two weeks, or until any wound has completely healed) major thoracic or abdominal surgery prior to study start, or a 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). Refer to the protocol document for specific guidance.

9.2 Olaparib (AZD2281, NSC 747856)

9.2.1 Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl) piperazin-1-yl] carbonyl}-4-fluorophenyl) methyl] phthalazin-1(2H)-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: C24H23FN4O3

9.2.6 Molecular Weight: 434.46

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

9.2.8 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.

9.2.9 Description: Crystalline solid

9.2.10 How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib as 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.

9.2.11 Storage: Store in a secure location below 30° C (86° F). 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 Stability: Shelf-life studies are ongoing. If a storage temperature excursion is identified, promptly return olaparib 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.

9.2.13 Route of Administration: Tablets can be taken by mouth.

9.2.14 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 (Pgp), 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 Pgp 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 and potentially induces CYP 2C9, 2C19 and Pgp. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of Pgp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. *In vitro* studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not

clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

9.2.15 Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryo fetal survival and development. Therefore, study participants and their partners who are of child-bearing potential should agree to use two (2) highly effective forms of contraception throughout their study participation and for three (3) months after the last dose of olaparib. See Appendix E of Olaparib IB for "Acceptable Birth Control Methods".

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.

9.3 AZD5363 (capivasertib), (NSC 782347) (24-MAY-2021)

9.3.1 Chemical Name: 4-Amino-N-[(1s)-1-(4-Chlorophenyl)-3-Hydroxypropyl]-1-(7h-Pyrrolo[2,3 D]pyrimidin-4-Yl)piperidine-4-Carboxamide

9.3.2 Classification: oral Akt inhibitor

9.3.3 Molecular Formula: $C_{21}H_{25}ClN_6O_2$ M.W.: 428.92

9.3.4 Approximate Solubility: In pH 1.2 simulated gastric fluid and pH 6.5 Fasted State Simulated Intestinal Fluid (v2) both at 37ºC the solubility is >20 mg/mL and 0.44 mg/mL, respectively.

9.3.5 Mode of Action: AZD5363 is a potent, oral inhibitor of kinase activity of serine/threonine specific protein kinase (Akt). AZD5363 inhibits activity of three Akt isoforms (Akt1, Akt2, Akt3), which are activated in different solid tumors. AKT is a hub of multiple signaling pathways promoting tumorigenesis, inhibiting apoptosis, promoting invasion and migration and is often associated with resistance to established cancer therapies. AZD5363 is expected to have efficacy when combined with cytotoxic cancer therapies or other targeted or anti-hormonal agents.

9.3.6 How Supplied: AstraZeneca supplies and PMB, CTEP, DCTD distributes AZD5363 as beige film-coated tablets in 160 mg and 200 mg strengths. Tablets are packed in high-density polyethylene (HDPE) bottles. Each bottle is secured with a heat induction seal, child-resistant closure and no desiccant.

- 160 mg tablet (round, 10 mm) in 76-count bottles
- 200 mg tablet (caplet shaped, 14.5 × 7.25 mm) in 76-count bottles

Each tablet contains AZD5363, microcrystalline cellulose, dibasic calcium phosphate, croscarmellose sodium and magnesium stearate. The tablet film coat contains hypromellose, titanium dioxide, polyethylene glycol, polydextrose, copovidone

plasdone, medium chain triglycerides, yellow iron oxide, red iron oxide and black iron oxide.

9.3.7 Storage: Store below 30°C.
If a storage temperature excursion is identified, promptly return AZD5363 to below 30°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.

9.3.8 Stability: Stability studies are ongoing.

9.3.9 Route and Method of Administration: Oral. Take on an empty stomach at least 2 hours after a meal and 1 hour before the next meal.

9.3.10 Potential Drug Interactions: AZD5363 is primarily metabolized by CYP3A4/5, with contributions from CYPs 2C9 and 2D6, and is substrate of the transporter P-gp. UGT2B7 is primarily responsible for the formation of the major human metabolite, the glucuronide conjugate. AZD5363 is a time-dependent and reversible inhibitor of CYP3A4/5 and a reversible inhibitor of CYPs 2C9, 2D6, and UGT1A1 in vitro. It also inhibited, to a lesser extent, CYPs 2B6, 2C19, and UGT2B7 and the transporters BCRP, OATP1B1, OATP1B3, OCT2, MATE1, and MATE2K1 in vitro.

Avoid co-administration of strong CYP3A4/5 and P-gp inducers/inhibitors, moderate inhibitors may be used with caution. Use caution with co-administered substrates of CYPs 2B6, 2C19, 2C9, 2D6, UGT1A1, and UGT2B7 or the transporters BCRP, OATP1B1, OATP1B3, OCT2, MATE1, and MATE2K1, depending on the sensitivity to inhibition and the therapeutic window of the substrate.

9.4 Durvalumab (MEDI4736) (NSC 778709) (24-MAY-2021)

9.4.1 Other Names: IMFINZI™

9.4.2 Classification: Anti-PD-L1 Mab

9.4.3 Molecular Weight: ~ 149 kDa

9.4.4 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.

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

9.4.6 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.

9.4.7 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.

9.4.8 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.

9.4.9 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.

9.4.10 Route of Administration: IV infusion

9.4.11 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.

9.4.12 Patient Care Implications: Refer to Section 6.0 for information on evaluation and management of potential immune-related adverse events.

9.5 **Agent Ordering, Accountability, Inventory, Investigator Brochures and** Links **(24-MAY-2021)**

9.5.1 Agent Ordering: Agent Ordering: 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.

NO STARTER SUPPLIES MAY BE ORDERED. Orders should be placed with CTEP after enrollment and treatment assignment. Provide the patient ID number in the comment box when submitting an order request. If expedited shipment is required, sites should provide an express courier account through the Online Agent Order Processing (OAOP) application.

9.5.2 Agent Inventory Records: 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 NCI Investigational Agent Oral (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.5.3 Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff 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.

Questions about IB access may be directed to the PMB IB coordinator.

9.5.4 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)

9.6 Blood Pressure Cuffs

A patient who is randomized to the cediranib only or olaparib and cediranib treatment arm (Arms 1 and 3) will be given a blood pressure cuff. Blood pressure cuffs that are supplied for this study, are only to be used for this study.

9.6.1 Supply and Distribution: Blood pressure cuffs will be supplied by VWR and distributed by Biologics. 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.

9.6.2 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 1 and 3). To obtain the kits, please complete the "Blood Pressure Kit Order Request Form" found on the CTSU website and submit it via email to the VWR contacts listed at the bottom of the form. Please allow 3 business days to process and ship orders. All orders will be shipped via FedEx Priority Overnight. **(27-APR-2022)**

10. PATHOLOGY/BIOSPECIMEN

10.1 Stained Pathology Slide Requirements for Central Review to Confirm Eligibility

Not applicable

10.2 Biospecimen Selection for Integral Biomarker Testing

Not applicable

10.3 Biospecimen Selection for Integrated Biomarker testing

10.3.1 Integrated Biomarker to be Tested

Homologous Recombination Deficiency (HRD) assayed in tumor collected prior to all treatment and prior to the study treatment will be used to determine if these mutations can predict response to olaparib alone or in combination with cediranib.

Plasma angiome will be used to assess if markers of angiogenesis in serial plasma samples are associated with response to cediranib alone or in combination with olaparib.

10.3.2 Integrated Biomarker Testing Requirements and Reporting

Archival FFPE tumor collected prior to all treatment and prior to starting study treatment will be used for HRD testing. See Mandatory Biospecimen Submission Table (Section 10.4.1) for details.

Serial plasma (2mL from each of three time points) will be used for plasma angiome assays. See Mandatory Biospecimen Submission Table (Section 10.4.1) for details.

10.3.3 Method of Integrated Biomarker Testing **(24-MAY-2021)**

HRD

Recurrent/persistent and primary archival FFPE tumor and DNA extracted from whole blood will be used to assess homologous recombination deficiency (HRD via the BROCA-HR assay under the direction of Dr. Elizabeth Swisher (University of Washington, Seattle, WA, USA)

Please refer to Appendix II for details.

Plasma Angiome

Serial plasma will tested using the plasma angiome assay by Dr. Andy Nixon (Duke University, Durham, North Carolina, USA).

Please refer to Appendix II for details.

10.3.4 Location of Integrated Biomarker Testing **(24-MAY-2021)**

BROCA-HR assay will be performed under the direction of Dr. Elizabeth Swisher at University of Washington, Seattle, WA, USA.

Plasma Angiome will tested under the direction of Dr. Andy Nixon at Duke University, Durham, North Carolina, USA.

Please refer to Appendix II for further details.

10.3.5 Biospecimen Submission for Integrated Biomarker Testing

Archival FFPE must be submitted for HRD testing. See Mandatory Biospecimen Submission Table (Section 10.4.1) for details.

Serial plasma must be submitted for plasma angiome assays. See Mandatory Biospecimen Submission Table (Section 10.4.1) for details.

10.4 Biospecimen Submission Tables

10.4.1 Mandatory Specimen Submissions

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

Please refer to Appendix I for details.

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
FFPE TUMOR (collected prior to study treatment) – Submit *one* of the following		
FFPE Recurrent Primary Tumor (FRP01)[1] 1st Choice: block 2nd Choice: 25 unstained consecutive slides (15 charged, 5 & 10µm uncharged, 10µm)[2]	Archival tumor collected prior to the patient receiving study treatment *(Recurrent or persistent are preferred specimen types - Submit **one**)*	NRG BB-Columbus within 8 weeks of registration[3]
FFPE Recurrent Metastatic Tumor (FRM01)[1]		

1st Choice: block 2nd Choice: 25 unstained consecutive slides (15 charged, 5& 10 µm uncharged, 10µm)[2]		
FFPE Persistent Primary Tumor (FPP01)[1] 1st Choice: block 2nd Choice: 25 unstained consecutive slides (15 charged, 5& 10 µm uncharged, 10µm)[2]		
FFPE Persistent Metastatic Tumor (FPM01)[1] 1st Choice: block 2nd Choice: 25 unstained consecutive slides (15 charged, 5& 10 µm uncharged, 10µm)[2]		
FFPE TUMOR (collected prior to all treatment) – Submit *one* of the following		
FFPE Primary Tumor (FP01)[1] 1st Choice: block 2nd Choice: 25 unstained consecutive slides (15 charged, 5& 10 µm uncharged, 10µm)[2]	*Archival tumor collected prior to the patient receiving any treatment (Submit **one** if recurrent or persistent tumor collected prior to study treatment is not submitted. If recurrent or persistent tumor collected prior to study treatment is submitted, **one** additional tumor type collected prior to all treatment may also be submitted.)*	NRG BB-Columbus within 8 weeks of registration[3]
FFPE Metastatic Tumor (FM01)[1] 1st Choice: block 2nd Choice: 25 unstained consecutive slides (15 charged, 5& 10 µm uncharged, 10µm)[2]		
BLOOD BIOSPECIMENS		
Whole Blood (WB01) 7-10mL drawn into purple top (K2EDTA) tube(s) and **frozen**[4]	Prior to or after starting study treatment	NRG BB-Columbus within 5 weeks of registration[3]
Pre-treatment Plasma (PB01) prepared from 7-10mL of blood drawn into purple top (K2EDTA) tube(s) **(see Appendix I for special processing instructions)**	Prior to study treatment	
C2D1 Plasma (PB02) prepared from 7-10mL of blood drawn into purple top (K2EDTA) tube(s) **(see Appendix I for special processing instructions)**	Cycle 2, day 1, prior to study treatment	
Final Plasma (PB03) prepared from 7-10mL of blood drawn into purple top (K2EDTA) tube(s) **(see Appendix I for special processing instructions)**	At disease progression or end of treatment *(optional)*	NRG BB-Columbus within 26 weeks of registration[3]

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

2 If less than the requested numbers of slides are available, please contact BPCBank@nationwidechildrens.org.

3 NRG BB-Columbus / Protocol NRG GY012 Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

4 Do not use glass blood collection tubes.

10.5 Banking Biospecimens for Future Research

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

Appendix I.

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable

12. DATA AND RECORDS

12.1 Data Submission/Data Reporting (24-MAY-2021)(27-APR-2022)(26-JUL-2023)(23-MAY-2024)

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

Requirements to access Rave via iMedidata:

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

Rave role requirements:

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

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

Upon initial site registration approval for the study in Regulatory application all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access in Rave will be automatically granted. 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 the study name.

No action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Pending study invitations (previously sent but not accepted or declined by a site user will be automatically accepted and study access in Rave will be automatically granted for the site user. Account

activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave resource materials (Medidata Account Activation and Study Invitation). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

12.2 Data Quality Portal (27-APR-2022)(26-JUL-2023)

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 that are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via 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, and DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

12.3 Rave-CTEP-AERS Integration (26-JUL-2023)

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**.

Pre-existing medical conditions (formerly referred to as baseline AEs) identified during baseline assessment are not considered AEs and therefore should not be reported on the Pre-treatment Adverse Event form. If these pre-existing conditions worsen in severity, the investigator must reassess the event to determine if an expedited report is required. Whether or not an expedited report is required, the worsened condition should be reported in Rave as a routine AE.

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 and 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 study 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 report 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.

12.4 Global Reporting/Monitoring

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

12.5 Collaborative Agreements Language

Protocols that involve agent(s) covered by a collaborative agreement with a biotech/pharma company (ies) must incorporate the NCI/ DCTD Collaborative Agreement Language shown below.

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

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

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

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

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

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

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

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

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

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

Email: ncicteppubs@mail.nih.gov

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

13. STATISTICAL CONSIDERATIONS

13.1 NRG-GY012 Governance (24-MAY-2021)

The NRG-GY012 protocol is being amended to allow for the addition of three new treatment arms:

- olaparib + AZD5363 (capivasertib)
- olaparib + durvalumab (MEDI4736)
- cediranib + durvalumab (MEDI4736)

Completing the Current three arms

This study includes regular safety reviews for a safety lead-in, DMC monitoring while patients are on protocol therapy, including planned interim and final analyses, and finally publication. The protocol includes specific thresholds for interim futility and efficacy to help the DMC decide whether to release the interim analysis results. For efficacy, the DMC (at their discretion) can release ALL of the efficacy information if at least one interim comparison p-value<0.001 (relative to the reference arm). Releasing all of the data will allow the Disease Site design team access to all the information available for the follow-on study design, with the caveat that none of the data on these arms is mature. At the final analysis, the statistical report makes the efficacy results public. The Disease Site Committees and their design teams decide whether and how to use that information in follow-on protocols. The DMC role reduces to an annual safety review while the remaining patients finish the prescribed protocol therapy.

The Reference Arm

The current reference arm, cediranib, will be maintained pending additional data from NRG-GY012 or other studies that suggest a change to the reference arm would be appropriate. Concurrent randomization to cediranib will occur while the three new treatment arms accrue. As per the original rationale and approval for NRG-GY012, the reference arm is required as response rates are low and comparisons of PFS with historical controls can be challenging. Cediranib was evaluated in a phase II trial (GOG-0229) in a mixed EC patient population with a partial response rate of 12.5% and 6-month event-free survival of 29%, meeting the protocol specified efficacy objective to warrant further investigation. Median progression free survival was 3.6 months and overall survival 12.5 months, comparable to other agents in this patient population. In addition, the consistent reference arm for the first three arms and the next three arms will allow for clear and precise evaluation of the response rates and PFS comparisons.

Designing the Definitive, Confirmatory Trial

At the conclusion of GY012, the data will be reviewed by the DMC. Treatment arms passing the pre-specified efficacy threshold will be considered for further development into a definitive phase II or III randomized trial. If more than one arm passes the efficacy threshold, the DMC will consider overall survival, tolerability/toxicity and comparative efficacy and any other information available to determine which arm(s) to recommend for a definitive comparison. The rationale for picking the best winner depends on the

treatment landscape and other factors present when the study completes analysis. These decisions may be informed by ancillary studies, including unplanned experimental arm comparisons or sub-group analyses within GY012, knowing that such studies are subject to bias and inflated error rates.

The study design will allow us to efficiently identify drug (s) of interest to take forward into definitive randomized clinical trials to establish new standard(s) of care for women diagnosed with EC.

13.2 Study Design

This is a randomized, open-label, three-arm study of women with recurrent, metastatic, or persistent endometrial cancer. Patients will be randomized in a 1:1:1 ratio to the three treatment arms:

- cediranib (the reference arm)
- olaparib
- olaparib + cediranib.

The randomization will be stratified by histology (serous vs. endometrioid).

The overall; objective of this study is to compare the relative efficacy and safety of each of the experimental treatment regimens to the reference arm of cediranib in patients with recurrent, metastatic, or persistent endometrial cancer.

(24-MAY-2021)

Accrual under Amendments 1-2 completed in June 2019.
Amendment 3 adds three new experimental arms with concurrent randomization to the cediranib-alone reference. Patients will be randomized in a 1:1:1:1 ratio to the four treatment arms:

- cediranib (the reference arm)
- olaparib + AZD5363 (capivasertib)
- olaparib + durvalumab (MEDI4736)
- cediranib + durvalumab (MEDI4736))

The randomization will be stratified by:

- Histology (serous vs. endometrioid)
- Prior immunotherapy (yes vs. no)

Dynamic allocation will be used for randomization in order to account for multiple stratification factors.

Details about a planned interim analysis and a planned safety analysis can be found in sections 13.5 and 13.8.3 respectively.

13.3 Study Endpoints (24-MAY-2021)

Efficacy Endpoints

- Progression-free survival (PFS) is defined as the time from the date of study enrollment to the investigator-determined date of progression (see Section 14.0 for RECIST v1.1 definition of progression), or death due to any cause, whichever occurs first. For individuals who are alive and progression free, the censored time at risk will be defined as the time from the study enrollment date to the date of the patient's last radiographic disease assessment.
- Overall survival (OS) is defined as the time from the date of study enrollment to the date of death regardless of the cause. For those individuals who have no death reported at the time of the analysis, the censored time at risk will be assessed from the date of study enrollment to the date that the patient was last contacted and known to be alive.
- Objective tumor response as assessed by the site investigator using RECIST v1.1 (see Section 14. Patients with complete or partial tumor response will be considered to have a response.

Safety endpoints

- The frequency and severity of adverse effects are defined using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Translational Endpoints

The translational endpoints below are approved and funded via BIQSFP for the first three treatment arms only: cediranib alone, olaparib alone, and the combination of olaparib and cedaranib. Biomarkers for added treatment arms require either amendment or correlative science proposal submission and secured funding. **(24-MAY-2021)**

- To assess if mutations in DNA Homologous Repair Genes (assayed prior to all treatment and prior to the study treatment) are predictive of response to olaparib alone or in combination with cediranib. (**Integrated Biomarker) BIQSFP funded for ARMS 1-3 only**
- To assess if markers of angiogenesis in serial plasma samples are associated with response to cediranib alone or in combination with olaparib. (**Integrated Biomarker**) **BIQSFP funded for 1-3 only**

13.4 Primary Objectives Study Design (24-MAY-2021)

13.4.1 Primary Hypothesis and Endpoints

The primary hypotheses compare PFS for the two experimental regimens versus the cediranib reference arm. Let l_C denote the PFS hazard for cediranib, and l_j $j=\{2,3,4,5,6\}$ indicate the experimental arms described in Section 5.1.

The null hypotheses are:

- $H_{0,j:C}$: $l_j/l_C \geq 1$, i.e., the hazard of progression or death (PFS-hazard) in this patient population treated with experimental arm (j) is not better than that for those treated with cediranib

The corresponding alternative hypotheses are one-sided:

- $H_{1,j:C}$: $l_j/l_C < 1$, i.e., the PFS-hazard in the patient population treated with experimental arm (j) is less than that for those treated with cediranib

13.4.2 How Primary Endpoints Will Be Analyzed

The null hypotheses above for PFS will be tested using pairwise log-rank tests stratified by the factors specified in section 13.2 above. Each comparison can be considered a separate phase II comparison, so no adjustments for multiplicity will be made; all comparisons will be tested using a one-sided α of 0.05.

The final analysis is planned when 39 PFS events are observed in the reference arm, which is what expected under the alternative hypothesis and with 73 events for the pairwise comparisons (see section 13.4.3 below).
For the primary analyses, patients will be grouped according to their randomly assigned treatment and patients will be included in the analysis, regardless of their compliance with their assigned treatment plan. The primary analyses will use the duration of PFS as it is determined by the clinical investigator responsible for treating the patient.

(24-MAY-2021):
For treatment assignments under Amendments 1 and 2, the null hypotheses comparing olaparib and olaparib+cediranib vs. cediranib for PFS will be tested using pairwise log-rank tests stratified by histology only as specified in section 13.2 above.

For treatment assignments under Amendments 3, the null hypotheses for PFS will be tested using pairwise log-rank tests, stratified by both histology and prior immunotherapy.

The 40 patients accrued to the cediranib arm under Amendment 1-2 will be used in the comparisons to the olaparib only arm and the olaparib+cediranib arm.

The 40 patients accrued to the cediranib arm under Amendment 3 will be used in the comparisons to the olaparib+AZD5363 (capivasertib) arm, olaparib+durvalumab (MEDI4736) arm, and cediranib+durvalumab (MEDI4736) arm.

The final analysis for Amendment 2 treatment comparisons (olaparib vs. cediranib and olaparib+cediranib vs. cediranib) will occur when data maturity for those comparisons is reached. These analyses are not contingent on the Amendment 3 maturity or treatment comparisons.

13.4.3 Sample Size and Power Calculations:

We project the median PFS on the cediranib arm to be approximately 3.6 months (based on GOG-0229-J). In order to have 90% power to detect a doubling of PFS to 7.2 months (i.e., hazard ratio of 0.5), using a one-sided test with α=0.05 per comparison, we require 73 events for each of the two comparisons and will do the final analysis when 39 events are observed in the control arm (which is what is expected under the planned alternative hypothesis), and thus plan to enroll 40 patients per arm (for a total of 120 patients). Calculations were done based on two-sample logrank test in East version 6.4.)

(24-MAY-2021)

The Amendment 3 treatment comparisons assume the same statistical considerations outlined above, including a median PFS in the cediranib arm of approximately 3.6 months, 90% power to detect doubling of PFS to 7.2 months (i.e., hazard ratio of 0.5), one-sided tests with α=0.05 per comparison, and 73 events for each comparison for the final analysis. Thus, 40 patients per arm for a total of 160 patients are required. This total includes 40 new patients accruing to the cediranib arm for concurrent randomization with the three new treatment arms. There are already 40 patients accrued to the cediranib arm. Thus, the cediranib arm will close with a total of 80 patients at the end of the study.

In order to allow for slight variation in the size per treatment arm due to dynamic allocation, a total sample size of 168 new patients will be targeted. Calculations were done based on two-sample log rank test in East version 6.4.

13.5 Study Monitoring of Primary Objectives

An interim analysis for futility is planned at 50% information time, i.e., when 37 PFS events are observed in any two combined treatments for which a pairwise comparison is being done; all interim analyses will be done at that time, meaning some will not be done at exactly 50% information time. At our expected accrual and event rates, we expect this to occur after approximately 17 months of accrual (with approximately 90 patients accrued). If the Z-score from the log-rank test (described in section 13.3.2 above) is >0 then that arm will be stopped for futility; this corresponds approximately to a hazard ratio being >1.0 (i.e., favoring cediranib) for the given experimental arm compared to cediranib (i.e., l_j/l_C j={2,3}). Under the null hypothesis, there is a 50% chance of stopping an arm for futility, and under the alternative hypothesis, there is a 1.8% chance of stopping.

The study will not be suspended during the futility analysis.

(24-MAY-2021)

The interim analysis for Amendment 1-2 was complete at the time of Amendment 3.

For the Amendment 3 treatment comparisons, an interim analysis for futility is planned at 50% information time, i.e., when 37 PFS events are observed in any two combined treatments for which a pairwise comparison is being done. All interim analyses for the three new treatment comparisons will be done at that time, meaning some will not be done at exactly 50% information time. At our expected accrual and event rates, we expect this to occur after approximately 11 months of accrual (with approximately 110 patients accrued). If the Z-score from the log rank test is >0, then the experimental arm will be stopped for futility; this corresponds approximately to a hazard ratio being >1.0 for the given experimental arm compared to cediranib. Under the null hypothesis, there is a 50% chance of stopping an arm for futility. Under the alternative hypothesis, there is a 1.8% chance of stopping.

If accrual is ongoing, accrual will not be stopped for the futility analysis.

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. If, at the interim analysis, at least one treatment/reference hazard ratio has a p-value <0.001, the DMC may consider early release of the interim results for possible development of a definitive trial, as described in Section 13.1.

13.6 Accrual/Study Duration Considerations

We plan on accruing a total of 120 patients (40 per arm) initially, but futility analyses are planned, which could reduce that number. We project accrual of 120 patients to take approximately 24 months (~5 patients per month) followed by an additional 10 months of follow up after the date the last patient is enrolled and begins treatment. The total accrual time could be lengthened by the suspension for the safety review (described below in section 13.8.3).

(24-MAY-2021)
Under Amendment 3, we plan on accruing a total of ~168 patients to the three new treatment arms and the reference arm (~40-42 patients per arm). Planned futility analyses could reduce that number. We project accrual of 168 patients to take approximately 17 months (~10 patients per month) followed by an additional 10 months of follow up after the date the last patient is enrolled and begins treatment. The monthly accrual rate was increased to 10 patients/month due to faster than anticipated accrual to under Amendment 1-2. The total accrual time could be lengthened by the suspension for the safety review (described below in section 13.8.3).

13.7 Dose Level Guidelines

Not applicable.

13.8 Secondary or Exploratory Endpoints (Including Correlative Science Aims)(24-MAY-2021)

13.8.1 Secondary Hypotheses and Endpoints:
The pairwise comparisons with respect PFS in the primary hypotheses ($H_{0,j:C}$) will also be tested for overall survival.
The pairwise comparisons with respect PFS in the primary hypotheses ($H_{0,j:C}$) will also be tested for objective tumor response.

For integrated biomarker-based hypotheses, the endpoints of PFS, OS, and objective tumor response are defined above, and the translational science endpoints are listed above. These are applicable to the first three treatment arms only: cediranib alone, olaparib alone, and the combination of olaparib and cedaranib. Biomarkers for added treatment arms require either amendment or correlative science proposal submission and secured funding. **(24-MAY-2021)**

The integrated biomarker-based hypotheses are:

- Mutations in DNA Homologous Repair Genes are predictive of response in the experimental arms, as compared to the reference

- Markers of angiogenesis determined by serum ELISA for VEGFA or IHC for VEGFR1, VEGFR2 and microvessel density (CD31) are associated with response in the experimental arms as compared to the reference

13.8.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

The Amendment 1-2 null hypotheses for OS will be tested using pairwise log-rank tests stratified by the factors specified in section 13.2 above. Each comparison can be considered a separate phase II comparison, so no adjustments for multiplicity will be made; both comparisons will be tested using a one-sided α of 0.05.
The null hypotheses for objective tumor response will be tested using pairwise Cochran-Mantel-Haenszel tests stratified by the factors specified in section 13.1 above. Each comparison can be considered a separate phase II comparison, so no adjustments for multiplicity will be made; both comparisons will be tested using a one-sided α of 0.05.
Proportional hazards models will be used to examine the prognostic association of integrated markers with PFS and OS; and interactions between markers and treatment arm will be used to examine the markers' predictive association with the clinical endpoints.

(24-MAY-2021)
The same statistical assumptions and methods described above apply to the three new treatment comparisons, with corresponding modification of the stratification factors.

13.8.3 Interim Analysis for All Other Endpoints **(24-MAY-2021)**:

We will conduct a formal safety review for the two arms that contain agents or combinations that have not been previously explored in this patient population: olaparib and olaparib+cediranib. This will occur after twenty-four (eight per arm) patients have been accrued—with the expectation that at least six patients on each of the arms will be treated with at least 1 cycle of treatment (rather than stopping after just six have been accrued on each arm with the greater possibility that <6 may get treated with one cycle).

The safety review will allow for close monitoring in this population that may represent an older age range than previously studied and who may have undergone prior exposure to pelvic radiation. Safety and tolerability will be reviewed by the study team (study chair and co-chairs, study statistician) and Developmental Therapeutics Chair before continuing accrual. Clinical judgment rather than arbitrary statistical rules will be used. No rigid stopping boundaries will be set, and no dose limiting toxicities will be defined. The number of adverse events will be tabulated by grade and treatment arm, and consideration will be given to the nature of the AEs and their potential relatedness to study therapy.

Under Amendment 3, patients in a safety lead-in will be monitored frequently according to NRG Oncology SOPs. We will conduct a formal safety review for the three new treatment arms, as these arms contain agents or combinations that have not been previously explored in this patient population. The safety review will occur after 36

patients have been accrued across all four arms, with a hard stop on accrual put in place by the NRG SDMC. It is expected that there will be approximately 8 patients per treatment arm, and at least six patients on each of the three new treatment arms will be treated with at least 1 cycle of treatment.

Accrual will stay suspended until the formal safety review is completed.

13.8.4 Power Calculations:

For the secondary endpoint of OS, we expect the median OS in the cediranib reference arm to be approximately 12.5 months (based on GOG-0229-J). At the time of the final analysis for the primary endpoint (i.e., PFS), we would expect approximately 29 events in the cediranib arm and thus would have 90% power to detect a hazard ratio of 0.42 (or an increase in OS to 29 months in each experimental arm) based on one-sided tests with α=0.05.

For the secondary endpoint of objective tumor response, we expect the response rate in the cediranib reference arm to be approximately 12.5% (based on GOG-0229-J). We would have 90% power to detect an increase in the response rate to 28% in each experimental arm based on one-sided tests with α=0.05.

13.9 Exploratory Hypothesis and Endpoints (24-MAY-2021)

For each combination arm: if it is deemed statistically significantly superior to the reference cediranib arm then that combination arm will be compared to the single-olaparib arm. This will be done for PFS, OS, and objective tumor response. These tests will be done one-sided with α=0.05.

Exploratory biomarker-based objectives require either amendment or correlative science proposal submission and secured funding. **(24-MAY-2021)**

13.10 Gender/Ethnicity/Race Distribution (24-MAY-2021)(27-APR-2022)

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	2	0	0	0	2
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	7	0	1	0	8
White	103	0	2	0	105
More Than One Race	1	0	1	0	2

Total	116	0	4	0	120

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

The planned Gender/Ethnicity/Race distribution for the first three treatment arms is displayed above. Here is the planned distribution for the additional 168 patients required for the second group of treatment arms:

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	3	0	0	0	3
Asian	2	0	0	0	2
Native Hawaiian or Other Pacific Islander	2	0	0	0	2
Black or African American	7	0	2	0	9
White	97	0	2	0	99
More Than One Race	2	0	1	0	3
Total	113	0	5	0	118

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	1	0	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	0	0	0	3
White	45	0	1	0	46
More Than One Race	0	0	0	0	0
Total	49	0	1	0	50

14. EVALUATION CRITERIA

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

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

14.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with reference or investigational therapy.

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

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

14.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area may be considered measurable if there has been interval progression since the time of radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the

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

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

14.3 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the

availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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.

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APPENDIX I: TRANSLATIONAL SCIENCE BIOSPECIMEN PROCEDURES

I. Obtaining a Bank ID for Translational Science Specimens

Only one Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational science specimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component. If a patient has previously been assigned a Bank ID, please ensure the Bank ID appearing in Rave is the same as the previously assigned Bank ID.

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

II. Requesting Translational Science Biospecimen Kits

Two single chamber kits will be provided per patient for the collection and shipment of frozen plasma and frozen whole blood.

Sites can order kits online via the Kit Management system(https://kits.bpc-apps.nchri.org/). Each site may order two kit types per protocol per day (daily max = 6 kits). **(27-AUG-21)**

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

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

Note: Unused supplied and kits should be returned to the NRG BB-Columbus. A pre-paid shipping label for the return of unused supplies and kits may be obtained via the Kit Management system. Select "Empty Kit" for package contents when returning unused kits.

III. FFPE Shipped to the NRG BB-Columbus

*****A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the NRG BB-Columbus.**

Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (e.g., primary, metastatic, recurrent, persistent).

- Archival **primary (FP01)** and **metastatic (FM01)** tumor must be collected prior to the patient receiving any treatment.

- Archival **recurrent** and **persistent** tumor must be collected prior to the patient receiving any study treatment. Recurrent or persistent tumor collected from the site of primary disease must be labeled **recurrent primary (FRP01)** or **persistent primary (FPP01)**, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g.,

lymph node) must be labeled **recurrent metastatic (FRM01)** or **persistent metastatic (FPM01)**, respectively.

Only **one** block may be submitted per tissue type.

Mandatory FFPE Biospecimen Requirement
Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 25 unstained slides (15 charged 5µm and 10 uncharged, 10µm) should be submitted. All tissue sections must be cut sequentially from **one** block.

Completing Form TR for FFPE Biospecimens
The type of biospecimen (block, slides) must be specified on Form TR. If submitting slides, the slide type, thickness, and count must also be specified.

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

Bank ID (# # # # - # # - G # # #)
protocol number (NRG – GY012)
specimen code (see section 10.4)
collection date (mm/dd/yyyy)
surgical pathology accession number
block number

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

IV. Whole Blood Shipped to the NRG BB-Columbus
1. Label the lavender/purple top (EDTA) collection tube(s) as described below. Multiple tubes may be used to collect the required amount. **Do not use glass blood collection tubes.**
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.
4. Immediately **freeze the whole blood in an upright position** in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

Labeling Whole Blood
A waterproof permanent marker or printed label must be used to label each translational science whole blood biospecimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG – GY012)
specimen code (see section 10.4)

collection date (mm/dd/yyyy)

V. Plasma Shipped to the NRG BB-Columbus
Note: The laboratory testing to be done is time sensitive. Plasma must be processed <u>within one hour</u> of collection. Special processing instructions are described below.

1. Label cryovials and a 15mL conical tube as described above. Use 2mL cryovials as plasma will be shipped to the NRG Oncology Biospecimen Bank-Columbus.
2. Draw 7-10mL of blood into lavender/purple top (EDTA) tube(s).
3. Immediately after collection, gently invert the blood collection tube 5-10 times to mix the blood and EDTA.
4. Centrifuge the blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the plasma (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Using one of the pipettes, transfer the plasma into a pre-labeled 15mL conical tube and gently mix.
6. **Centrifuge the plasma <u>again</u> at 1000g for 15 minutes at 4ºC (preferred) or room temperature.**
7. Using the second pipette, evenly dispense (aliquot) the plasma into the pre-labeled cryovials and cap the tubes securely. Place a minimum of 0.25mL into each cryovial. **Avoid any residual cells that pellet at the bottom of the conical tube.**
8. Immediately **freeze the plasma in an upright position** in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

Labeling Plasma
A waterproof permanent marker or printed label must be used to label each translational science plasma biospecimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG – GY012)
specimen code (see section 10.4)
collection date (mm/dd/yyyy)

VI. Submitting Form TR
A specimen transmittal form (i.e., Form TR) 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 Form TR must accompany each biospecimen shipped to the NRG BB-Columbus (or alternate laboratory). Handwritten forms will not be accepted.

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

Form TR **<u>must</u>** 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.

Note: Biospecimens will not be marked as received in Rave without receipt of a corresponding electronically completed Form TR. **Incomplete forms or those containing incorrect information will not be processed and may result in a data query.**

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@nrgoncology.org; Phone: 716-845-7767).

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

An electronically completed copy of Form TR must be included for each translational science biospecimen. Handwritten forms will not be accepted.

Note: Biospecimens will not be marked as received in Rave without receipt of a corresponding electronically completed Form TR. Incomplete forms or those containing incorrect information will not be processed.

All translational science biospecimens should be shipped to:

NRG BB-Columbus / Protocol NRG GY012
Nationwide Children’s Hospital
700 Children’s Dr., WA1340
Columbus, OH 43205
Phone: 614-722-2865
FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

A. FFPE Tissue Shipped to the NRG BB-Columbus
FFPE tissue and a copy of the corresponding pathology report must be shipped using your own container at your own expense to the NRG BB-Columbus (address above).

Do not ship FFPE tissue for Saturday delivery.

B. Frozen Biospecimens Shipped to the NRG BB-Columbus
Frozen plasma and whole blood should be shipped together to the NRG BB-Columbus (address above) using the biospecimen kit provided.

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

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

Shipping Frozen Translational Science Biospecimens in a Single Chamber Kit

1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen biospecimens from each time point in a separate zip-lock bag.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 25 cryovials in a single chamber kit. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen biospecimens into the kit and fill the chamber to the top with dry ice.
5. Insert a copy of Form TR for each biospecimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Print a pre-paid FedEx air bill using the Kit Management link (: https://kits.bpc-apps.nchri.org/). Attach the air bill. **(27-AUG-21)**
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

VIII. Banking Translational Science Biospecimens for Future Research

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

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

The patient's biospecimen consent choices will be recorded on the signed informed consent document and electronically via 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 II: TRANSLATIONAL SCIENCE LABORATORY TESTING PROCEDURES (24-MAY-2021)

I. BROCA-HR

a. Overview

The Swisher laboratory has previously published methodology and validation experiments for targeted capture and massively parallel sequencing of cancer genes (1-5). In brief, DNA will be extracted from peripheral blood mononuclear cells (PBMCs) and formalin-fixed, paraffin-embedded (FFPE) tumor containing at least 30% tumor nuclei. A targeted capture and massively parallel sequencing approach called BROCA will be applied to samples.

For the proposed study, a more recent version of BROCA-HR will be utilized, which has been developed to target 72 key genes leading to HRD as well as key targets for mutation in endometrial cancers that serve as a single assay to test for inherited risk and for germline and somatic mutations that influence response to therapy. This test includes an anlaysis of MSI and of total genomic LOH. Library preparation has been fully automated to increase sample turnaround and lower cost.

Table 1: BROCA-HR Genes

ABCB1	BRAF	CHD4	ERCC6	MAD2L2	NF1	POLE	RAD51D	SMARCA4
ARID15B	BRCA1	CHEK1	EZH2	MLH1	NRAS	PPM1D	RB1	SPRTN
ARID1A	BRCA2	CHEK2	FAM111A	MRE11	PALB2	PPP2R1A	RIF1	TP53
ATM	BRIP1	CTCF	FANCM	MSH2	PARP1	PTEN	RPL22	TP53BP1
ATR	CCND1	CTNNB1	FAT3	MSH6	PIK3CA	RAD50	SHLD1	TSC1
BAP1	CCNE1	ERBB2	FBXW7	MYC	PIK3R1	RAD51	SHLD2	TSC1
BARD1	CDK12	ERCC2	GABRA6	MYCN	PMS2	RAD51B	SHLD3	WRN
BLM	CDKN2A	ERCC4	KRAS	NBN	POLD1	RAD51C	SLCA5A40	XRCC6

Paired-end libraries with 350bp inserts will be prepared from 1ug of constitutional or neoplastic DNA and hybridized to a custom pool of oligonucleotides targeting genomic regions as previously described (2) using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples.

Single nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipeline (2). Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described (3), supplemented with additional alignments generated by SLOPE (6). All germline loss of function mutations in cancer susceptibility genes will be confirmed with PCR amplification and Sanger sequencing. Cases will be identified as HR proficient or deficient based on sequencing data of known Fanconi anemia (FA)-BRCA genes and then correlate HR proficiency with response to platinum or PARPi on the trial. Later, in exploratory analyses, the Swisher laboratory will add in analyses of NHEJ and other modifying genes, genomic scarring, or other somatic tests by

their lab or others to complement the determination of HR deficiency.

B. Laboratory Testing Procedures

Assay and specimen parameters: If sample is fluid (blood, ascites, pleural, cyst or other fluid, samples will be initially stabilized with acid citrate dextrose, and both fixed (with 10% neutral buffered formalin) and frozen types of tumor specimens will be used for BROCA-HR testing. Minimum 3 micrograms of DNA from blood, or 2 tumor sections by 1 cm diameter and 10 microns thickness will be required. An adjacent tissue section will be stained and examined by H&E to assess cellularity and tumor content; reference images of the H&E section will be kept and % cells that are tumor cells are reported as tumor content. Macrodissection will be used to enrich the sample for tumor cells.

Design of Mutation Assay and Data Analysis: Swisher laboratory has fully automated library preparation to increase sample turnaround and lower cost. Agilent 2200 TapeStation will be used to assess DNA concentration. DNA purity will be assessed using Agilent 2200 TapeStation and DNA integrity will be evaluated using Agilent Bioanalyzer. Swisher laboratory will prepare paired-end libraries with ~200 bp inserts from 300 ng of constitutional DNA and hybridize to a custom pool of oligonucleotides for the genomic regions listed above (3) using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples will be sequenced on a single lane of a HiSeq flowcell (Illumina) in rapid mode with 2x101 base pair paired end reads and a 7 base pair index read. Sequencing reads will be processed from real-time base calls with RTA 1.17.20 (Bustard) and converted to qseq.txt files in house on a Dell PowerEdge R900 server. Following demultiplexing, the reads will be aligned to the human reference genome (hg19) using BWA36. Duplicate reads and those not mapping within 2 standard deviations of the 250bp insert size will be removed. Variants will be identified using GATK37 after indel realignment and base quality recalibration. Variants from low quality (≤50) and depth of coverage regions (<5 reads) are filtered out. Single nucleotide variants and insertions and deletions will be detected as previously described (3). Deletions and duplications of exons will be detected by a combination of depth of coverage and split read analysis as previously described (1), supplemented with additional alignments generated by split read algorithms (6). Missense mutations and in-frame deletions will only be classified as deleterious if a specific functional assessment has been carried out (i.e., BRCA1 C61G, RAD51C Q143R (7, 8)). Swisher laboratory will continue to update bioinformatics pipeline and integrate new alignment algorithms as they become available.

Data Reports and Assay Accuracy: Assay results will be reported as “Positive for mutation”. Swisher laboratory has established assay accuracy by comparison to a reference method (Sanger Sequencing, MLPA) and using reference materials (e.g., specimens with a variety of known mutations). For true positive; Swisher laboratory has verified mutations with Sanger Sequencing in 500 cases. For true negative; there were no false positives in >2000 samples tested to date and verified with Sanger sequencing. False positives have only been verified when they decrease the read count and/or quality limits in order to increase sensitivity in tumor samples, in this case Swisher laboratory always verify the mutation with Sanger sequencing and they usually do, the total number of samples: 2000. Swisher laboratory has shown >99% of concordance for within-run repeats and >99% of concordance for between-run repeats. With regard to limit of detection ((lowest amount of analyte that gives an informative result), Swisher laboratory has

demonstrated that the lowest 5% of mutant or variant allele could be reliably detected in a wild type background.

C. References

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5. Pennington KP, et al. (2012) BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. Cancer.
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7. Osorio A, et al. (2012) Predominance of pathogenic missense variants in the RAD51C gene occurring in breast and ovarian cancer families. Hum Mol Genet 21:2889-2898.
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II. Plasma Angiome (Integrated Biomarker)

A. Overview

Plasma samples will be analyzed by multiplex ELISA assays for plasma-based biomarkers utilizing the Aushon Cirascan Imaging System. The Aushon Cirascan Imaging System is used specifically for the imaging and analysis of chemiluminescent protein arrays in a 96-well plate. The protein arrays are created by spotting up to 16 different capture antibodies per well in each well of the 96-well plate. The advantage of this system is that multiple target proteins of interest can be analyzed at the same time reducing the amount of sample required for analysis. In brief, a small volume of sample and/or standard is added to each well of the 96-well plate resulting in the capture of the target proteins by the arrayed antibodies. Biotinylated antibodies are then added that specifically bind the captured target proteins. Streptavidin conjugated to HRP (horseradish peroxidase) is then added followed by a chemiluminescent substrate. Imaging of the plate is performed using Aushon Cirascan Imaging System. Protein concentrations in the samples are quantified by comparing the intensity of the spots in the unknown wells to standard curves.

B. Laboratory Testing Procedures

Dilution of Patient Samples:

1) Add dilution buffer to staging plate followed by patient sample.
2) Dilution strategies vary depending on target analyte.

Reconstitution of Standards:

1) Add proper volume of Sample Diluent to each standard vial; let stand for 1-2 minutes followed by gentle inversion.
2) Ensure lyophilized standard on sides of tube and cap are added to solution.

3) Allow standards to sit at room temperature while preparing standard serial dilutions.

Serial Dilution of Standards:
1) Perform serial dilutions for 7 standards and one blank as per Aushon instructions.
2) Pipette 150-200ul of each standard to the pre-designated area on the staging plate.

Loading Samples onto Ciraplex Plates:
1) Once staging plates have been prepared; remove Ciraplex plates from package and label accordingly.
2) Add 50ul of each patient sample and standard, in duplicate, onto Ciraplex Plate using a Rainin multi-channel manual pipetman without changing tips between replicates.
3) Cover plates using adhesive plate sealer and incubate 2 hour at room temperature while shaking at setting 6 (Barnstead 4625).

Washing plates:
1) Washing plates is performed using the BioTek ELx405 plate washer. (See *BioTek Plate Washer Instructions* below)
2) Use the Vacuboy Multi-Channel to remove all wash buffer followed by 20 second spin in Labnet MPS1000 plate spinner.

Biotinylated Antibody Reagent Addition:
1) Add the entire bottle of biotinylated antibody to a 50ml reagent reservoir.
2) Pipette 50ul of biotinylated antibody reagent to each well using a Rainin multi-channel manual pipetman. Do not change tips during the addition of this reagent.
3) Cover plates using adhesive plate sealer and incubate 30 minutes at room temperature while shaking at setting 6 (Barnstead 4625).
4) After 30 minutes, wash plates as described above.

Streptavidin-HRP Reagent Addition:
1) Add the entire bottle of streptavidin-HRP to a fresh 50ml reagent reservoir.
2) Pipette 50ul of streptavidin-HRP reagent to each well using a Rainin multi-channel manual pipetman. Do not change tips during the addition of this reagent
3) Cover plates using adhesive plate sealer and incubate 30 minutes at room temperature while shaking at setting 6 (Barnstead 4625).
4) After 30 minutes, wash plates as described above.

Signal Detection:
1) Once plates have been washed and all wash buffer and bubbles have been removed; mix 4.0ml Super Signal and 4.0ml Peroxidase solutions in a 15ml conical tube and mix by inverting five times.
2) Pipette 50ul of detection solution using a reagent reservoir and multi-channel pipetman.
3) Protect from light and incubate 2 minutes at room temperature while shaking at setting 2 (Barnstead 4625).
4) Read immediately on the Aushon Cirascan Instrument.

C. References

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5. Liu Y, Starr MD, Brady JC, Dellinger A, Pang H, Adams B, Theuer CP, Lee NY, Hurwitz HI, Nixon AB. (2014) Modulation of circulating protein biomarkers following TRC105 (anti-endoglin antibody) treatment in patients with advanced cancer. Cancer Med. Jun; 3(3): 580-91.

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APPENDIX III: 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 β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	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
Dihydro-pyridine 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 IV: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARDS (24-MAY-2021)

CEDIRANIB

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.

Version *DEC 2019*

(Next page: Patient Drug Interaction Wallet Card)

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI	NIH NATIONAL CANCER INSTI
EMERGENCY INFORMATION		**DRUG INTERACTIONS**	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** 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***	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

Fold at dotted lines:

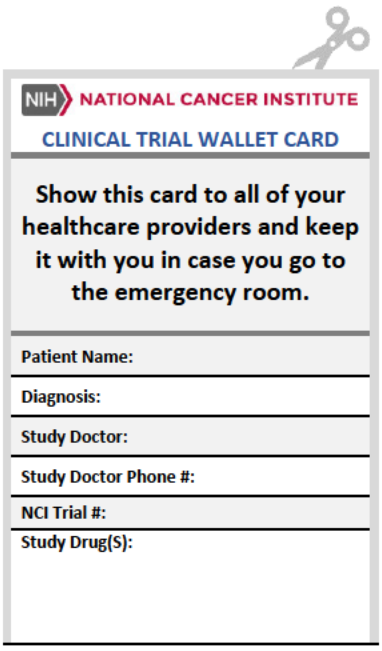
OLAPARIB (24-MAY-2021)

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):** Olaparib (AZD2281)

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.

PATIENT CLINICAL TRIAL WALLET CARD



AZD5363 (CAPIVASERTIB) (24-MAY-2021)

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):** AZD5363 (capivasertib)

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:
AZD5363 (capivasertib) interacts with certain specific enzymes in your liver and certain transport proteins that help move drugs in and out of cells.

	Explanation
CYP isoenzymes	The enzymes in question are **CYP3A4/5, 2B6, 2C19, 2C9, 2D6, and UGT1A and UGT2B7**. AZD5363 (capivasertib) is broken down by CYP3A4/5, UGT1A9 and UGT2B7 and may be affected by other drugs that inhibit or induce these enzymes. AZD5363 (capivasertib) also inhibits CYP3A4/5, 2B6, 2C19, 2C9, 2D6, UGT1A1 and UGT2B7, and may affect other drugs that use these enzymes to be broken down.
Protein transporters	The proteins in question are **P-gp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K.** AZD5363 (capivasertib) is moved in and out of cells/organs by P-gp and may be affected by other drugs that inhibit or induce this protein. AZD5363 (capivasertib) inhibits BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K and may affect other drugs that are moved in and out of cells/organs by these transport proteins.

These are the things that you need to know:
The study drug AZD5363 (capivasertib), may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health

care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors of CYP3A4/5, UGT1A9, UGT2B7, and P-gp, or substrates of CYP3A4/5, 2B6, 2C19, 2C9, 2D6, UGT1A1, UGT2B7, BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K.

- 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.
    - Do not eat or drink grapefruit juice, grapefruit, or Seville oranges while taking AZD5363 (capivasertib).
- 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.

Version *Feb/2020*

Patient Drug Interaction Wallet Card

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**	NIH NATIONAL CANCER INSTITUTE
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** AZD5363 (capivasertib) interacts with CYP3A4/5, UGT1A9, UGT2B7, 2B6, 2C19, 2C9, 2D6, UGT1A1, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, MATE2K and P-gp and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):** AZD5363 (capivasertib)	**Use caution and avoid the following if possible:** Do not eat or drink grapefruit juice, grapefruit, or Seville oranges while taking AZD5363 (capivasertib).	Your healthcare providers should be aware of any medicines that are considered strong inducers/inhibitors of CYP3A4/5, UGT1A9, UGT2B7, and P-gp, or substrates of CYP3A4/5, 2B6, 2C19, 2C9, 2D6, UGT1A1, UGT2B7, BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K. • Avoid strong inducers/inhibitors of CYP3A4/5, UGT1A9, UGT2B7, and P-gp, use caution with moderate inducers/inhibitors of CYP3A4/5, UGT1A9, UGT2B7, and P-gp. • Avoid substrates of CYP3A4/5 with a narrow therapeutic index. • Use caution with other substrates of CYP3A4/5, 2B6, 2C19, 2C9, 2D6, UGT1A1, UGT2B7, BCRP, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2K. **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 FEB/2020
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

APPENDIX V: PATIENT DRUG DIARIES (27-APR-2022)

CEDIRANIB (ARM 1)

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 scheduled dose, as a result of forgetting or vomiting, you should take your next allotted dose at the scheduled time. If you miss a dose 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.**

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

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature Date

OLAPARIB (ARM 2)(27-APR-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 scheduled dose, as a result of forgetting or vomiting, you should take your next allotted dose at the scheduled time. If you miss a dose, write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

OLAPARIB

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

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

Patient's Signature: _____ Date: _____

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

CEDIRANIB AND OLAPARIB (ARM 3) (24-MAY-2021)(27-APR-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 scheduled dose, as a result of forgetting or vomiting, you should take your next allotted dose at the scheduled time. If you miss a dose, 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**.

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

OLAPARIB

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

Day	Date	100mg	150mg	AM	PM
1	*1/1/15*	*2*	*0*	*8:00*	*8:00*
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
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25					
26					
27					
28					

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature Date

OLAPARIB and AZD5363 (capivasertib) (ARM 4) (24-MAY-2021)(27-APR-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 scheduled dose, as a result of forgetting or vomiting, you should take your next allotted dose at the scheduled time. If you miss a dose, 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.

AZD5363 (CAPIVASERTIB)

Take ____ (number) _____ mg and _____ mg tablets twice a day 12 hours apart. Take for 4 days and then do not take for 3 days each week. Continue this sequence until you reach Day 28. **Take without food, at least 2 hours after a meal or one hour before a meal. May be taken with Olaparib.**

OLAPARIB

Take _____ (number) _____ mg and _____ (number) _____ mg tablets twice a day 12 hours apart. **Take without food, at least 2 hours after a meal or one hour before a meal. May be taken with AZD5363 (Capavasertib).**

Day	Date	160mg	200mg	AM	PM	Day	Date	100mg	150mg	AM	PM
1	*1/1/15*	*2*	*0*	*7:00*	*7:00*	*1*	*1/1/15*	*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/Data Manager's Signature Date

OLAPARIB AND DURVALUMAB (MED4736) (ARM 5) (24-MAY-2021)(27-APR-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 scheduled dose, as a result of forgetting or vomiting, you should take your next allotted dose at the scheduled time. If you miss a dose write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

OLAPARIB

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

Day	Date	100mg	150mg	AM	PM
1	*1/1/15*	*2*		*8:00*	*8:00*
1					
2					
3					
4					
5					
6					
7					
8					
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27					
28					

Patient's Signature: _____ Date: _____

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

CEDIRANIB AND DURVALUMAB (MEDI4736) (ARM 6) (24-MAY-2021)(27-APR-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 scheduled dose, as a result of forgetting or vomiting, you should take your next allotted dose at the scheduled time. If you miss a dose 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 for 5 days on/2 days off each week. **Take on an empty stomach.**

Day	Date	15mg	20mg	AM
1	*1/1/15*	*2*	*0*	*7:00*
1				
2				
3				
4				
5				
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7				
8				
9				
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Patient's Signature: _____ Date: _____

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

APPENDIX VI: 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 heartbeat (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/Data Manager's Signature _____ Date _____

APPENDIX VII: ACTIONS REQUIRED IN CASES OF INCREASE IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on the managing liver abnormalities can be found in Section 6.7 of the protocol.
During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.
The Investigator participates, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).
The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)
Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)
AST or ALT ≥ 3x ULN together **with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN