To: CTEP Protocol and Information Office

From: Timothy Yap, M.D., Ph.D.

Branch: Investigational Drug Branch, CTEP, DCTD, NCI

Date: 9/25/2024

Re: Amendment 20 of Protocol #**10217**: "A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and Durvalumab (MEDI4736) in Patients with Advanced Solid Tumors"

SUMMARY OF CHANGES – Protocol

I. PI-initiated changes:

#	Section	Comments
1.	Title page and throughout	**PI Response**: The protocol version date was updated throughout the protocol on the title page and headers **New Text**: May 13, 2024 **New Text**: September 25, 2024

II. CTEP-requested protocol language changes for specimen transfer:

#	Section	Comments
2.	5.5.1.4	The EET Biobank is moving to a new facility effective 10/7/24. Accordingly, revise the Shipping Address for the EET Biobank to the following: EET Biobank 2200 International Street Columbus, OH 43228 PH: (614) 722-2865 FAX: (614) 722-2897 E-mail: BPCBank@nationwidechildrens.org **PI Response:** Changes were made to section 5.5.1.4 as specified above
3.	5.5.1.5	Revise the Contact Information for Assistance to update the EET Biobank's phone number to the following: For all queries, please use the contact information below:

#	Section	Comments
		EET Biobank Phone: (614) 722-2865 E-mail: BPCBank@nationwidechildrens.org **PI Response:** Changes were made to section 5.5.1.5 as specified above
4.	5.5.3	In the Biomarker Plan Table, replace the laboratory in the Assay Laboratory and Lab PI Column for the WES (tumor and blood), RNAseq, and ctDNA sequencing as shown: MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich **PI Response:** Changes were made to section 5.5.3 as specified above.
5.	5.7.2.2 -5.7.2.4	For WES, replace the current text in Section 5.7.2.2 -5.7.2.4 with the following revised text: 5.7.2.2 Site Performing Correlative Study WES will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the leadership of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). 5.7.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study Specimens will be shipped from the EET Biobank to: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton 5.7.2.4 Contact information for notification of specimen shipment Thomas Forbes (mochasamplereceiving@nih.gov) **PI Response:** Changes were made to sections 5.7.2.2 -5.7.2.4 as specified above.
6.	5.8.1.2-5.8.1.4	For RNAseq, replace the current text in Section 5.8.1.2 -5.8.1.4 with the following revised text:

#	Section	Comments
		5.8.1.2 Site Performing Correlative Study RNAseq will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). 5.8.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study Specimens will be shipped from the EET Biobank to: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton 5.8.1.4 Contact information for notification of specimen shipment Thomas Forbes (mochasamplereceiving@nih.gov) **PI Response:** Changes were made to sections 5.8.1.2 - 5.8.1.4 as specified above.
7.	5.8.2.2-5.8.2.4	For ctDNA sequencing, replace the current text in Section 5.8.2.2 -5.8.2.4 with the following revised text: 5.8.2.2 Site Performing Correlative Study ctDNA sequencing will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). 5.8.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study Specimens will be shipped from the EET Biobank to: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton

#	Section	Comments
		5.8.2.4 Contact information for notification of specimen shipment Thomas Forbes (mochasamplereceiving@nih.gov) **PI Response:** Changes were made to sections 5.8.2.2-5.8.2.4 as specified above.
8.	13.5	Remove Section 13.5 Genomic Data Sharing Plan **PI Response:** Section 13.5 was removed as specified above.
9.	13.6	MoCha will not report incidental findings. Accordingly, please remove Section 13.6. **PI Response:** Section 13.6 was removed as specified above.

III. Recommendations:

#	Section	Comments
10.	6.1.3.1	Based on updated information, please change durvalumab infusion duration from: "Durvalumab will be administered over 60 minutes (± 15 minutes)" Change to: "Durvalumab will be administered over 60 minutes (± 10 minutes)" **PI Response:** Changes were made to section 6.1.3.1 as specified above.
11.	9.2	Per the previous comment, please insert an "International Estimated Enrollment Report" table for the treatment phase of the study since Princess Margaret Cancer Center is listed as a participant. PI Response: As no new enrollment will be supported for this study, we kindly request not to update the enrollment table at this time given that Princess Margaret Cancer Center did not enroll any patients to this trial. New comment: Kindly include the International Estimated Enrollment Table as per the requirements. The figures should be considered "estimated." If necessary, please fill in any empty spaces with zeros to represent the enrollment numbers.

#	Section	Comments
		PI Response: An 'International Estimated Enrollment Table' was added section 9.2 as specified above.
12.	13.2	**Please revise within this section as shown as shown, to reflect the updated CTEP protocol template language.** Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access to the study in Rave will be automatically granted. ~~To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management > Rave Home* and click to accept the invitation in the Tasks pane located in the upper right corner of the iMedidata screen.~~ Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name. No action will be required by ~~S~~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 ~~will receive a separate invitation from iMedidata to activate their account~~. 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 Data Management Help Topics > Rave resource materials ~~the Rave resource materials~~ (Medidata Account Activation and Study Invitation ~~Acceptance~~). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response:** Changes were made to section 13.2 as specified above

#	Section	Comments
13.	10.3.3	**PI Response:** The expedited reporting guidance in section 10.3.3. was updated to reflect the most recent AE reporting table (effective date 08-30-2024).

NCI Protocol #: 10217

Local Protocol #: **NCI10217**

ClinicalTrials.gov Identifier: TBD

TITLE: A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and Durvalumab (MEDI4736) in Patients with Advanced Solid Tumors

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LAO-TX035 / University of Texas MD Anderson Cancer Center LAO

Participating Organizations Dose Expansion:

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LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
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NCI-Supplied Agents: Copanlisib (NSC 784727), Olaparib (AZD2281; NSC 747856), and Durvalumab (MEDI4736; NSC 778709)

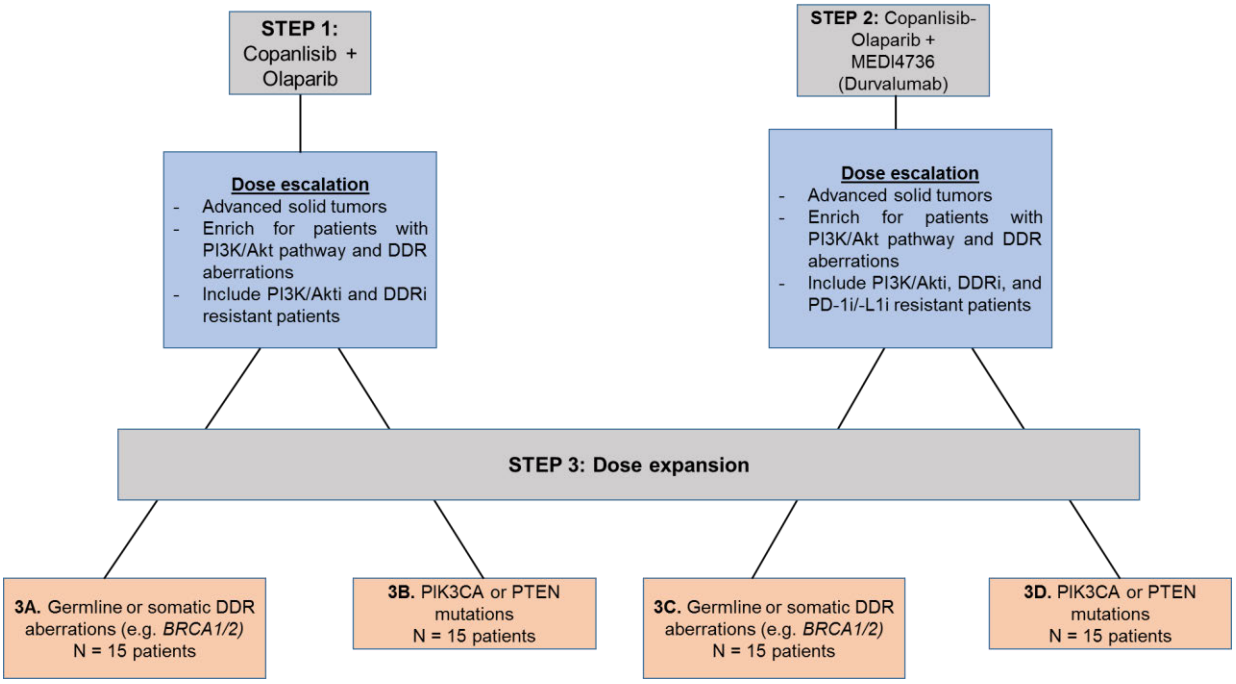
IND #: [redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / July 9, 2018
Revision 1 / September 14, 2018
Revision 2 / November 5, 2018
Revision 3 / December 12, 2018
Revision 4 / January 7, 2019
Revision 5a / March 28, 2019
Revision 6 / May 8, 2019
Revision 7 / May 31, 2019
Revision 8/ June 21 2019
Revision 9/ August 15 2019
Revision 10/March 2 2020
Amendment/August 13, 2020
Amendment/October 22, 2020
Amendment/ January 20, 2021
Amendment/ September 15, 2021
Amendment/ September 25, 2021
Amendment/ October 11, 2021
Amendment/ April 4, 2022
Amendment/ July 29, 2022
Amendment/January 20, 2023

Amendment/May 10, 2023
Amendment/ July 20, 2023
Amendment/December 14, 2023
Amendment/ May 13, 2024
Amendment/September 25, 2024

SCHEMA



Dose escalation schema for the doublet combination of copanlisib and olaparib (Step 1)

Dose Escalation Schedule		
	Copanlisib*	Olaparib*
Level -1**	45 mg (D1, D15), 28-day cycle	200 mg BID
Level 1***	45 mg QW, D1, D8, D15, 28-day cycle	200 mg BID
Level 2	45 mg QW, D1, D8, D15, 28-day cycle	300 mg BID
Level 3****	60 mg QW, D1, D8, D15, 28-day cycle	300 mg BID
Level 3a	60 mg D1 and D15, 28-day cycle	300 mg BID
*Alternative schedules may be pursued depending on toxicities, pharmacokinetic and pharmacodynamic data generated from this and other trials. **Doses to pursue at dose level -1 will depend on the dose-limiting toxicities observed at dose level 1. ***Starting dose level. **** If DLT is observed at dosing Level 3, and the dose escalation is complete, a maximum of 6 patients will be treated with a less intensive schedule of copanlisib 60 mg Day 1 and 15 and olaparib 300 mg BID (dose level 3a) to improve the safety profile.		

D = Day; BID = twice a day; QW = once a week.

Dose escalation schema for the triplet combination of copanlisib, olaparib, and durvalumab (MEDI4736) (Step 2)

Dose Escalation Schedule			
	Copanlisib	Olaparib	Durvalumab (MEDI4736)
Level -1*	45 mg (D1, D15), 28-day cycle	200 mg BID	1500 mg D1 28-day cycle (Starting Cycle 2, Day 1)
Level 1	60 mg (D1, D15), 28-day cycle	300 mg BID	1500 mg D1 28-day cycle (Starting Cycle 2, Day 1)
*Doses to pursue at dose level -1 will depend on the dose-limiting toxicities observed at dose level 1.			

D = Day; BID = twice a day
RP2D = recommended phase 2 dose; MTD = maximum tolerated dose

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1. OBJECTIVES

Primary Objective

1.1 Primary Objective

1.1.1 To evaluate the safety and establish the recommended phase 2 dose (RP2D) of the doublet combination of copanlisib and olaparib and of the triplet combination of copanlisib, olaparib and MEDI4736 (durvalumab) in patients with molecularly-selected solid tumors.

1.2 Secondary Objectives

1.2.1 To observe and record anti-tumor activity of the doublet combination of copanlisib and olaparib, and of the triplet combination of copanlisib, olaparib and MEDI4736 (durvalumab) in patients with molecularly-selected advanced solid tumors, as measured by objective response rate (ORR) (complete response [CR] + partial response [PR]). Although the clinical benefit of the doublet and triplet combination of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.2 To assess overall duration of response (DoR), progression free survival (PFS) and overall survival (OS).

1.2.3 To assess the pharmacokinetic (PK) profiles of these combinations, and explore exposure-response relationships.

1.2.4 To correlate molecular alterations with OR (CR+PR).

2. BACKGROUND

2.1 Study Diseases

The phosphatidylinositol-3 kinase (PI3K) pathway is one of the most frequently activated pathogenic signaling routes in human cancers, making it a rational and important target for innovative anticancer drug development and precision medicine (Yap *et al*., 2015). Different PI3K isoforms have the potential to interfere with cancer growth and survival, either by acting on the transformed cells directly, or by interfering with the supportive stroma and nutrient supply, or by stimulating more potent immune responses against the transformed cells (Figure 1). PI3K alpha (α) inhibitors have shown promising results in cancers driven by activating *PIK3CA* mutations, such as p110α H1047R. Evidence suggests that phosphate and tensin homolog (PTEN)-deficient tumors are often (but not always) more sensitive to PI3K beta (β) inhibitors. PI3K gamma (γ) inhibition has been shown to reduce the infiltration of tumor-suppressive macrophages, diverting them from an immune suppressive (wound healing) M2 to an immunostimulatory M1 phenotype and reducing the production of fibroblast-stimulating growth factors. PI3K delta (δ) inhibitors can

stimulate a more potent CD8+ T-cell-mediated cytotoxic anti-tumor response by activating dendritic cells (DCs) to produce more interleukin 12 (IL-12) and by inhibiting regulatory T-cell (Treg) and myeloid derived suppressor cells (MDSCs), which antagonize cell-mediated immunity in tumors.

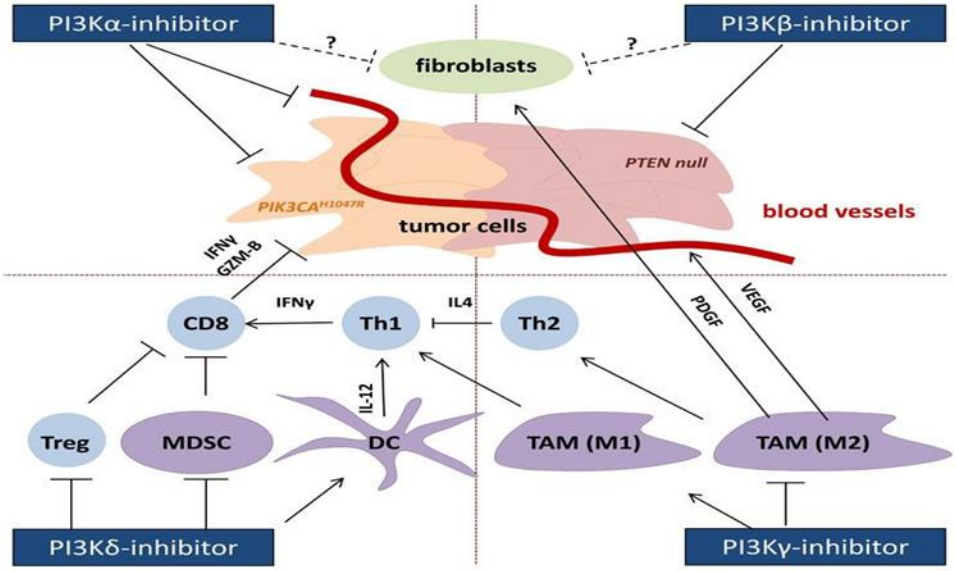


Figure 1: Direct and indirect anti-cancer effects of inhibiting PI3K isoform activity. Different PI3K isoforms have the potential to interfere with cancer growth and survival, by acting on the transformed cells directly, by interfering with the supportive stroma or nutrient supply, or by stimulating more potent immune responses against the transformed cells (Okkenhaug *et al*., 2016)

The three main classes of PI3K inhibitors currently in clinical testing comprise dual pan-Class I PI3K/ mechanistic target of rapamycin (mTOR) inhibitors, pan-Class I PI3K inhibitors lacking significant mTOR activity and isoform-selective PI3K inhibitors. A major step forward in recent years is the progression of over 30 small molecule PI3K inhibitors into clinical trials and the first regulatory approval of the PI3Kδ inhibitor idelalisib for multiple B-cell malignancies. Copanlisib has also demonstrated preliminary antitumor responses in patients with non-Hodgkins lymphoma (NHL), which is likely to be driven by its sub-nanomolar half maximal inhibitory concentration (IC_{50}) potency against PI3Kδ. However, despite favorable pharmacokinetic–pharmacodynamic profiles, only modest evidence of single agent antitumor activity has been observed in patients with advanced solid tumors with the pan-Class I PI3K inhibitors.

2.2 CTEP IND Agents

2.2.1 Copanlisib (BAY 80-6946)

Copanlisib (BAY 80-6946) is a novel small-molecule pan-class I PI3K inhibitor with exceptional inhibitory potency against δ and α PI3K isoforms (Copanlisib Investigator's Brochure, 2017). Copanlisib is an active ingredient (free base) of copanlisib dihydrochloride (BAY 84-1236), which is intended for an intravenous (IV) administration in humans. The copanlisib hydrochloride product for clinical use is formulated as a lyophilized product for reconstitution in saline to be administered by IV. Copanlisib dihydrochloride product is supplied in three formulation strengths: 20 mg, 60 mg, or 80 mg (free base) in a 6 mL injection vial for

reconstitution with 2 mL, 4.4 mL, or 4 mL of saline, respectively, to produce copanlisib solution for injection at concentration of 10 mg/mL, 15 mg/mL, or 20 mg/mL, respectively.

On September 14, 2017, the FDA granted approval to copanlisib solution (IV) for the treatment of adult patients with relapsed follicular lymphoma who have received at least two prior systemic therapies (Food and Drug Administration, 2017).

PI3K transmits signals from receptor tyrosine kinases (RTKs) to numerous cellular targets that are important for cell proliferation, survival, differentiation, and migration (Liu *et al.*, 2013). PI3K/AKT signaling is commonly dysregulated in human cancers *via* various mechanisms, *e.g.*, gene amplification, rearrangement, or activating and/or loss-of-function mutations of the pathway's molecular components (Westin, 2014). Aberrant activation of class I PI3Ks has been associated with intrinsic and acquired resistance of tumors to targeted agents, chemotherapy, and radiotherapy (Liu *et al*., 2013).

Four PI3K isoforms (PI3Kα, PI3Kβ, PI3Kγ, and PI3Kδ), all of which have a catalytic p110 subunit (p110α/β/γ/δ), comprise the class I PI3K subfamily (Liu *et al.*, 2013; Westin, 2014). PI3Kα signaling is frequently active in human malignancies, and tumors with activating mutations in PIK3CA or loss of PTEN have been found to be sensitive to PI3Kα inhibitors. PI3Kδ-specific inhibitors have shown remarkable therapeutic efficacy in some human leukemias and lymphomas (Yang *et al*., 2015). A major component of the mechanism of action of PI3Kδ inhibition in the B-cell malignancies is to attenuate the responsiveness of the tumor cells to supportive stimuli from the microenvironment (Okkenhaug and Burger, 2016). Inhibition of PI3Kδ has been shown to protect mice against a broad range of cancers, including non-hematological solid tumors (Ali *et al*., 2014). Inactivation of PI3Kδ breaks Treg-mediated immune tolerance that unleashes a cytotoxic T-cell response and resulting in tumor regression. Copanlisib is a pan-class I PI3K small-molecule inhibitor exhibiting activity predominantly against the PI3Kα and PI3Kδ isoforms. Preclinical data suggest that copanlisib may be more efficient in inhibiting survival of leukemia cells than idelalisib (PI3Kδ inhibitor) or duvelisib [PI3Kα/γ] (Gockeritz *et al*., 2015).

2.2.1.1 Nonclinical Studies

A majority of nonclinical data were produced using the copanlisib free-base.

2.2.1.1.1 Mechanism of Action

Copanlisib is a stronger inhibitor of PI3Kα (IC_{50} 0.5 nmol/L) and PI3Kδ (IC_{50} 0.7 nmol/L) than of PI3Kβ (IC_{50} 3.7 nmol/L) or PI3Kγ [IC_{50} 6.4 nmol/L] (Liu *et al.*, 2013). Compared to the PI3K isoforms, copanlisib was a much weaker inhibitor of mTOR (IC_{50}=45 nmol/L). In a panel of ~220 kinases, copanlisib (1 mcmol/L) failed to achieve a 50% inhibition of any kinase other than PI3K isoforms and mTOR. In tumor cell lines with hyperactive PI3K signaling, copanlisib antitumor activity was paralleled by a robust decrease in basal levels of phosphorylated protein kinase B (AKT), both at serine 473 (AKTpS473) and threonine 308 (AKTpT308), and by increases in caspase-9 levels, which is suggestive of induction of apoptosis.

2.2.1.1.2 Nonclinical in vitro Antitumor Activity

Copanlisib potently inhibited tumor cell proliferation (IC_{50} of 1-760 nmol/L) in human tumor cell lines of various histologies, including breast, ovary, endometrial, prostate, colon, lung, liver, brain, kidney, melanoma, pancreas, and hematological tumors (Figure 2); many of which exhibit constitutively activated PI3K signaling resulting from somatic mutations in *PIK3CA* and *PTEN* (Liu *et al.*, 2013).

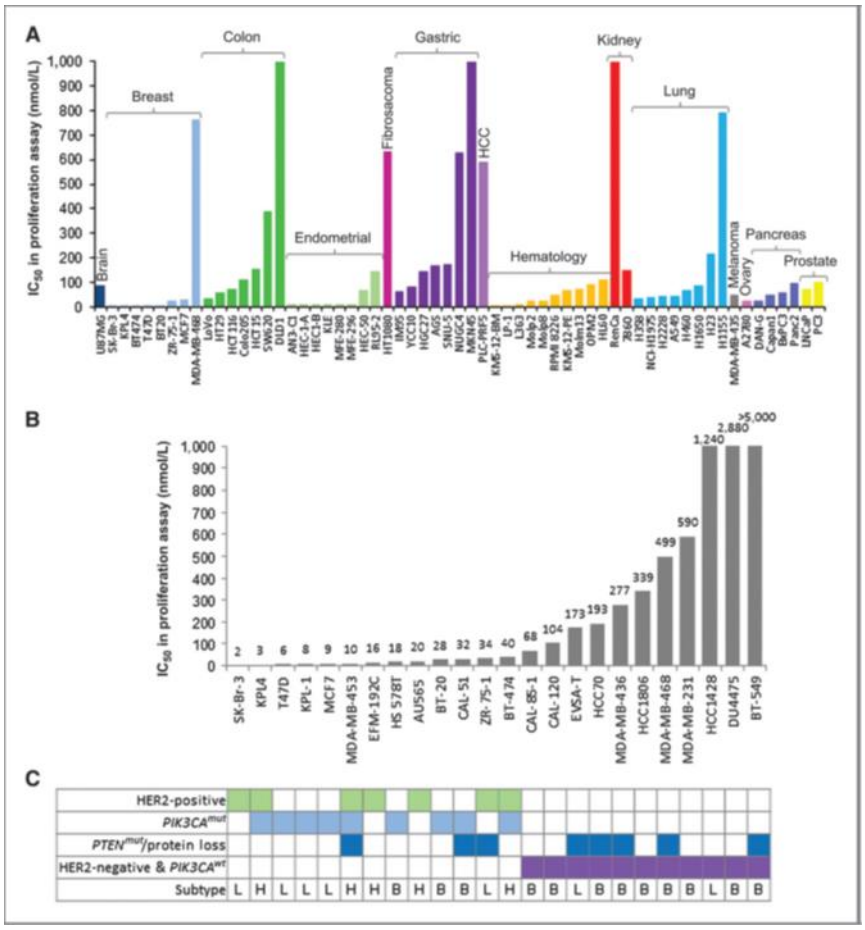


Figure 2: Antiproliferative activity against a panel of human tumor cell lines.
Panel A: Cell lines of various tumor histologies. Panel B: Breast cancer cell lines. Panel C: Molecular and histological characterization of breast cancer cell lines shown in panel B. Subtype Legend: B: basal–like breast cancer cell lines; L: luminal-type breast cancer cell lines; H: human epidermal growth factor receptor 2 (HER 2)-positive breast cancer cell lines (Copanlisib Investigator's Brochure, 2017).

To further analyze a relationship between molecular features and copanlisib activity, copanlisib was tested against 24 breast cancer cell lines with known *PI3KCA* gene mutation, *PTEN* gene mutation or expression, and *HER2* expression status (Liu *et al.*, 2013). Antiproliferation IC_{50s} of copanlisib were ~40-fold lower in cells with activating mutations in *PIK3CA* (IC_{50}=19 nmol/L; n=9) or *HER2*-positive cells (IC_{50}=17 nmol/L; n=7) than for cells with *PIK3CA* wild-type (WT) and *HER2*-negative status (average IC_{50}=774 nmol/L; n=11). However, no clear correlation has been found between sensitivity of cells to copanlisib and the loss of PTEN. Of note, copanlisib efficiently inhibited cell proliferation of breast cancer cell lines that are resistant to HER2

inhibitors (trastuzumab or lapatinib) such as T47D (mutant *PIK3CA*), ZR-75-1 (*PTEN* null), or MCF7 (mutant *PIK3CA)* with IC_{50s} of 6, 24, and 27 nmol/L, respectively.

Following a 24-hour incubation of the BT20 breast cancer cells (mutant *PIK3CA* and resistant to the HER2 inhibitor lapatinib) in the presence of copanlisib at a dose of 62 nmol/L induced 2- to 3-fold increases in caspase-9 activities [Figure 3A] (Liu *et al.*, 2013). After 24-hour and 48-hour incubations with copanlisib (200 nmol/L), several fold increases in phosphorylated p53 at serine 15 [p53pS15] (Figure 3B) and cleaved poly adenosine diphosphate ribose polymerase [PARP] (Figure 3C) were observed. These results were consistent with increased caspase-9 activity. In the lapatinib-sensitive breast cancer cell line BT474, copanlisib alone caused caspase-9 activation at a half maximal effective concentration (EC_{50}) of 340 nmol/L. In contrast, lapatinib, was not able to activate caspase-9, even at a concentration as high as 10 mcmol/L. When BT474 cells were exposed to a combination of copanlisib and lapatinib, the same level of caspase-9 activation was achieved at markedly lower concentrations of copanlisib (61 nmol/L) and lapatinib (184 nmol/L).

Collectively, these data suggest that copanlisib could induce apoptosis in both HER2 inhibitor-resistant and sensitive breast cancer cell lines at clinically achievable concentrations.

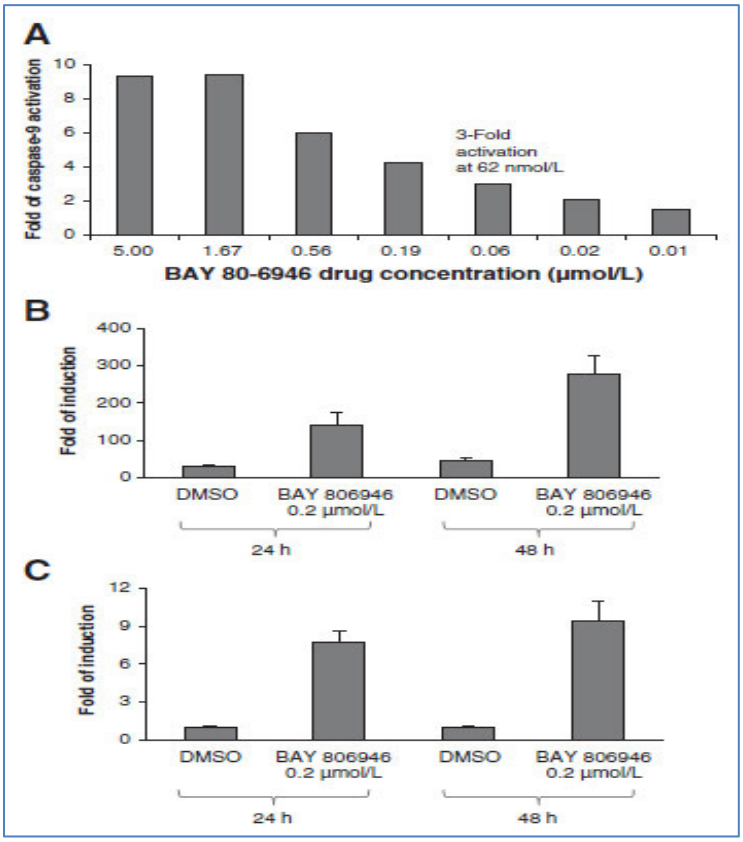


Figure 3: Induction of apoptosis by copanlisib (BAY 806946) in lapatinib-resistant breast cancer cell line BT20. Panel A: Activation of caspase-9 by copanlisib. Panel B: Induction of phosphorylation of p53 at serine 15 by copanlisib. Panel C: Induction of cleaved PARP by copanlisib.

Copanlisib was also tested against a panel of 32 human hematological cancer cell lines

(Copanlisib Investigator's Brochure, 2016). Copanlisib was a more potent inhibitor than idelalisib, the PI3Kδ-selective inhibitor; idelalisib IC_{50s} were 1.4-fold to several thousand-fold higher than copanlisib IC_{50s} against these cell lines. Copanlisib IC_{50s} were <100 nmol/L for 14 cell lines, including acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), NHL, and myeloma. Some of the strongest responses to copanlisib (IC_{50} <10 nmol/L) occurred in AML (Kasumi-1, IC_{50}=1.1 nmol/L), the Burkitt's lymphoma subtype of NHL (NAMALWA, IC_{50}=1.7 nmol/L), the diffuse large B-cell lymphoma (DLBCL) subtype of NHL (Pfeiffer, IC_{50}=0.8 nmol/L), and myeloma (MM-1R, IC_{50}=1.0 nmol/L; and NCI-H929, IC_{50}=2.7 and 2.2 nmol/L in 2 different experiments). Copanlisib was also more potent inhibitor against an aggressive NHL type such as DLBCL than idelalisib or a Bruton's tyrosine kinase (BTK) inhibitor ibrutinib (Figure 4).

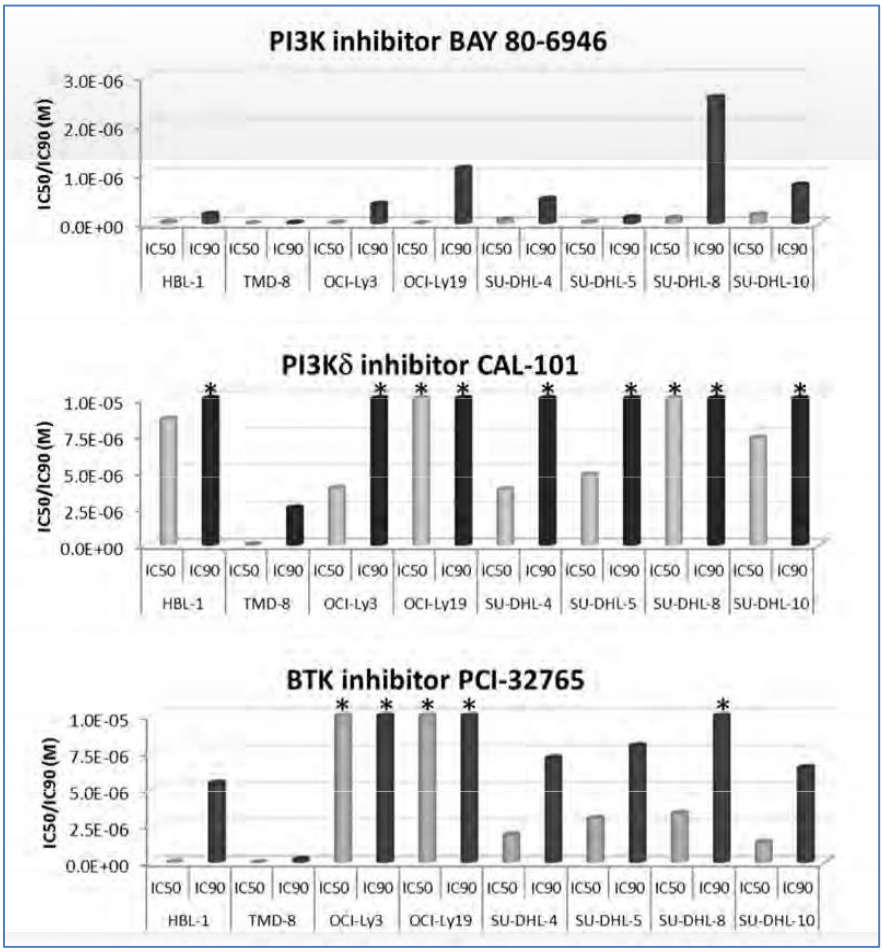


Figure 4 Antiproliferative effects of copanlisib (BAY 80-6946), idelalisib (CAL-101), and ibrutinib (PCI-32765) against DLBCL cell lines. Legend: IC50: a drug concentration causing 50% inhibition of cell proliferation.

Concurrent treatment with copanlisib and ibrutinib resulted in synergistic effects of the two inhibitors against ibrutinib-sensitive cell lines but antagonistic effects in ibrutinib-resistant cell lines.

2.2.1.1.3 In vivo Antitumor Activity

Copanlisib demonstrated antitumor activity *in vivo* in a variety of xenograft models of tumors exhibiting an activated PI3K pathway (Liu *et al*., 2013). The drug displayed robust antitumor activity in the nude rat xenograft model of the KPL4 breast tumor cell line, which is an estrogen-independent HER2-positive breast carcinoma that carries a somatic *PIK3CA* mutation. Copanlisib was administered on day 14 post-implant at doses ranging from 0.5-6 mg/kg IV every second day (Q2D) for a total of five doses. On day 25, 3 days after the last dose, tumor growth inhibition (TGI) rates of 77%-100% were observed in the dose range (Figure 5A). The complete tumor regressions were observed in 100% of animals receiving dose of 3 or 6 mg/kg, and all rats remained tumor free at the termination of the study on day 73. Delays in tumor growth of >25 days were observed in the 0.5 and 1 mg/kg groups. Copanlisib administered at 3 and 6 mg/kg IV Q2D x 5 in *PIK3CA* and mutant *KRAS* HCT 116 xenograft rat models resulted in the TGI of 75% and 88% (Figure 5B). Copanlisib was also effective in the nude mouse patient-tumor xenografts of Lu7860 (erlotinib-resistant non-small cell lung carcinoma [NSCLC]) and MAXF1398 (luminal breast tumor). Copanlisib administered at 14 mg/kg twice a day (BID), Q2D for 10 days resulted in the 88% TGI in the NSCLC model (Figure 5C) and 71% TGI in the breast cancer model (Figure 5D).

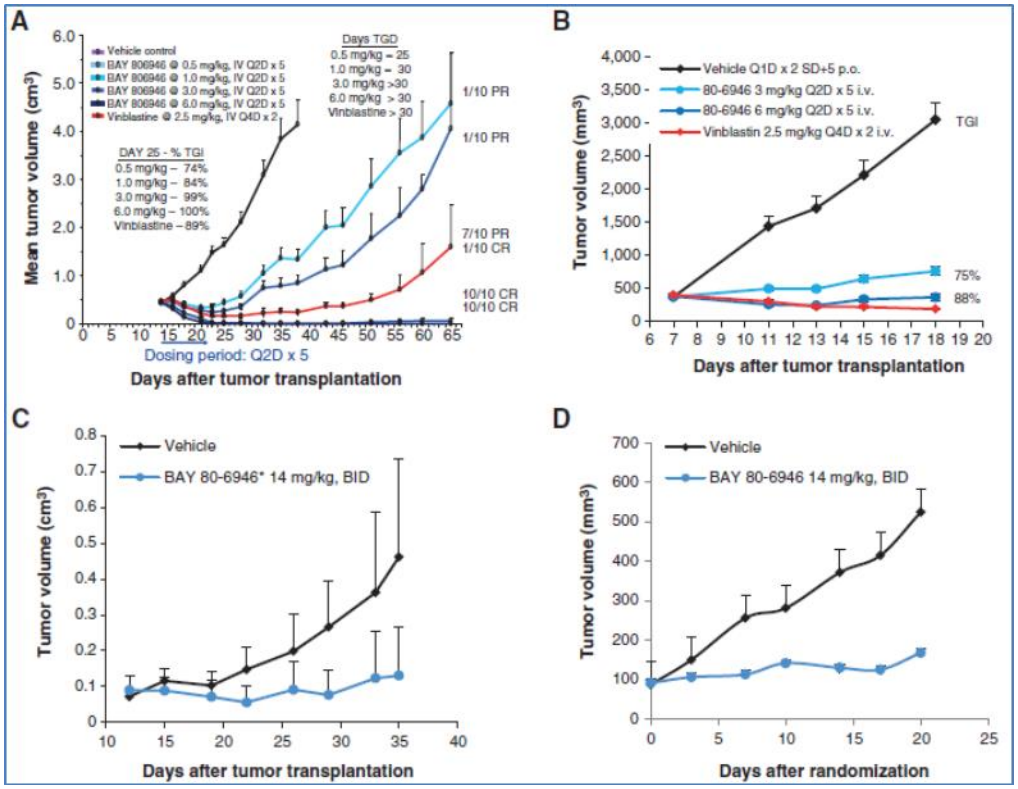


Figure 5: Activity of copanlisib (BAY 80-6946) in xenograft models using Q2D treatment schedule. Panel A: KPL4 breast cancer xenografts in nude rats (n=10/group). Panel B: HCT116 colon cancer xenografts in nude rats (n=10/group). Panel C: Lu7860 erlotinib-resistant, patient-derived NSCLC xenografts in nude mice (n=5/group). Panel D: MAXF1398 patient-derived luminal breast cancer xenografts in nude mice (n=6/group). Legend: Q2D: every 2 days; BID: twice a day; IV: intravenously; TGD: tumor growth delay; PR: partial response; CR: complete response

Copanlisib was also evaluated on a weekly schedule. Two doses of 9 mg/kg on day 1/week caused 64% TGI in the HCT-116 xenograft model, which was equivalent to the effect of copanlisib given at 6 mg/kg Q2D for 10 doses (Figure 6A).

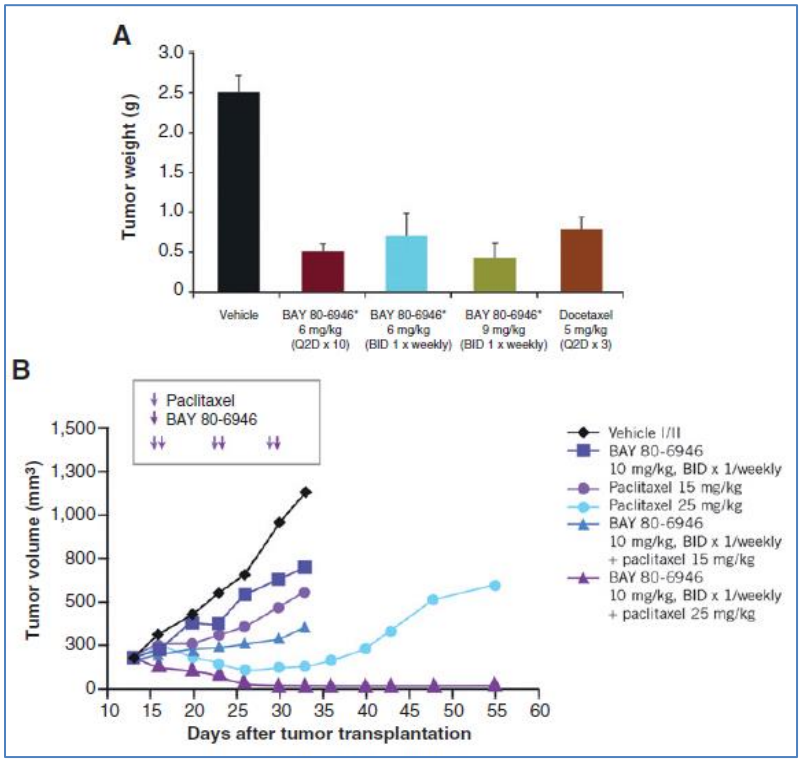


Figure 6: Activity of copanlisib (BAY 80-6946) in xenograft models using a twice a day (BID) once-weekly schedule. Copanlisib was formulated in 5% mannitol vehicle. Panel A: HCT-116 colon cancer xenografts in nude rats (8 rats/group). Panel B: Lu7343 patient-derived NSCLC xenografts in nude mice (10 mice/group). Legend: BID: twice a day; Q2D: every 2 days

In vivo antitumor activity of copanlisib was also tested in combination with cytotoxic agent paclitaxel in the mutant PIK3CA squamous cell NSCLC patient-derived Lu7343 xenograft mouse model (Liu *et al*., 2013). Paclitaxel was given weekly at 15 or 25 mg/kg on days 14, 21, and 28, followed 24 hours later by copanlisib at 10 mg/kg BID on weekly schedule (days 15, 22, and 29) in a group of 10 animals. In addition, both drugs were tested as single agents (n=10); the control group received a vehicle (no drug). The drug combination was more potent in inhibiting tumor growth than either drug alone (Figure 6B). Although single-agent paclitaxel dosed at the maximum-tolerated dose (MTD) of 25 mg/kg was highly efficacious for the duration of treatment (33 days), showing tumor regression in 70% of animals, discontinuation of the treatment dropped the response rate to 30% (day 55), with 60% of animals demonstrating tumor re-growth. In contrast, the copanlisib + paclitaxel combination produced long-lasting tumor regressions, with a CR observed in 6/10 animals and a PR observed in 4/10 animals 22 days after stopping treatment (day 55).

Copanlisib was well tolerated at all doses and schedules tested in these studies without producing any lethality (Liu *et al*., 2013). The MTD in rats was 6 mg/kg Q2D. A maximum mean body weight loss of 6%-10% occurred during the first few days at this dose and then consistently returned to the normal range by the end of the dosing period. The MTD in mice was more than

14 mg/kg Q2D.

Based on the promising *in vitro* antitumor activity of copanlisib against DLBCL cell lines, copanlisib was tested *in vivo* alone and in the combination with ibrutinib in the TMD-8 severe combined immunodeficiency (SCID) mouse model (Copanlisib Investigator's Brochure, 2017). The TMD-8 DLBCL cell line harbors activating mutations in *CD79B* and *MYD88*. Copanlisib hydrochloride was dosed at 14 mg/kg IV daily (QD) for 2 days on and 5 days off/week and ibrutinib was administered at 20 mg/kg orally (PO) QD. The combination demonstrated synergistic activity, with 100% response rate (5 CRs and 3 PRs in 8 animals) observed compared to 12.5% (1 PR in 8 animals) and no responses seen in the copanlisib alone treatment group.

2.2.1.1.4 Nonclinical Pharmacokinetics and Pharmacodynamics

Copanlisib plasma-free fraction across species was as follows: 35% in rats, 14% in mice, 33% in dogs, and 16% in humans (Liu *et al*., 2013). The pharmacokinetic (PK) profile of copanlisib was evaluated following single and multiple IV doses in nude rats. Single-dosed copanlisib exhibited a very large volume of distribution (V_d=32 L/kg), high plasma clearance (3.95 L/kg/h) and a long half-life [$t_{1/2}$] (6.0 h). The copanlisib PK parameters at repeat dosing (Q2D x 5 doses), were similar those from single-dosing studies and suggested no drug accumulation in plasma. Copanlisib had a higher clearance (16 L/kg/h), shorter $t_{1/2}$ (0.7 h) and smaller volume of distribution [V_d] (12.9 L/kg) in mice than rats. A single bolus IV dose of copanlisib (6 mg/kg) in the H460 NSCLC xenograft rat model produced 100 times higher concentration of the drug in tumor tissue than in plasma at 48 hours post-dosing; the drug clearance from the tumor was slower than from plasma. The pharmacodynamics analysis showed 90% inhibition of AKTpS473 at 24 hours post-dosing compared to the control animals, and the AKTpS473 level remained suppressed up to 72 hours. In addition, 65% and 75% reductions in Ki-67 and phospho-histone H3 levels, respectively, were observed at 24 hours in the copanlisib group compared to the control group, suggesting copanlisib-induced G0 cell-cycle arrest. Copanlisib also demonstrated sustained inhibition (over 24-48 hours) of ^{18}F-deoxyglucose (FDG) uptake in tumor. These preclinical data suggested that high and prolonged copanlisib tumor exposures can be reached *in vivo*, and there was a correlation between copanlisib exposure and inhibition of the PI3K pathway in the tumor.

In the rat tumor xenograft model studies, the efficacious exposure of copanlisib was estimated as the area under the concentration-time curve (AUC) for the unbound/free drug (AUCu) in plasma of 370 mcg•h/L based on weekly dosing (Copanlisib Investigator's Brochure, 2017).

2.2.1.1.5 Summary of Nonclinical Metabolism

Copanlisib is primarily metabolized by the cytochrome P450 (CYP)3A4 with a minor contribution of CYP1A1 (Copanlisib Investigator's Brochure, 2017). Copanlisib is a weak substrate of P-glycoprotein (P-gp) and of breast cancer resistance protein (BCRP). There is a low risk for clinically relevant PK drug-drug interactions (DDI) through inhibition or induction of CYP enzymes, inhibition of uridine diphosphate glucuronosyltransferase (UGT) enzymes and inhibition of dihydropyrimidine dehydrogenase (DPD) by copanlisib. Copanlisib also inhibited P-gp- and BCRP-mediated transport *in vitro*. Furthermore, copanlisib was a strong inhibitor of

the drug transporter multidrug and toxin extrusion protein 2 (MATE2K). Copanlisib also inhibited P-gp- and BCRP-mediated transport *in vitro* at concentrations much higher than those observed at the approved 60 mg clinical dose.

2.2.1.1.6 Summary of Nonclinical Safety

IV infusion of copanlisib caused vasoconstriction, enhanced insulin and glucose levels, impaired glucose tolerance, reduced gastrointestinal (GI) motility, increased renal volume and electrolyte excretion, and central nervous system (CNS) depressant effects in nonclinical species (Copanlisib Investigator's Brochure, 2017). A majority of these effects could be explained by inhibition of PI3K-dependent signaling, and they occurred at or slightly above the plasma concentrations shown to be efficacious in tumor xenograft rat models (maximum concentration [C_{max}]=30-80 mcg/L; C_{max} of unbound fraction [$C_{max,u}$] 11-28 mcg/L). The CNS depressant effects occurred at high plasma concentrations and are considered secondary to hyperglycemia. At pharmacodynamically relevant concentrations, copanlisib does not interfere with cardiac repolarization *in vitro* or *in vivo*.

Based on the findings from repeat-dose toxicity studies in nonclinical species, copanlisib is expected to adversely affect male and female reproduction. Developmental and reproductive toxicity of PI3K inhibitors is known. Maternal toxicity of increasing severity, severe post-implantation loss, and developmental toxicity, including teratogenicity, were seen in rats starting at low doses. Copanlisib was not genotoxic *in vitro* or *in vivo*. There is no evidence that copanlisib has phototoxic potential. Significant toxicities were observed in animals at doses achieving plasma concentrations observed in humans.

2.2.1.2 Effects in Humans

2.2.1.2.1 The First-in-Human Copanlisib Study

In the first-in human (FIH) phase 1 trial in patients with advanced and/or refractory malignancies, of 57 patients (51 non-diabetic) treated, 17 took part in the dose-escalation phase with copanlisib (0.1-1.2 mg/kg) administered IV weekly for 3 weeks of a 4-week cycle (Patnaik *et al.*, 2016). The copanlisib MTD was 0.8 mg/kg IV (1 h) weekly for 3 weeks on a 28-day cycle. An additional 34 patients were treated in the MTD expansion cohorts: the solid tumor cohort (n=25), NHL cohort (n=9; 6 patients with follicular lymphoma [FL] and 3 patients with DLBCL). Finally, 6 patients with diabetes mellitus were treated with copanlisib at 0.4 mg/kg weekly x 3 weeks.

2.2.1.2.2 Clinical Safety

The most common (≥20%) copanlisib-related adverse events [AEs] (regardless of grade) included hyperglycemia (63%), nausea (37%), and hypertension (21%). The most common drug-related grade 3 AEs were hyperglycemia (30%), hypertension (14%), and rash (7%) (Patnaik *et al.*, 2016). Grade 3+ diarrhea occurred in one patient. Two patients (4%) experienced three drug-related grade 4 AEs: a dose-limiting hyperglycemia and increased aspartate aminotransferase (AST) in one patient and elevated serum amylase in another patient.

Overall, serious AEs (SAEs) with positive association to copanlisib were observed in six patients (11%): grade 3 left ventricular systolic dysfunction (LVSD) which was a dose-limiting toxicity (DLT), chest pain, hypertension, and hyperglycemia (in one patient each), and pneumonitis (in two patients). None of seven grade 5 AEs (12%) was considered drug related. Dose modifications (delays, interruptions, and reductions) caused by drug-related AEs occurred in 14 patients (25%). Four patients discontinued treatment due to toxicity. One drug-related AE (dose-limiting LVSD) led to permanent discontinuation of treatment. No patient discontinued the study because of hyperglycemia.

Hyperglycemia was transient, with a glucose level peaking at 5–8 hours after copanlisib infusion on cycle 1 day 1 and declining to baseline by the time of the next infusion. Sixty-five percent of non-diabetic patients (33/51) received at least one dose of short-acting insulin to manage high blood glucose (>200 mg/dL). There was no trend for increased pre-dose glucose values over time, and no patients developed diabetic ketoacidosis during the study. Hemoglobin A1c (HbA1c) levels changed only modestly over the course of copanlisib treatment. Post-infusion increases in blood pressure (BP) peaked at 1–2 hours and resolved within 24 hours post-infusion.

A similar transient pattern of elevated blood glucose post-infusion was seen for the cohort of six diabetic patients treated with 0.4 mg/kg copanlisib, all of whom received insulin following the first copanlisib infusion. The AE profile in the diabetic cohort of patients was similar to that in non-diabetic patients, with a total of four drug-related grade 3 AEs observed in three patients: hypertension in two patients, and hyperglycemia and rash/desquamation in one patient each.

2.2.1.2.3 Pharmacokinetics/Pharmacodynamics

Copanlisib plasma C_{max} was typically reached between 0.5 and 1 hour (time to maximum concentration [t_{max}]) following the infusion (Patnaik *et al*., 2016). Copanlisib exposure, expressed either as C_{max} or AUC between 0-25 hours ($AUC_{0–25h}$), increased proportionally with dose between 0.1 and 1.2 mg/kg, and exhibited a moderate to high inter-patient variability. The terminal $t_{1/2}$ was 38.2 hours and no accumulation was observed after once-weekly administration. The trough levels of copanlisib on cycle 1 day 8 were 4.92 mcg/L (range, 2.74–23.0 mcg/L).

A pharmacodynamic effect event was defined as an increase in plasma glucose level of ≥50 mg/dL from baseline within 2 hours after the completion of the copanlisib infusion, and / or an increase in plasma insulin level to greater than two times the baseline value (Copanlisib Investigator's Brochure, 2017). At the MTD (0.8 mg/kg), 100% of patients showed the pre-defined increases in glucose and insulin. Overall, 53/57 (93%) patients experienced a predefined pharmacodynamics effect of an increased glucose plasma level following the first copanlisib infusion. Increases in glucose levels strongly correlated with copanlisib exposure (AUC_{0-25h}) (Patnaik *et al*., 2016). A weak correlation between exposure and change in tumor FDG uptake (via ^{18}FDG-positron emission tomography [PET]) from baseline to cycle 1 day 3 or day 4 was seen in 19/21 patients evaluated, with >25% reduction in the FDG uptake observed in the tumor of 7 patients (33%).

2.2.1.2.4 Antitumor Activity/Response

Among patients with solid tumors (n=48), clinical responses were observed only in patients treated at the copanlisib MTD (Patnaik *et al.*, 2016). The responses were: 1 CR (2%) in a patient with endometrial cancer, 2 PRs (4%) in patients with breast cancer, 15 cases of stable disease patients (SD) (31%), and 15 cases of progressive disease (PD) (31%) according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In comparison, by clinical assessment, 7 patients (15%) had PD, and 8 patients (17%) were not assessed. Overall clinical benefit rate (CBR) was 38%.

The CR responder had endometrial cancer with *PIK3CA* and *PTEN* mutations and complete PTEN loss. Of the two breast cancer patients who had PR, both had tumors positive for estrogen receptor (ER) and progesterone receptor. One was negative and the other positive for HER2; 1 had mutant and the other WT *PIK3CA*; and PTEN status was unavailable in both. No clear relationship was found between PI3KCA mutational status and disease control (P=1.0).

All 9 patients with NHL were evaluable for response using the International Working Group criteria. There were 1 CR (FL), 6 PRs (5 FL and 1 DLBCL), and 2 PD (DLBCL). A post-hoc radiologic review determined that two patients with FL achieved a CR. In addition, two FL patients had long-term durable responses, one of whom was on treatment for approximately 4 years before coming off study because of disease progression; the other patient was still on treatment as of 19 January 2016 (>3 years). All seven NHL responders had *PI3KCA* WT status; by immunohistochemistry (IHC), one patient had complete PTEN loss, two had low PTEN expression, two had positive PTEN expression, and two had unknown PTEN expression. Both patients with disease progression had low PTEN expression.

2.2.1.2.5 The Copanlisib Phase 2 Study in Refractory Lymphoma

In the phase 2 study of copanlisib in patients with various indolent and aggressive, relapsed or refractory NHL, copanlisib demonstrated antitumor activity (Copanlisib Investigator's Brochure, 2017). At the time of the data analysis, seven patients (8.3%) still were ongoing treatment, including four patients in the indolent NHL / chronic lymphocytic leukemia (CLL) cohort and three patients in the aggressive NHL cohort.

Among 32 patients with indolent NHL (15 with FL, 3 with marginal-zone lymphoma [MZL], and 1 with small lymphocytic lymphoma [SLL]) and 13 patients with CLL, 14 patients achieved objective tumor responses (2 CR, 1 unconfirmed CR, and 11 PR) resulting in an ORR of 44%. In addition, 15 patients (47%) achieved SD; 1 patient had PD. Of 48 patients with aggressive lymphoma, 13 patients achieved objective tumor responses (2 CR, 2 unconfirmed CR, and 9 PR) resulting in 27% ORR. In addition, 11 patients achieved SD (23%); 16 had PD (33%). The ORR was also analyzed by histological subtype; the data are summarized in the following table.

Clinical Activity Stratified by Histology Subtype

Histology	N	Total OR (ORR)	CR	CRu	PR	SD	PD	NE	NA
INDOLENT									
Indolent NHL	19	9 (47%)	2	1	6	9	0	0	1
FL	15	6 (40%)	2	2	3	8	0	0	1
MZL	3	2 (67%)	0	0	2	1	0	0	1

Histology	N	Total OR (ORR)	CR	CRu	PR	SD	PD	NE	NA
SLL	1	1 (100%)	0	0	1	0	0	0	0
CLL	13	5 (38%)	0	0	5	6	1	0	1
AGGRESSIVE									
DLBCL	15	1 (6.7%)	0	0	1	0	4	1	3
MCL	11	7 (64%)	0	2	5	0	3	0	1
Transformed indolent NHL	6	2 (33%)	0	0	2	0	3	0	1
Peripheral T-cell lymphoma	14	3 (21%)	2	0	0	1	5	0	1
Mediastinal large B-cell lymphoma	1								
FL grade3b	1								

N: total number of patients; NE: non-evaluable; NA: not available; OR: objective response: ORR: OR rate; CR: complete response; CRu: unconfirmed complete response; PR: partial response; SD: stable disease; PD: progressive disease; NHL: non-Hodgkin's lymphoma; FL: follicular lymphoma; CLL: chronic lymphocytic leukemi; MZL: marginal-zone lymphoma; SLL: small lymphocytic lymphoma; DLBCL: diffuse large B-cell lymphoma; MCL: mantle cell lymphoma. Copanlisib Investigator's Brochure, 2017.

2.2.1.2.6 Safety

Hyperglycemia and hypertension are on-target AEs for PI3K inhibitors. The most common copanlisib-related AEs (all grades), by the medical dictionary for regulatory activities preferred term (MedDRA PT), that occurred in ≥20% of the patients in this study were hyperglycemia (54.8%), hypertension (51.2%), diarrhea (32.1%), neutropenia (23.8%) [by Common Terminology Criteria for Adverse Events (CTCAE) terms: neutrophil count decreased (28.6%)], and fatigue [20.2%] (Copanlisib Investigator's Brochure, 2017).

2.2.1.2.7 Copanlisib Clinical Pharmacology Summary

Copanlisib plasma exposure (C_{max} and AUC) increased in a dose-proportional manner over an absolute dose range of 5 to 93 mg (0.08 to 1.55 times the approved recommended dose of 60 mg). There is no time-dependency and no accumulation in the PK of copanlisib administered weekly. The geometric mean terminal elimination half-life (CV%) of copanlisib was 39.1 h (40.8%) based on the pooled analysis of 3 Phase 1 studies (12871, 15205 and 16270). The geometric mean clearance (CV%) was 17.9 L/hr (45.6%). Copanlisib is eliminated predominantly via feces (64% of the administrative radioactive dose mean recovery with 30% unchanged copanlisib) compared to urine (22% mean recovery with 15% unchanged copanlisib) (Copanlisib Investigator's Brochure, 2017).

Population PK analyses suggest that body weight, age (20 to 90 years), gender, race (White, Asian, Hispanic and Black), smoking status, body weight (41 to 130 kg), mild hepatic impairment and mild to moderate renal impairment had no clinically significant effect on the pharmacokinetics of copanlisib (Copanlisib Investigator's Brochure, 2017). No dose adjustment is necessary based on these specific populations. Preliminary analysis of central tendency and exposure-response analyses suggest that copanlisib does not prolong QT/QTc interval. Further details can be found in the latest available version of the investigator's brochure (2017), which contains comprehensive information on the study drug and also the US prescription drug

label.

2.2.1.3 Copanlisib Reference Safety Information

2.2.1.3.1 The recommended dose and administration of copanlisib

Based on the FIH company-sponsored study, the MTD of copanlisib in non-diabetic patients with solid malignancies was 0.8 mg/kg (equivalent to 60mg approved dose) administered IV over 1 hour once weekly for 3 weeks (days 1, 8, and 15) on a 28-day cycle (Copansilib Investigator's Brochure, 2017).

A preliminary population PK analysis revealed no impact of either body weight, body surface area (BSA), or other body size-related factors on the clearance of copanlisib and thus a flat-dose regimen of copanlisib has been recommended (Copansilib Investigator's Brochure, 2017).

Based on these data, the RP2D of copanlisib monotherapy is 60 mg given over a 1-hour IV infusion once a week for 3 weeks (days 1, 8, and 15) every 4 weeks. A dose reduction to 45 mg for toxicities have been allowed.

2.2.1.3.2 Drug-drug interactions

Copanlisib metabolism is predominantly mediated by CYP3A4 (> 90%) and to a minor extent by CYP1A1 (< 10%) (Copanlisib Investigator's Brochure, 2017). Itraconazole, a strong CYP3A4 inhibitor and a P-gp and BCRP transporter inhibitor, increased copanlisib (60 mg) AUC by 1.53-fold with no effect on C_{max} (1.03–fold). If concomitant use with strong CYP3A inhibitors cannot be avoided, a dosage reduction to 45mg is recommended. Rifampin, a strong CYP3A4 inhibitor and a P-gp transporter inhibitor, decreased the AUC of copanlisib (60 mg) by 63% with minimal effect on C_{max} (15%) and strong inducers should be avoided (Copanlisib Investigator's Brochure, 2017).

2.2.1.3.3 Pregnancy and lactation

Due to a mechanism of action as a PI3K inhibitor, adverse effects on development and reproduction are expected for copanlisib (Copanlisib Investigator's Brochure, 2017). Nonclinical repeat-dose toxicity studies demonstrated adverse effects of copanlisib on male and female reproduction. Maternal toxicity of increasing severity, severe post-implantation loss, and developmental toxicity, including teratogenicity were seen in a rat pilot developmental toxicity study beginning at a low dose. In the rat study with ^{14}C-labeled copanlisib, radioactivity was secreted into the milk of lactating animals although at a low extent (1.7% of dose). No data are available on the distribution of copanlisib to human milk. Therefore, unless potential benefits to patients outweigh unknown risks, women who are pregnant or nursing and children should be excluded from the clinical studies of copanlisib. In addition, women of child-bearing potential or female partners of male patients will be required to use an adequately effective barrier method of birth control.

2.2.1.3.4 Special safety warnings and precautions

Nonclinical studies suggest and clinical studies confirm, blood glucose increases persisting for approximately 1-3 days after study copanlisib administration (Copansilib Investigator's Brochure, 2017). Blood or serum glucose, serum and urine ketones, and electrolytes should be monitored while on copanlisib treatment.

Standard cardiovascular parameters, including pulse and BP should be monitored because of hypertension (during the first 3 h after start of infusion) that has been observed.

Respiratory infections (including pneumonia, *Pneumocystis jirovecii* pneumonia, cryptococcosis and bronchopulmonary aspergillosis) have been observed in studies with monotherapy and combination therapies. Some of these infections may have life-threatening or fatal outcome. Cases of pneumonitis observed in studies with monotherapy and in combination therapies were generally ≤grade 3 in severity and responded well to corticosteroid treatment; occasional events with life-threatening or fatal outcome have been observed. Since the early symptoms of pneumonitis overlap with those of a respiratory infection, monitoring of patients for typical clinical symptoms like cough, dyspnea or fever and further evaluation for respiratory infections is recommended. Patients suspected of having a respiratory infection or noninfectious pneumonitis should be promptly treated with appropriate antimicrobial agents and/or corticosteroids as indicated.

2.2.2 Olaparib (AZD2281)

In December 2014, the European Commission approved olaparib capsules as a maintenance treatment for platinum-sensitive, relapsed, high grade serious epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients with breast cancer (*BRCA*) mutations (germline [g*BRCA*m] and/or somatic [s*BRCA*m]) who are in a CR or PR to platinum-based chemotherapy. In December 2014, the Food and Drug Administration (FDA) approved olaparib capsules as monotherapy for advanced ovarian cancer in patients with deleterious or suspected g*BRCA*m who have been treated with three or more prior lines of chemotherapy. In August 2017, the FDA approved the tablet formulation of olaparib for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a CR or PR to platinum-based chemotherapy; olaparib tablets were also approved for the December 2014 indication. On January 12, 2018, the FDA granted regular approval to olaparib tablets for the treatment of patients with deleterious or suspected deleterious germline *gBRCAm*, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been treated with chemotherapy either in the neoadjuvant, adjuvant, or metastatic setting.

2.2.2.1 Mechanism of action

Olaparib inhibits PARP, a protein that repairs single-strand breaks (SSBs) via base excision repair (BER), a backup repair system to homologous recombination (HR) repair (Farmer *et al.*, 2005; Olaparib Investigator's Brochure, 2018). Olaparib potently inhibits PARP1 (IC_{50}=5 nM), PARP2 (IC_{50}=1 nM), and PARP3 (IC_{50}=4 nM) *in vitro* (Olaparib Investigator's Brochure, 2018). The inhibition of PARP and disruption of BER via olaparib treatment leads to accumulation of

double-strand breaks (DSBs); in tumors with defective components of HR repair, these DSBs cannot be accurately repaired, resulting in genomic instability and induction of synthetic lethality (Farmer *et al.*, 2005; Olaparib Investigator's Brochure, 2018). Cultures of cells deficient in HR repair factors, notably BRCA1 and BRCA2, are particularly sensitive to treatment with olaparib (Olaparib Investigator's Brochure, 2018). Furthermore, olaparib may enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

2.2.2.2 Overview of Clinical Pharmacology

Single PO dosing of olaparib tablets was rapidly absorbed with peak plasma concentrations typically observed at 1.5 hours (Olaparib Investigator's Brochure, 2018). A population PK analysis characterized the absorption phase of olaparib as a sequential zero- and first-order absorption and showed a significant impact of olaparib tablet strength on the absorption rate constant. Once t_{max} was reached, plasma concentrations of olaparib declined in a biphasic manner with an average $t_{1/2}$ of 14.9 hours (standard deviation [StD]: 8.2 hours). The mean apparent clearance (CL) after a single dose of olaparib tablets at 300 mg PO was approximately 7.4 L/h (StD: 3.9 L/h). Olaparib exhibited a mean volume of distribution (Vd) of 158 L (StD: 136 L), indicating distribution into the tissues. The plasma protein binding *in vitro* was moderate and showed evidence of concentration dependence (81.9% at 10 mcg/ml).

Multiple-dose PK was reasonably well predicted from single-dose data, and accumulation on multiple dosing was not extensive (Olaparib Investigator's Brochure, 2018). At a 300 mg BID dose, olaparib PK appeared to be slightly time dependent with a temporal change parameter (TCP; AUC at steady state/AUC following a single dose) of approximately 1.45 (StD: 0.6). Exposure (measured by AUC from zero to 12 hours [AUC_{0-12}]) increased approximately proportionally with olaparib tablets at 25-450 mg; C_{max} increased slightly less than proportionally for the dose range. The estimated geometric mean (Gmean) maximum steady state plasma concentration ($C_{max\ ss}$), AUC_{0-12}, and minimum plasma concentration (C_{min}) after dosing with 300 mg tablet BID were 9.13 mcg/mL, 57.9 mcg.h/mL and 1.76 mcg/mL: equivalent to unbound concentrations of 1.65 mcg/mL, 10.5 mcg.h/mL and 0.318 mcg.h/mL, respectively. The inter-individual variability was moderate to high (36% for $C_{max\ ss}$, 49% for AUC_{0-12}, and 104% for the minimum steady state plasma concentration [$C_{min\ ss}$]). After administration of a radiolabeled dose of olaparib capsules (100 mg BID) in study D0810C00010, unchanged drug accounted for approximately 70% of the circulating material in the plasma with the remainder accounted for by three other components (each approximately 10% of the material), all of which were also present in the excreta. Drug-related material was eliminated in the urine (approximately 44% of the dose) and in the feces (approximately 42% of the dose) predominantly as metabolites. Metabolism was extensive. The metabolites produced were predominantly a consequence of oxidation of the piperazine carboxycyclopropyl, the fluorophenyl, and phthalazinone ring systems. The pharmacological activity of the three circulating metabolites is not known.

Although based on limited data, there was no evidence of any marked ethnic difference in the PK of olaparib tablets between Japanese, Chinese, and Caucasian patients for the olaparib tablet formulation (Olaparib Investigator's Brochure, 2018). In a population analysis, age, body weight, and gender covariates were not found to be predictors of olaparib plasma exposure.

Data from a renal impairment study (D0816C00006) showed that olaparib tablets (300 mg BID) mean Cmax and AUC were approximately 15% and 24% higher, respectively, in patients with mild renal impairment (creatinine CL determined by Cockcroft-Gault: 51-80 mL/min; N=14), and olaparib mean Cmax and AUC were 26% and 44% higher, respectively, in patients with moderate renal impairment (creatinine CL determined by Cockcroft-Gault: 31-50 mL/min; N=14) (Olaparib Investigator's Brochure, 2018).

2.2.2.3 Overview of Safety

As of 15 December 2020, approximately 17209 patients are estimated to have received olaparib in the clinical programme including AstraZeneca-sponsored studies and AstraZeneca-Merck Alliance sponsored studies (8348 patients), a MAP (1880 patients), ISSs and collaborative group studies (6981 patients). An estimated 10228 patients with ovarian, breast, pancreatic, gastric, prostate and a variety of other solid tumors are estimated to have received treatment with olaparib in AstraZeneca-sponsored interventional studies and AstraZeneca-Merck Alliance sponsored studies (8348 patients) and the MAP (1880 patients). Since 2013, most new clinical studies have utilized the tablet formulation which was designed to deliver the therapeutic dose of olaparib in fewer dose units than the capsule. Of the 8348 patients, 1579 received the capsule formulation, 6744 received the tablet formulation and 25 received both capsule and tablet. In these studies, olaparib was given either as monotherapy (5333 patients) or in combination with chemotherapy or other anti-cancer agents (e.g., capecitabine, vinorelbine, eribulin, abiraterone, topotecan, gemcitabine, carboplatin and paclitaxel, paclitaxel or liposomal doxorubicin), including studies where patients received monotherapy and combination therapy sequentially (3015 patients). Approximately 3201 patients have received comparator or placebo across the olaparib development programme in AstraZeneca-sponsored studies and AstraZeneca-Merck Alliance sponsored studies. The recommended olaparib monotherapy capsule dose is 400 mg BID. The recommended olaparib monotherapy tablet dose is 300 mg BID.

Administration of olaparib in combination with DTIC, topotecan, gemcitabine, cisplatin, paclitaxel or carboplatin + paclitaxel resulted in a lower MTD of olaparib compared with its administration as a monotherapyAdministration of olaparib with abiraterone in patients with mCRPC resulted in a numerical imbalance of cardiovascular events between the treatment arms in Part B, with a greater number of patients in the olaparib + abiraterone arm experiencing such events, most notably those of greater severity. The clinical significance of this is unclear and the interpretation is limited by the small sample size of the Safety Analysis Set, some imbalances in relevant baseline characteristics, lack of confirmation of cardiac failure diagnoses and lack of biological plausibility that olaparib would contribute to, and increase, the cardiovascular risk over that known for abiraterone monotherapy.

Toxicities considered to be associated with administration of olaparib (ADRs) include hematological effects (anemia, neutropenia, lymphopenia, leukopenia, thrombocytopenia, MCV elevation), decreased appetite, nausea and vomiting, diarrhea, dyspepsia, stomatitis, upper abdominal pain, dysgeusia, fatigue (including asthenia), increase in blood creatinine, headache, dizziness, hypersensitivity, rash, dermatitis, cough, dyspnea, angioedema, MDS/AML, erythema nodosum, and venous thromboembolism (Olaparib Investigator's Brochure, 2023).

Cases of pneumonitis and new primary malignancies have been reported. Evidence from across the development programme for olaparib does not support a conclusion that there is a causal relationship between olaparib and these events. These are AEs of special interest for olaparib and are being kept under close pharmacosurveillance. Similarly, MDS/AML remains an AE of special interest, despite being considered an ADR, and is still subject to additional reporting requirements.

2.2.3 Durvalumab (MEDI4736)

2.2.3.1 Mechanism of action

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the immunoglobulin (Ig) G (IgG) 1 kappa subclass that blocks the interaction of programmed cell death ligand (PD-L) 1 (but not PD-L2) with programmed cell death 1 (PD-1) on T cells and cluster of differentiation (CD) 80 (B7.1) on immune cells [IC] (durvalumab [MEDI4736] Investigator's Brochure, 2017). Durvalumab (MEDI4736) has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. *In vitro* studies demonstrate that durvalumab (MEDI4736) antagonizes the inhibitory effect of programmed death ligand 1 (PD-L1) on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ) (Stewart *et al*., 2015).

2.2.3.2 Clinical pharmacokinetics and rationale for fixed dosing

A population PK model was developed for durvalumab (MEDI4736) using monotherapy data from a Phase 1 study (study 1108; N=292; doses=0.1 to 10 mg/kg every two weeks (Q2W) or 15 mg/kg every 3 weeks (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 (MEDI4735) 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 1,000 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 (durvalumab [MEDI4736] Investigator's Brochure, 2017).

Similar findings have been reported by others (Ng *et al*., 2006, Wang *et al*., 2009, and Zhang *et al*., 2012). Wang and colleagues (2009) 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. 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 Q28D durvalumab (MEDI4736) is included in the current study.

2.2.3.3 Clinical safety summary

Risks with durvalumab (MEDI4736) include diarrhea, colitis, pneumonitis /ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, diabetes insipidus, hypophysitis and adrenal insufficiency) hepatitis/hepatotoxicity/increases in transaminases, neurotoxicities, nephritis/increases in creatinine, pancreatitis, rash/pruritus/dermatitis, infusion-related reactions, anaphylaxis, hypersensitivity or allergic reactions, immune complex disease, pemphigoid, myositis/polymyositis, and immune thrombocytopenia. Further information on these risks can be found in the durvalumab (MEDI4736) Investigator's Brochure (2021).

In monotherapy clinical studies, AEs (all grades) reported very commonly (≥20% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 5% of patients experienced an SAE that was considered to be related to durvalumab by the study investigator. A detailed summary of durvalumab (MEDI4736) monotherapy AE data can be found in the current version of the durvalumab (MEDI4736) Investigator's Brochure (2021).

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see the Dosing Modification and Toxicity Management Guidelines Table in Section 7.3).

2.2.3.3.1 AEs of special interest (AESI):

The AESIs reported in durvalumab (MEDI4736) studies are defined as AEs that include, but are not limited to, events with a potential inflammatory or immune-mediated mechanism that may require more frequent monitoring and/or interventions such as corticosteroids, immunosuppressants, and/or endocrine therapy durvalumab (MEDI4736) Investigator's Brochure, 2021).

Early recognition of signs and symptoms potentially related to an inflammatory or immune-mediated mechanism is important for proper management of toxicities (durvalumab [MEDI4736] Investigator's Brochure, 2021). For guidance on identifying, evaluating, and treating AESIs/inflammatory or immune mediated adverse events (imAEs), see the Toxicity Management Guidelines.

AESI/imAEs observed with anti PD-L1/PD-1 agents such as durvalumab (MEDI4736) include pemphigoid, diabetes insipidus, encephalitis, subcutaneous injection site reaction, immune thrombocytopenia, pneumonitis, hepatitis, diarrhea/colitis and intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency,

hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, pancreatitis, myocarditis, myositis/polymyositis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, hematological and rheumatological events. 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.

The summary information for the AESIs below, unless stated otherwise, are based on the data cut off (DCO) of July 12, 2017.

Pneumonitis

Across the durvalumab (MEDI4736) monotherapy pooled dataset pneumonitis events observed (pneumonitis, interstitial lung disease [ILD], acute interstitial pneumonitis, and pulmonary fibrosis) were reported at a frequency rate of Common (98/1889; 5.2%). Most were Grade 1 or 2 in severity and most were reported as pneumonitis (88 patients [4.7%]). CTCAE Grade 3 pneumonitis was reported in 15 patients (0.8%); CTC Grade 4 in 1 patient (<0.1%) and CTC Grade 5 pneumonitis in 5 patients (0.3%). CTCAE Grade 3 ILD (pneumonitis) has been reported from studies outside of the pooled dataset. There were no CTCAE Grade 4 or 5 events of ILD.

Presentations of pneumonitis can range from asymptomatic lung infiltrates to those that mimic severe bacterial pneumonia (Teply and Lipson, 2014). Early consideration of pneumonitis should be realized when patients present with new onset or worsening of respiratory symptoms such as dyspnea or cough. Prompt treatment with steroids is important as per current established Toxicity Management Guidelines.

Hepatitis

Immune-mediated hepatitis/hepatic toxicity is the inflammation of the liver. Hepatic AEs induced by PD-1/PD-L1 inhibitors commonly present as asymptomatic increase of AST and alanine aminotransferase (ALT), rarely total bilirubin. A proportion of patients may be presenting with fatigue, fever and radiologic appearances including hepatomegaly, periportal lymphadenopathy and periportal edema (Zhang *et al.*, 2016).

As a grouped term, selected hepatic events including laboratory abnormalities were reportedly 12.0% (227 patients) across 1889 patients who have received durvalumab (MEDI4736) monotherapy 10 mg/kg Q2W. Hepatitis events (autoimmune hepatitis, hepatitis toxic, hepatocellular injury, hepatotoxicity and hepatitis) were reported at a frequency rate of uncommon (14 patients; 0.7%). Seven of the 14 events of hepatitis were Grade 3. There were no Grade 4 events with the exception of hepatitis acute (1 patient) reported outside of the pooled

dataset. One patient experienced a CTCAE Grade 5 event of autoimmune hepatitis. Other AESIs such as hepatic failure (5 patients), jaundice (5 patients), hyperbilirubinemia (15 patients) and laboratory abnormality AESIs have been observed, 3 of which were CTCAE Grade 5 (hepatic failure, hyperbilirubinemia and transaminases increased).

Monitoring liver function tests while receiving study medication is important as hepatitis often manifests as asymptomatic elevated levels of hepatic transaminases [ALT, AST, and bilirubin] (Kim *et al.*, 2013). Prompt treatment with steroids is important.

Colitis

Diarrhea is the most frequent AESI reported across the phase 1 to phase 3 clinical studies with durvalumab (MEDI4736) monotherapy with a frequency of very common (329/1889; 17.4%) in patients receiving 10 mg/kg durvalumab (MEDI4736) IV Q2W. Most of these were Grade 1. Treatment-emergent colitis-type AESIs were reported at a frequency of common (21 of 1889 patients; 1.1%). Most were Grade 2 or 3. CTCAE Grade 4 colitis was reported in 1 patient (rare; <0.1%).

Patients should be monitored for signs and symptoms of colitis or diarrhea. Investigators are instructed to begin diarrhea management early to minimize the risk of colitis (Section 7.3). Early initiation of diarrhea treatment guidelines has been shown to reduce bowel perforation and colectomy rates, drug-related diarrhea, and serious gastrointestinal imAEs by up to 50% in patients treated with ipilimumab (Tarhini, 2013).

Intestinal perforation

Full thickness injury of the bowel wall and subsequent perforation of the gastrointestinal tract can be due to a variety of etiologies, commonly instrumentation, surgery, bowel injury, bowel obstruction, neoplasms (particularly colon carcinoma) and concomitant medications such as prolonged use of non-steroidal inflammatory drugs (NSAIDs). Spontaneous perforation can be related to inflammatory changes or tissues weakened by medications or connective tissue disorders.

Across the durvalumab (MEDI4736) monotherapy pool of studies, intestinal perforation was reported at a frequency rate of Uncommon (2/1889; 0.1%); Grades 2 and 4. There were no Grade 5 events.

Monitor for symptoms that may be related to bowel perforation such as sepsis, peritoneal signs, and ileus (Section 7.3). Investigators should adhere to the overall management for immune-mediated toxicities by performing a thorough evaluation to rule out alternative etiologies and by initiating prompt treatment including steroids.

Endocrinopathies

Immune-mediated endocrinopathy is the inflammation of any organ in the hypothalamic-pituitary-adrenal axis, but is most typically reported to affect the pituitary, thyroid and/or adrenal

glands, leading to hypophysitis/hypopituitarism, thyroid dysfunction, and/or adrenal insufficiency (Teply and Lipson 2014). The clinical presentation of immune-mediated endocrinopathies most often include hypothyroidism, hyperthyroidism, and nonspecific symptoms of headache and fatigue, but may also include myalgias, visual field defects, behavioral changes, electrolyte disturbances, loss of appetite and hypotension (Tarhini, 2013). Patients with endocrinopathies may present with abnormal endocrine laboratory test results including thyroid stimulation hormone (TSH), free thyroxine 4 (T4), total and free T3, cortisol, adrenocorticotrophic hormone, luteinizing hormone, follicle-stimulating hormone, and testosterone.

Frequencies for immune-mediated endocrinopathy, as grouped terms of AESIs including laboratory abnormality AEs, are indicated in the table below.

Endocrinopathy AESIs

Endocrinopathy	durvalumab (MEDI4736) monotherapy (10 mg/kg Q2W) (N=1889)	durvalumab (MEDI4736) + tremelimumab (20 mg/kg Q4W and 1 mg/kg) (N=1088)
Hypothyroidism [a]	Very common 206 (10.9%)	Very common 137 (12.6%)
Hyperthyroidism [a]	Common 135 (7.1%)	Common 78 (7.2%)
Adrenal insufficiency [a]	Uncommon 13 (0.7%)	Common 21 (1.9%)
Hypophysitis/Hypopituitarism [a]	Rare 1 (<0.1%)	Uncommon 24 (0.4%)
Type 1 diabetes mellitus	Rare 1 (<0.1%)	0 (0.0%)

[a] Grouped term based on a number of individual MedDRA PTs.
AESI adverse event of special interest; MedDRA Medical Dictionary for Regulatory Activities; N total number of patients; PT preferred term; Q2W every 2 weeks; Q4W every 4 weeks.

Most endocrinopathy events reported were Grade 1 or 2. In the monotherapy pool, Grade 3 events consisted of adrenal insufficiency (2 patients), hypophysitis/hypopituitarism (1 patient), hyperthyroidism (1 patient) and hypothyroidism (2 patients). There were no CTCAE Grade 4 or 5 events. In the combination, AESIs for hypothyroidism and hyperthyroidism (including laboratory abnormalities) were the most frequently observed events with frequency rates of Very common (12.6%) and Common (7.2%), respectively. The severity of these events are predominantly Grades 1 and 2 with Grade 3 events observed with hyperthyroidism only (0.5%). Adrenal insufficiency was reported as mostly Grades 2/3 with 1 Grade 4 event and no Grade 5 events. Hypophysitis or hypopituitarism was reported as mostly Grade 3 with no Grade 4 or 5 events.

Across the monotherapy pool of studies, 1 patient (<0.1%) experienced Grade 3 Type 1 diabetes mellitus

Prompt recognition and management of endocrinopathies is important. Refer to the endocrinology section of Section 7.3.

Nephritis

The major clinical syndromes produced by immune-mediated renal injury include nephrotic syndrome, rapidly progressive glomerulonephritis, and acute renal failure (Cunard and Kelly, 2003). In association to immune-checkpoint inhibitors, two different forms of ipilimumab-induced renal damage are reported, acute kidney injury due to predominant acute granulomatous tubulointerstitial nephritis and nephrotic syndrome in lupus nephritis (Izzedine *et al.*, 2014). Signs and symptoms include increase in serum creatinine, decrease in urine output, peripheral edema, hematuria, loss of appetite.

As a grouped term, selected renal events including laboratory abnormalities were reported at a frequency of 6.3% (119 patients) across the 1889 patients included in the durvalumab (MEDI4736) monotherapy pool. Blood creatinine was the most common event reported (4.0%), of which the majority were Grade 1 or 2 in severity. Nephritis events were reported at a frequency rate of Uncommon (6 patients [0.3%]) with 1 event each of Grade 2 autoimmune nephritis, glomerulonephritis, glomerulonephritis membranous, and nephritis and 2 tubulointerstitial nephritis (Grade 2 and 3).

Patients should be monitored for changes in renal function (*e.g.*, that manifest as elevated serum blood urea nitrogen and creatinine, decreased creatinine CL, electrolyte imbalance, decrease in urine output, or proteinuria and any other findings that may be indicative of nephritis) prior to and periodically during treatment. Prompt treatment with steroids is important.

Rash/dermatitis

Immune-mediated dermatitis is generally mild and presents as mild local or diffuse maculo-papular, erythematous rash on the trunk or extremities, which may be accompanied by pruritus, alopecia, and vitiligo, suggestive of inflammatory response to melanocytes (Lacouture *et al.*, 2014). 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 manifestations (Tarhini, 2013; Kaehler *et al.*, 2010).

AESIs of rash (as a composite term) were reported as very common in 283 (15.0%) patients receiving durvalumab (MEDI4736) monotherapy and very common in 256 (23.5%) patients receiving the combination. The majority of events were CTCAE Grade 1, with 11 and 7 patients, respectively, experiencing CTCAE Grade 3 events.

AESIs falling under the grouped term of dermatitis include milder events such as pruritus, eczema and erythema to more specific or severe skin toxicities such as events of dermatitis bullous, dermatitis exfoliative or dermatitis psoriasiform. Overall, these events have been reported as very common (n=299; 15.8%) in monotherapy. Most events were Grade 1, with 3 patients experiencing Grade 3 events in the monotherapy.

Close monitoring, early detection and prompt treatment with steroids (topical or systemic based on severity) is important. Refer to the Toxicity Management Guidelines.

Myocarditis

In the literature for other immune checkpoint inhibitors, a variety of clinical presentations, diagnostic evidence (laboratory, imaging, histopathology), and resulting diagnoses have been described in cases of myocarditis, including heart failure, brady- and tachyarrhythmias, and acute coronary syndrome-like presentations without evidence of ischemia. Treatments are variable, and include immunosuppression and beta blockers, angiotensin converting enzyme (ACE) inhibitors, and diuretics. Outcomes can range from rapid response and resolution with immunosuppression to fulminant, fatal events.

Across the durvalumab (MEDI4736) monotherapy pool of studies, as of the data cut off of July 12, 2017, there has been 1 SAE of Grade 3 myocarditis and 2 additional cases (Grade 3 and Grade 4) outside of the pooled dataset. In all cases the patients recovered or were improving with corticosteroid therapy.

Investigators should be aware of such rare, but severe immune-mediated adverse events including myocarditis with its presenting signs/symptoms (*e.g*., decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block). For patients with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection) and the appropriate management that includes discontinuing drug (permanently if myocarditis is confirmed) and the prompt use of steroids or other immunosuppressives. Patients with pre-existing cardiac disorders should be closely monitored for deterioration in their cardiac condition, which could suggest new onset myocarditis.

Myositis/polymyositis

The diagnosis of myositis or polymyositis should be suspected in patients who present with proximal muscle weakness and the evaluation should include an examination of the skin, muscle enzyme measurement, antibody testing, any systemic disease manifestations and exclusion of other diseases including drug-induced myopathy. Cases of myositis have been reported with myocarditis in which immune infiltration has been described in skeletal and cardiac muscle (Johnson *et al.*, 2016).

In the durvalumab (MEDI4736) pool of studies as of the data cut off, 3 patients (0.2%) reported the event of myositis, including 1 Grade 3 in severity. Outside of the pooled dataset, there were 2 fatal events of polymyositis considered as treatment-related by the Investigator.

Investigators should adhere to the Toxicity Management Guidelines by performing a thorough evaluation to rule out alternative etiologies and initiating prompt treatment with steroids and modification of study drug dose regimen depending on the severity of the event. Refer to Section 7.3.

Pancreatitis

Pancreatitis is an inflammatory condition of the pancreas that typically manifests initially as asymptomatic elevations of amylase and lipase in patients treated with immune checkpoint inhibitors. Clinical presentation frequently includes low-grade abdominal pain with

accompanying fever and malaise (Weber *et al.*, 2012, Di Giacomo *et al.*, 2010). Biopsies showed diffuse T-cell infiltrate consistent with immune-mediated pancreatitis (Weber *et al.*, 2012).

Across the 1,889 patients in the monotherapy program, events of pancreatitis were uncommon to Rare. Four patients (0.2%) experienced pancreatitis (Grade 2, Grade 3 and Grade 4 in severity) and 1 patient (<0.1%) with Grade 3 acute pancreatitis. Elevations in amylase and lipase were reported as Uncommon (0.6% and 0.5%, respectively).

Patients should be monitored for signs and symptoms of pancreatitis including Grade 3 or 4 elevations in lipase and/or amylase. Close monitoring, early detection and prompt treatment of these events are important. Refer to Section 7.3.

Other rare or less frequent AESIs and immune-mediated adverse events

Events with an inflammatory or immune mediated mechanism could occur in nearly all organs. ImAEs that are less frequent with a potential immune-mediated etiology include, but are not limited to: pericarditis, sarcoidosis, uveitis, and other events involving the eye (*e.g*., keratitis and optic neuritis), skin (*e.g*., scleroderma and vitiligo), hematological (*e.g*., hemolytic anemia and, immune thrombocytopenic purpura) and rheumatological events (polymyalgia rheumatic and autoimmune arthritis).

Neuropathy/neuromuscular toxicities such as Guillain-Barre Syndrome and myasthenia gravis have also been observed. One patient receiving durvalumab (MEDI4736) monotherapy outside of the pooled dataset experienced Grade 4 myasthenia gravis.

Prompt treatment of these conditions as per Section 7.3 is required.

Infusion-related reactions, anaphylaxis and allergic reactions

Adverse reactions that occur during or shortly after infusion may include fever, chills, hypotension, dyspnea, tachycardia, cyanosis, respiratory failure, urticarial and pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension rash, headache, flushing, sweating, myalgia, nausea, vomiting, unresponsiveness, and hemodynamic instability. The typical onset can be within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10% and 30% occur during subsequent treatments.

Anaphylaxis is a systemic, immediate hypersensitivity reaction that is mediated by interactions between factors released from immunoglobulin E (IgE) and mast cells; these interactions result in an antigen-antibody reaction. Clinical manifestations of acute allergic reactions may range from localized skin reactions at the injection site to AEs, which can include, but are not limited to, those events similar to infusion-related reactions to severe reactions including anaphylaxis and drug hypersensitivity syndromes. These reactions may be more common with higher rates of infusion, and in patients with a history of allergies.

Across the durvalumab (MEDI4736) monotherapy and durvalumab (MEDI4736) + tremelimumab combination therapy program, 52 (2.8%) and 49 (4.5%) patients, respectively, have experienced either an infusion related reaction or hypersensitivity/anaphylactic reaction. The majority of events were Grade 1 or 2, with 5 patients experiencing a Grade 3 infusion related reaction, 1 patient with Grade 3 urticaria, and 1 patient with Grade 4 hypersensitivity (all receiving durvalumab [MEDI4736] monotherapy). There have been no reported Grade 5 events as of the DCO.

Patients participating in durvalumab (MEDI4736) clinical studies should be closely monitored during and after infusions. Severe hypersensitivity reactions should be managed according to standard clinical practice, and medical equipment and staff trained to treat acute anaphylactic reactions must be immediately available at all sites that perform mAb infusions.

Immune-complex disease

The potential risk of immune complex disease for durvalumab (MEDI4736) is theoretical based on the known risk associated with mAbs and other proteins. The incidence of durvalumab (MEDI4736) anti-drug antibodies (ADA)-positive patients in clinical studies is low, and hence the risk of immune complex disease is likely to be low. Specifically, of 1124 patients treated with durvalumab (MEDI4736) 10 mg/kg Q2W and evaluable for the presence of ADAs, 3.3% of patients tested positive for treatment-emergent ADAs. Neutralizing antibodies against durvalumab (MEDI4736) were detected in 0.3% of patients. The presence of ADAs did not have a clinically relevant effect on PK. There have been no reported events of immune complex reactions in patients receiving durvalumab (MEDI4736) monotherapy or in combination with tremelimumab.

Considering the low incidence of immunogenicity of durvalumab (MEDI4736) and the lack of clinically apparent immune complex disease to date, samples for ADA monitoring may be collected in studies if clinical AEs consistent with immune complex disease are observed.

For guidance on identifying, evaluating, and treating an imAE please see Section 7.3.

2.2.3.3.2 Infections

In addition to infections determined as adverse drug reactions (ADRs), other infections are considered as potential risks based on the potential mechanism of action of checkpoint inhibitors.

Serious and/or ≥Grade 3 infections requiring hospitalization including, but not limited to, sepsis, pneumonia, lung infections, have been reported in clinical studies with durvalumab (MEDI4736), but are often confounded by underlying disease and use of concomitant medications (*e.g.*, steroids and other immunosuppressives). As of the data cut off, events from the MedDRA Infections and Infestations system organ class (SOC), events with a severity ≥Grade 3 and frequency of ≥1% in the monotherapy pool included lung infection (n=19; 1%), pneumonia (n=51; 2.7%), sepsis (n=35; 1.9%) and urinary tract infection (n=21; 1.1%). Overall, CTCAE Grade 3 events were reported in 143 patients (7.6%), CTCAE Grade 4 events were

reported in 36 patients (1.9%) and CTC Grade 5 infection events in 18 patients (1.0%).

Non-serious infections have been reported in clinical studies with durvalumab (MEDI4736). Of the ADRs under the MedDRA Infections and Infestations SOC, events reported as non-serious only and with a frequency of >1% included nasopharyngitis (n=92; 4.9%), oral candidiasis (n=49; 2.6%), pharyngitis (n=20; 1.1%) and rhinitis (n=39; 2.1%).

2.2.3.4 FDA-approved indications

Durvalumab (MEDI4736) (IMFINZI™) is indicated for the treatment of: 1) patients with locally advanced or metastatic urothelial carcinoma and 2) patients with unresectable, stage III non-small cell lung cancer (NSCLC) (IMFINZI™ Package Insert, 2018).

2.3 Rationale

There have been modest clinical effects observed so far in patients with advanced solid tumors with single agent PI3K inhibitors. The clinical activity is certainly less than that seen with serine/threonine-protein kinase B-raf (BRAF), mitogen activated protein kinase (MEK), epidermal growth factor receptor (EGFR), and anaplastic lymphoma kinase (ALK) inhibitors in the corresponding vulnerable cancer genotypes. It is therefore important that rational combinations of PI3K inhibitors are pursued to maximize the chances of revealing their full therapeutic potential in patients with advanced cancers. Moreover, this is additionally important because the PI3K pathway is a common mechanism of resistance to multiple targeted agents, and conversely, resistance to PI3K inhibitors may also develop due to aberrant compensatory signaling through other pathways.

An example of rational combination therapy is that of PI3K pathway inhibitors with PARP inhibitors, which lead to an accumulation of DNA SSBs and result in synthetic lethality with different molecularly-driven tumors, such as BRCA1/2 mutant cancers. The initial rationale for this combination is based on preclinical findings of synergy between buparlisib and the PARP inhibitor olaparib (Ibrahim *et al*., 2012; Juvekar *et al*., 2017) (Figure 7). The underlying mechanism by which buparlisib sensitizes to PARP inhibitors is not entirely clear, but has been linked to the capacity of buparlisib on its own to increase markers of DNA damage and to reduce expression of the BRCA1/2 DNA repair enzymes.

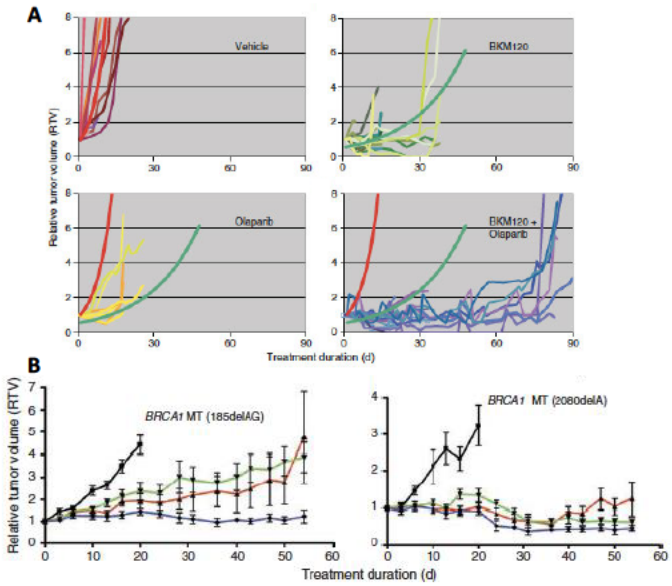


Figure 7: Antitumor efficacy of PI3K inhibitor NVP-BKM120 alone and in combination with olaparib. (A) Tumor-bearing MMTV-Cre Brca1 f/f Trp53 +/− were treated with either vehicle control, or BKMM120 or olaparib or the combination of BKM120 + olaparib. (B) Responses of human BRCA1-related breast cancers implanted as xenotransplants into nude mice to NVP-BKM120, olaparib, or their combination. Breast cancer tissues from 2 patients, one with a 185delAG germline mutation (left) and the other one with a 2080delA germline mutation (right) were propagated as subcutaneous implants in nude mice (Ibrahim *et al*., 2012).

In early phase clinical trials conducted to date, these combinations have been shown to be safe and well tolerated. Matulonis and colleagues (2017) conducted a phase 1/2 trial of the combination of olaparib and buparlisib and demonstrated antitumor responses in *BRCA1/2* mutant and *BRCA1/2* wild-type patients with advanced breast and high grade serous ovarian cancers. Meghani and co-workers (2017) presented preliminary phase 1/2 trial data of olaparib and alpelisib. Impressively, this combination resulted in an overall response rate of 29% in patients without *gBRCA1/2* mutations with platinum-resistant ovarian cancers. Michalarea and colleagues (2016) also presented preliminary data of the combination of olaparib and AKT inhibitor AZD5363. In their population of patients with advanced solid tumors, antitumor responses were demonstrated in *BRCA1/2* mutant and *BRCA1/2* wildtype patients with breast cancers, high grade serous ovarian cancers, castration-resistant prostate cancer, and mesothelioma. Importantly, these responses were observed in those patients who had previously received and were resistant to platinum chemotherapy, PI3K/AKT pathway inhibitors, and PARP inhibitors, providing early proof of concept that this is an active combination.

With these olaparib and PI3K/AKT inhibitor regimens, the predominant combination-related toxicity was gastrointestinal (GI) toxicities, which may be in part due to the orally administered PI3K/AKT pathway inhibitors. Such GI toxicities may potentially be reduced with copanlisib, which is given intravenously. Also potentially observe other potential benefits of improved pharmacokinetic and pharmacodynamic parameters with copanlisib *versus* the combinations involving the oral PI3K/AKT pathway inhibitors.

There have been recent evidence supporting the combination of PARP inhibitors and PD-1/PD-L1 inhibitors. For example, PARP inhibition has been shown to activate stimulator of interferon genes (STING)-dependent innate immune signaling, priming of antitumor T-cells, and associated

upregulation of PD-L1 expression (Parkes, *et al*., 2017). A group at MD Anderson Cancer Center has shown that PARP inhibition inactivates glycogen synthase kinase-3 beta (GSK3β), leading to PD-L1 upregulation, and in vivo synergy between olaparib and PD-1/PD-L1 inhibition (Jiao *et al*., 2017). Multiple clinical trials assessing the combination of PARP inhibitors with PD-1/PD-L1 inhibitors are currently underway. For example, the combination olaparib and the PD-L1 inhibitor durvalumab (MEDI4736) has been shown to be safe and well tolerated, with preliminary antitumor responses. This combination is currently being assessed in the phase II MEDIOLA trial (Domchek *et al*., 2016).

There is already strong evidence from similar combinations for the doublet combination of copanlisib + olaparib to be efficacious in DNA damage response (DDR)-associated cancers, such as ovarian cancer. Preliminary results from a phase 1b trial involving a similar olaparib + PI3K inhibitor combination recently demonstrated an OR of 29% in patients without *gBRCA1/2* mutations with platinum-resistant ovarian cancers. This is an area of great unmet need where this combination of copanlisib + olaparib may show great promise. There are also other areas where this combination may show great potential; these include the indications where olaparib has demonstrated antitumor activity, such as BRCA1/2 mutant breast, castration-resistant prostate and pancreatic cancers, as well as other non-BRCA1/2-related, DDR-associated cancers, such as castration-resistant prostate cancers. Prostate cancer has a high frequency of PTEN loss, and therefore the combination of copanlisib and olaparib would make rational sense in this tumor context. The addition of durvalumab (MEDI4736) is expected to synergize with both copanlisib and olaparib, with an expectation of manageable toxicity in patients. Apart from all the indications above, such a triplet combination would also have a role in PD-1/PD-L1 inhibitor resistant patients, which is an area of unmet clinical need as discussed above. By testing this triplet combination in molecularly-selected cohorts of patients, we will be able to select the optimal patient population for such a regimen.

In this study, we therefore propose the development of rational doublet and triplet copanlisib-based combinations in patients with molecularly-selected advanced solid tumors. This trial is geared to test both doublet and triplet combinations in patients with germline and also somatic DDR aberrations, as well as PIK3CA and PTEN abnormalities. These studies will be biomarker driven, through the use of both tumor biopsies and circulating tumor DNA taken sequentially.

2.4 Correlative Studies Background

2.4.1 Integral Studies

In this molecular targeted therapy study, patient eligibility will be determined based upon the following criteria: i) activating mutations within the oncogene PI3K, ii) inactivating mutations within the tumor suppressor gene PTEN, iii) mutations within the DDR genes associated with increased response to PARP inhibitors.

2.4.1.1 PIK3CA Mutations

To be eligible for this study, patients must have advanced solid tumors, with mutations in the *PIK3CA* gene. Hotspot mutations in PIK3CA to be considered include: E542, E545, and

H1047. PIK3CA mutational status will be determined prior to study initiation based on next generation sequencing (NGS) or equivalent clinical laboratory improvements amendment (CLIA)-certified assay. All mutational variants will be assessed for actionability by the MD Anderson Precision Oncology Decision Support (PODS) team. Clinical benefit in patients with advanced solid tumors with PIK3CA mutations will be assessed, as measured by ORR. PIK3CA mutations result in aberrant activation of the PI3K/Akt cell signaling pathway, causing proliferative and cell survival advantages to tumor cells. By specifically targeting PIK3CA mutations, we hope to induce significant anti-tumor responses in patients with cancers harboring these mutations.

2.4.1.2 PTEN Mutations

To be eligible for this study, patients must have advanced solid cancers, with actionable mutations in the *PTEN* gene. PTEN mutational status will be determined prior to study entry based on NGS or equivalent CLIA-certified assay. All mutational variants will be assessed for actionability by the MD Anderson PODS team. Clinical benefit in patients with advanced solid tumors with PTEN mutations will be assessed by objective response rate. PTEN is an important cellular phosphatase that regulates PI3K/Akt signaling. As a tumor suppressor, PTEN functions to limit the PI3K/Akt pathway and prevent uncontrolled cell growth. Therefore, tumor cells with defects in PTEN exhibit constitutive activation of the PI3K/Akt pathway, and proliferative and survival advantages.

2.4.1.3 DDR Mutations

To be eligible for this study, patients must have advanced solid cancers, which may have germline or somatic mutations in genes involved in DDR. Eligible genes include: BRAC1 associated RING domain 1 (*BARD1*)*, BRCA1*, *BRCA2*, BRCA1 interacting protein C-terminal helicase 1 (*BRIP1*)*,* Fanconi anemia complementation group A (*FANCA*), Nibrin (*NBN*), partner and localizer of BRAC2 (*PALB2*), *RAD51*, *RAD51B, RAD51C,* and *RAD51D*. Aberrations in DDR genes will be determined prior to study entry using NGS or CLIA-certified equivalent assay. All mutational variants will be assessed for actionability by the MD Anderson PODS team. Clinical benefit in patients with germline or somatic DDR aberrations will be assessed by objective response rate. Defects in the ability of the cell to respond to DNA insults allow tumor cells to bypass cell cycle and DNA repair checkpoints and continually replicate and accumulate further malignant changes that allow them to grow and survive.

2.4.2 Integrated Studies

2.4.2.1 Reverse Phase Protein Array (RPPA)

RPPA assay will be used to assess treatment induced changes in PI3K pathway signaling (*e.g.* phosphorylated Akt (pAkt), phosphorylated ribosomal protein S6 (pS6), phosphorylated 4E binding protein 1 (p4EBP1), and to correlate said changes with treatment response and progression; and to evaluate changes in signaling pathways that may be reflective of treatment resistance.

2.4.2.2 Whole Exome Sequencing (WES)

The molecular landscape of cancer is just beginning to be defined. However, we do not know enough about the genomic and molecular landscape of tumors from patients who enter early phase clinical trials. With this study, we will attempt to learn more about specific molecular features of cancers from this patient subgroup. It is particularly important to learn, as early as possible, if there are molecular features within a particular malignant histology or across malignant histologies that can inform about potential response or resistance to treatments in early phase clinical trials. Such knowledge will be used to design more efficient later stage clinical trials for more efficient and more effective drug development.

Whole exome sequencing will be used to correlate single nucleotide variation (SNV) and copy number variation (CNV) profiles with treatment response. We will also use WES data to assess the correlation between tumor mutational burden (TMB) and treatment response.

2.4.2.3 Pharmacokinetics

Copanlisib clearance is dependent (~40%) on CYP3A4 metabolism. Copanlisib is a p-gp and BCRP substrate, and may inhibit pgp, BCRP, MATE2K and MATE1.
Olaparib is a CYP3A4/5 substrate, inhibits CYP3A4, and induces CYP1A2, 2B6, and 3A4. Olaparib is also a Pgp substrate, and may inhibit OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K; and is a weak inhibitor of Pgp and BCRP.
Because of the theoretical risk of PK interactions between copanlisib and olaparib, we will study the PK of copanlisib and olaparib in their combination and compare this with historical data.
In addition, we will evaluate exposure response relationships for all 3 drugs with limited sampling.

2.4.2.4 Rationale for Copanlisib Combination Treatment

PI3K inhibitors have an effect on lymphocyte recruitment and activation, maintenance of vascular integrity, and various other aspects of the tumor microenvironment, ultimately slowing tumor growth by inducing apoptosis and boosting tumor immune surveillance. As PI3K inhibition has been shown to sensitize tumors to T cell mediated cytotoxicity, the combination of copanlisib, olaparib, and durvalumab (MEDI4736) is expected to result in clinical benefit by driving robust anti-tumor T-cell responses and promoting immune-mediated tumor cell death.

2.4.3 Exploratory Studies

2.4.3.1 Immune Correlates

We will determine the expression of immune related genes in tumor biopsies using multiplex immunofluorescence characterization of immune cell infiltrate and immune checkpoint proteins, immune gene expression signature analysis using Nanostring platform, as well as RNA-sequencing (RNA-Seq) and T-cell Receptor sequencing (TCR-Seq). Immune correlates in blood samples will be studied using flow cytometry to determine the proportion of different immune cells, cytokine analysis, and circulating tumor DNA (ctDNA) genotyping using targeted NGS.

2.4.3.2 RNA Sequencing (RNA-seq)

RNA sequencing analysis will be used to correlate gene expression profiles with treatment response and resistance.

2.4.3.3 Circulating Tumor DNA (ctDNA) Sequencing

We will undertake targeted NGS analysis using serial samples of ctDNA collected at baseline and at different time points on treatment and chart the levels of targeted DNA anomalies over time in patients and correlate these with levels of tumor burden over time. We will also correlate ctDNA mutation profiles with tumor sequencing, assess changes in ctDNA mutations (particularly in DDR or PI3K pathway genes) during treatment, correlate changes in ctDNA variant allele frequencies with response, and assess emergent resistant mutations at progression (*e.g.*, *BRCA* reversions). Additionally, we will identify new resistance mechanisms by assessing ctDNA levels in long term responding patients who have developed disease progression.

3. PATIENT SELECTION

3.1 Eligibility Criteria for enrollment into Steps 1, 2, and 3

3.1.1 Patients must have germline or somatic mutations in DDR genes: BARD1, BRCA1, BRCA2, BRIP1, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D; or actionable mutations in the PTEN gene, or hotspot mutations in the PIK3CA gene (E542, E545 or H1047 are accepted). Local testing in CLIA-certified laboratory will be accepted. Only mutations that have been recognized as actionable by the MD Anderson PODS team will be accepted.

3.1.2 Patients must have histologically confirmed malignancy that is metastatic or unresectable and for which standard curative or palliative measures do not exist or are no longer effective.

3.1.3 Patients must have measurable disease by RECIST 1.1.

3.1.4 Patients must be ≥3 weeks beyond treatment with any chemotherapy or ≥4 weeks beyond treatment with other investigational therapy to include hormonal, biological, or targeted agents; or at least 5 half-lives from hormonal, biological, or targeted agents, whichever is shorter at the time of treatment initiation.

3.1.5 Age ≥18 years. Because no dosing or AE data are currently available on the use of copanlisib in combination with olaparib ± durvalumab (MEDI4736) in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.6 Patients with a mutation within both the DDR and PTEN/PIK3CA pathways will be assessed by the genomics Precision Oncology Decision Support group at MD Anderson, and the patient will be allocated to the PI3K or DDR expansion group deemed to be the main driver. If the actionability between the groups is deemed to be equivocal, then the

patient will be allocated to the expansion cohort with fewer patients.

3.1.7 ECOG performance status (PS) ≤1 (Karnofsky ≥60%, see Appendix A).

3.1.8 Patients must have normal organ and marrow function as defined below:

– hemoglobin	≥10 g/dL with no blood transfusion in the past 28 days
– leukocytes	≥3,000/mcL
– lipase	≤1.5 x upper limit of normal (ULN)
– absolute neutrophil count	≥1,500/mcL
– platelets	≥140,000/mcL
– total bilirubin	≤1.5 × institutional ULN
– serum bilirubin	≤1.5 × institutional ULN
– AST(SGOT)/ALT(SGPT)	≤2.5 × institutional ULN, unless liver metastases are present in which case they must be ≤5 × ULN
– Activated partial thrombin time	≤1.5 x ULN unless subject is receiving anticoagulant therapy as long as prothrombin time (PT) or partial thromboplastin time (PTT) is within the therapeutic range of intended use of anticoagulants
– International normalized ratio	≤1.5 × ULN
– glomerular filtration rate (GFR)	≥51 mL/min, based on a 24-hour urine test for creatinine clearance or estimated using the Cockcroft-Gault equation of:

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

[a] where F=0.85 for females and F=1 for males.

3.1.9 Left ventricular ejection fraction (LVEF) ≥50%.

3.1.10 Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and international normalized ratio (INR)/PTT is stable.

3.1.11 Prophylactic antiemetics may be administered according to standard practice. The routine use of standard antiemetics, including 5-Hydroxytryptamine type 3 (5-HT3) blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics prior to copanlisib administration will not be allowed.

3.1.12 Postmenopausal or evidence of non-childbearing status, a negative urine or serum pregnancy test within 28 days of study treatment and confirmed prior to treatment on day

1. Postmenopausal is defined as:
- Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
- Luteinizing hormone (LH) and Follicle stimulating hormone (FSH) levels in the postmenopausal range for women under 50
- 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)

3.1.13 Women of child-bearing potential MUST have a negative serum or urine human chorionic gonadotropin (HCG) test unless prior tubal ligation (>/= 1 year before screening), total hysterectomy or menopause (defined as 12 consecutive months of amenorrhea). Patients should not become pregnant or breastfeed while on this study.

3.1.14 Patients and their partners, if sexually active and of childbearing potential, must agree to the use of two highly effective forms of contraception in combination throughout the period of taking study treatment and for 6 months after last dose of study drug(s) to prevent pregnancy in the study patient or partner. Male patients should avoid donating sperm for 3 months following the last dose of olaparib.

3.1.15 Human Immunodeficiency Virus (HIV)-infected (HIV1/2 antibody-positive; HIV testing pre-study not required) patients may participate IF they meet all the following eligibility requirements:
- They must be on an anti-retroviral regimen with evidence of at least two undetectable viral loads within the past 6 months on this same regimen; the most recent undetectable viral load must be within the past 12 weeks.
- They must have a CD4 count ≥250 cells/mcL over the past 6 months on this same anti-retroviral regimen and must not have had a CD4 count <200 cells/ mcL over the past 2 years, unless it was deemed related to the cancer and/or chemotherapy-induced bone marrow suppression.
    - For patients who have received chemotherapy in the past 6 months, a CD4 count <250 cells/mcL during chemotherapy is permitted as long as viral loads were undetectable during this same chemotherapy.
- They must have an undetectable viral load and a CD4 count ≥250 cells/mcL within 7 days of enrolment.
- They must not be currently receiving prophylactic therapy for an opportunistic infection and must not have had an opportunistic infection within the past 6 months.

3.1.16 Ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) must have a legally authorized representative or caregiver who gives such consent.

3.1.17 Patient is willing and able to comply with the protocol for the duration of the study, including undergoing treatment and scheduled visits and examinations.

3.1.18 Patients with a tumor that is readily accessible for biopsy.

3.2 Eligibility Criteria for enrollment into Step 2 and 3 only

3.2.1 Body weight >30 kg.

3.2.2 **Life expectancy ≥16 weeks**.

3.3 Exclusion Criteria for Steps 1, 2, and 3

3.3.1 Persistent toxicities (>CTCAE Grade 2) caused by previous cancer therapy, excluding alopecia.

3.3.2 Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment.

3.3.3 Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

3.3.4 Patients who are receiving any other investigational agents.

3.3.5 Other malignancy unless curatively treated with no evidence of disease for ≥5 years except: adequately treated non-melanoma skin cancer, curatively treated *in situ* cancer of the cervix, ductal carcinoma *in situ* (DCIS), or Stage 1, grade 1 endometrial carcinoma. A patient with a history of localized triple negative breast cancer may be eligible, provided the patient completed the adjuvant chemotherapy >3 years prior to registration, and the patient remains free of recurrent or metastatic disease.

3.3.6 Patients with MDS/AML or with bone marrow findings consistent with MDS/AML.

3.3.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to olaparib, copanlisib, PI3K inhibitors or durvalumab (MEDI4736 or any of the excipients of any study products.

3.3.8 Concomitant use of strong CYP3A inhibitors and inducers.
Olaparib: Concomitant use of known strong CYP3A 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 for strong or moderate CYP3A inhibitors prior to starting olaparib is 2 weeks.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new

medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product (Please refer to Appendix D).

Concomitant use of known strong CYP3A inducers (*e.g.*, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate CYP3A inducers (*e.g.*, bosentan, efavirenz, modafinil). The required washout period for strong or moderate CYP3A inducers prior to starting olaparib is 5 weeks for enzalutamide or phenobarbital and 3 weeks for other agents (Please refer to Appendix D).

Copanlisib: Copanlisib is primarily metabolized by CYP3A4. Therefore, the concomitant use of strong inhibitors of CYP3A4 (*e.g*., ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir and saquinavir), and strong inducers of CYP3A4 (*e.g*. rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort) are not permitted from 14 days prior to enrollment until the end of the study.

Other medications that are prohibited while on copanlisib treatment:
1. Herbal medications/preparations (except for vitamins)
2. Anti-arrhythmic therapy other than beta blockers or digoxin

For the list of specific medications prohibited while on copanlisib treatment refer to the Appendix B-List of Prohibited Meds. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix C should be provided to patients. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.3.9 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on High Resolution Computed Tomography (HRCT) scan, symptomatic congestive heart failure, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.3.10 Resting electrocardiogram (ECG) indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (*e.g.*, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QT corrected by the Fridericia formula [QTcF] prolongation of >500 msec, electrolyte disturbances), or patients with congenital long QT syndrome.

3.3.11 Women who are breast feeding or pregnant are excluded from this study because olaparib is a PARP inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with olaparib*,* breastfeeding should be discontinued if the mother is treated with olaparib and copanlisib ± durvalumab (MEDI4736).

3.3.12 Previous allogenic bone marrow transplant or double umbilical cord blood transplantation

(dUCBT).

3.3.13 Packed red blood cell or platelet transfusion in the last 28 days prior to study entry.

3.3.14 Whole blood transfusions in the last 120 days prior to study entry. Whole blood transfusions performed within 120 days of study entry may interfere with blood samples taken for exploratory analysis.

3.3.15 Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. However, systemic corticosteroids may be indicated after starting the study drugs to treat immune-related adverse reactions. Inhaled or topical steroids and adrenal replacement doses ≤ 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3.3.16 Patients with non-healing wound, ulcer, or bone fracture.

3.3.17 Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis or pulmonary embolism within 6 months before the start of study medication

3.3.18 Patients with active, clinically serious infections > Grade 2 (CTCAEv5.0). Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), or hepatitis C. Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. HBV/HCV screening is required 28 days prior to starting the study drug using a routine hepatitis virus lab panel.

3.3.19 Active infection requiring IV antibiotics or other uncontrolled intercurrent illness requiring hospitalization.

3.3.20 Patients unable to swallow orally administered medication and any medical condition or diagnosis that would likely impair absorption of an orally administered drug (*e.g.* gastrectomy, ileal bypass, chronic diarrhea, gastroparesis).

3.3.21 Known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.3.22 Known active CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of

new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

3.3.23 New York Heart Association class III or IV heart disease.

3.3.24 History or concurrent interstitial lung disease of any severity and/or severely impaired lung function (as judged by the investigator).

3.3.25 Uncontrolled arterial hypertension despite optimal medical management (per investigator's opinion).

3.3.26 Patients with uncontrolled Type I or II diabetes mellitus, defined as fasting blood glucose >160 mg/dL and HbA1c >8%, are ineligible.

3.4 Exclusion Criteria for Steps 2 and 3 only

3.4.1 Patients who have not recovered from Grade ≥2 adverse events due to prior anti-cancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
- Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician.

3.4.2 Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

3.4.3 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [*e.g.*, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, *etc*.]). The following are exceptions to this criterion:
- Patients with vitiligo or alopecia.
- Patients with hypothyroidism (*e.g.*, following Hashimoto syndrome) stable on hormone replacement.
- Any chronic skin condition that does not require systemic therapy.
- Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician.
- Patients with celiac disease controlled by diet alone.

3.4.4 Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

3.4.5 Patients with unstable angina pectoris.

3.4.6 Patients who have received prior anti-PD-1, anti PD-L1 or anti CTLA-4:

- Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy. All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study.
- Must not have experienced a Grade ≥3 immune-related AE or an immune-related neurologic or ocular AE of any grade while receiving prior immunotherapy. Note: Patients with an endocrine AE of Grade ≤2 are permitted to enroll if they are stably maintained on appropriate replacement therapy and are asymptomatic.
- Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses of >10 mg prednisone or equivalent per day.

3.4.7 Live vaccination, including virus vaccination and yellow fever vaccination, within 6 months before start of study treatment.

3.4.8 Cytomegalovirus (CMV) infection. Patients who are known to be CMV PCR positive at baseline will not be eligible.

3.5 Inclusion of Women and Minorities

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

4. REGISTRATION PROCEDURES

4.1 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) at https://ctepcore.nci.nih.gov/rcr/. The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types:

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

RCR requires the following registration documents:

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

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

- Addition to a site roster,
- Selection as the treating, credit, or 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 act as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (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.

4.2 Site Registration

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

IRB Approval

Sites participating with the NCI Central Institutional Review Board (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 emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (i.e., the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an Active CTEP status,
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) 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,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile,
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO),
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download 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 on to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of your 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 LAO-TX035 and protocol 10217.
- 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)

4.2.2 Requirements For 10217 Site Registration

- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal

    The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. Users are strongly encouraged to take a refresher of the training if they have not entered specimen data for an extended period of time.
  - This training will need to be completed before the first patient enrollment at a given site
  - Please contact STS Support at Theradex for the training (STS.Support@theradex.com).

4.2.3 Submitting Regulatory Documents

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

To access the Regulatory Submission Portal, log on 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.

4.2.4 Checking **Site** Registration Status

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

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

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems.
- To perform enrollments patients or request slot reservations: Must be on an LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.

Have an approved site registration for a protocol prior to patient enrollment.

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

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

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

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

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

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

4.3.2 Special Instructions for Patient Enrollment

Results from previous NGS or an equivalent local CLIA-certified assay will be used to molecularly stratify patients after all selected alterations are reviewed by MD Anderson's Precision Oncology Decision Support (PODS) team prior to enrolling patients to this study in OPEN. A de-identified NGS or CLIA-certified assay report that includes the mutation of interest will be sent by email to the PODS team (**emailpct@mdanderson.org**) at MD Anderson for actionability review. PODS will annotate whether the mutation identified is actionable and will send a response via email. For sites outside of MD Anderson, include the following details when emailing the PODS team: reference the NCI 10217 study number, the designated ETCTN site number of the site submitting the request, and a subject identification number. If a subject identification number is not available for this study, a temporary identification number should be submitted in the following format: ETCTN site number–patient date of birth (for example: TX035–MMDDYYYY), which is assigned and tracked by the submitting ETCTN site. Do not submit medical record numbers or any protected health information.

Notify the lead site of any screen failures. Ensure that all patients who sign consent and subsequently screen fail are registered in OPEN as a screen failure and have data entered in the NCI's clinical data management system, Medidata Rave. Sites cannot replace patients who screen fail using the slot originally designated to the screen failed patient. An additional slot must be requested and approved for all subsequent patients planned to sign consent and enroll on the study.

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.

- The system is accessed through special Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the NCI Early-Phase and Experimental Clinical Trials Biospecimen Bank (EET Biobank, formerly known as the ETCTN Biorepository).
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in Section 4.5.4.

4.3.3 OPEN/IWRS Questions?

4.3.3.1 Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 855-828-6113 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 8 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Note: All blood collections are mandatory. Tumor biopsy at baseline is mandatory. Tumor biopsy at Cycle 1 Day 15 is mandatory. Tumor biopsies at Cycle 2 and Cycle 24 (or disease progression, whichever comes first) are optional. Tumor biopsies at Cycle 2, Day 15 are *only* for the Triplet Combination. See Appendix I for further details on PK analysis of olaparib (O), copanlisib (C), and durvalumab (D).

No PK collection will be performed on patients treated in Step 3 expansion cohorts.

Time Point	Specimen and Quantity	Send Specimens to:
Pre-study tumor tissue to local CLIA certified laboratory or MD Anderson		
	Archival FFPE tumor block (preferred) If a FFPE tissue block cannot be submitted, then sequentially section and number: • 2 H&E stained slide (minimum of 1 is required) • 15-20 unstained, charged slides at 4 microns	EET Biobank
Baseline		
	Mandatory collections • 1 tissue core snap-frozen[1] • 2 tissue cores in formalin[1] • 2 x 10 mL blood in cfDNA Streck tube	EET Biobank
PK Timepoints: -pre-dose	**Mandatory collections (only for patients treated in Step 2 of triplet combination with D)** • 1 x 3-4 mL blood in red top tube (for serum sPD-L1)	Jan Beumer, UPMC Hillman Cancer Center
Cycle 1 Day 8 (C1D8)		
PK Timepoints: (administer O at start C infusion) -Trough (pre-dose) -30 min post start C -55 min (5 pre-end infusion C) -1 h post end C -3 h post end C -5 h post end C -7 h post end C -23 h post end C (pre-dose D8 O) **NOTE: For patients treated at dose level 3a in Step 1 or patients treated in Step 2 or Step 3: no PK samples will be collected on this day.**	**Mandatory collections (Not applicable to patients treated in Step 3)** PK collection timepoint • 1 x 3-4 mL blood in purple top EDTA tube (for plasma) for each PK time point before and after copanlisib (C) infusion.	Jan Beumer, UPMC Hillman Cancer Center

Time Point	Specimen and Quantity	Send Specimens to:
Cycle 1 Day 15 (C1D15)		
PK Timepoints: (administer O at start C infusion) -Trough (pre-dose) -30 min post start C -55 min (5 pre-end infusion C) **<u>NOTE: For patients treated at dose level 3a in Step 1 or patients treated in Step 2 (collect only as listed below for C1D15):</u>** **PK Timepoints: (administer O at start C infusion)** -Trough (pre-dose) -30 min post start C -55 min (5 pre-end infusion C) -1 h post end C -3 h post end C -5 h post end C -7 h post end C -23 h post end C (pre-dose D8 O)	**Mandatory collections (Not applicable to patients treated in Step 3)** • 1 x 3-4 mL blood in purple top EDTA tube (for plasma) for each PK time point before and after copanlisib (C) infusion.	Jan Beumer, UPMC Hillman Cancer Center
	Mandatory collections • 1 tissue core snap-frozen[1] • 2 tissue cores in formalin[1] • 2 x 10 mL blood in cfDNA Streck tube	EET Biobank
Cycle 2 Day 1 (C2D1) (For the triplet combination only)		
PK Timepoints: -Trough (pre-dose) -50 min (10 pre-end infusion D)	**Mandatory collections (only applicable to patients treated in Step 2 of the triplet combination with D)**	Jan Beumer, UPMC Hillman Cancer Center

Time Point	Specimen and Quantity	Send Specimens to:
	• 1 x 3-4 mL blood in red top tube (for serum) for each PK time point before and after durvalumab (D) infusion.	
Cycle 2 Day 15 (C2D15)		
	Mandatory collections • 2 x 10 mL blood in cfDNA Streck tube **Optional collections (only applicable to patients treated in the triplet combination in Steps 2 and 3)** • 2 tissue cores in formalin[1] • 1 tissue core snap-frozen[1]	EET Biobank
Cycle 3 Day 1 (C3D1) (For the triplet combination only)		
PK Timepoints: -Trough (pre-dose) -50 min (10 pre-end infusion D)	**Mandatory collections (only applicable to patients treated in Step 2 of the triplet combination with D)** • 1 x 3-4 mL blood in red top tube (for serum) for each PK time point before and after durvulamab (D) infusion.	Jan Beumer, UPMC Hillman Cancer Center
Cycle 4 Day 1 (C4D1) (For the triplet combination only)		
PK Timepoints: -Trough (pre-dose) -50 min (10 pre-end infusion D)	**Mandatory collections (only applicable to patients treated in Step 2 of the triplet combination with D)** • 1 x 3-4 mL blood in red top tube (for serum ADA) before durvalumab (D) infusion. • 1 x 3-4 mL blood in red top tube (for serum) for each PK time point before and after durvalumab (D) infusion.	Jan Beumer, UPMC Hillman Cancer Center
Cycle 5 Day 1 (C5D1) (For the triplet combination only)		
PK Timepoints: -Trough (pre-dose) -50 min (10 pre-end infusion D)	**Mandatory collections (only applicable to patients treated in Step 2 of the triplet combination with D)** • 1 x 3-4 mL blood in red top tube (for serum) for each PK time point before and after durvalumab (D) infusion.	Jan Beumer, UPMC Hillman Cancer Center
Each Restaging		

Time Point	Specimen and Quantity	Send Specimens to:
	Mandatory collections • 2 x 10 mL blood in cfDNA Streck tube	EET Biobank
EOT/Disease progression (Optional biopsy for both the doublet and triplet combinations)		
	Mandatory collections • 2 x 10 mL blood in cfDNA Streck tubes **Optional collections** • 2 tissue cores in formalin[1] • 1 tissue core snap-frozen[1]	EET Biobank
[1]For new biopsies, the Tissue Biopsy Verification Form (Appendix J), a copy of the radiology and operative reports from the tissue removal procedure *and* the diagnostic anatomic pathology report must be sent with the tissue to the EET Biobank. When completed, upload the corresponding pathology reports to Rave and send a copy to the EET Biobank.		

After completion of the dose escalation phase, available PK data will be reviewed and the protocol may be modified to convert from olaparib and copanlisib rich sampling to sparse sampling.

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Shipping Kits

Kits for the collection and shipment of specimens to the EET Biobank can be ordered online via the Kit Management system: https://kits.bpc-apps.nchri.org/.

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the Biorepository. Institutional supplies must be used for all other specimen collection and processing.

5.2.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:

- Tumor tissue specimens collected during biopsy procedures and fixed in formalin must

be shipped on the same day of collection.
- Tissue in formalin can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.
- **Snap-frozen specimens/surgical resections** may be shipped in a provided dry shipper or on dry ice on the same day of collection. Tissue can be collected Monday through Thursday (FedEx Priority Overnight).
- Fresh blood specimens may be collected and shipped Monday through Friday.

5.2.3 Scheduling of Specimen Collections for UPMC Hillman Cancer Center (Jan Beumer)
Blood samples will be collected at the timepoints specified in Section 5.1. Frozen plasma and serum will be shipped overnight on either Monday, Tuesday, or Wednesday (and not before a federal or university holiday) to Dr. Beumer's Laboratory at UPMC Hillman Cancer Center.

5.3 Specimen Collection

5.3.1 Core Needle Biopsy (CNB) and Other Small Biopsy Specimens

A maximum number of 3 cores (1 cm in length) or small biopsies (3 mm diameter) will be obtained from the procedure. The number of specimens obtained will be affected by the patient's clinical condition at the time of biopsy and determined by the specialist performing the procedure. Core biopsy should be performed using a 16-18-gauge needle, condition permitting.
- At least 2 cores (1 cm in length) or small biopsies (3 mm diameter) should be obtained for nucleic acid analysis. At least 1 core (1 cm in length) or small biopsy (3 mm diameter) should be obtained for analysis at the MD Anderson RPPA Core Laboratory.
- Alternating passes: First obtain a core for FFPE processing (core 1 is for WES), followed by a core for flash freezing (core 2 is for RPPA), followed by a core for FFPE (core 3 is for RNASeq).

5.3.2 Collection of Frozen Biopsies

Flash Freezing of Core Needle Biopsy and Surgical Resection Samples

1. Arrive at the biopsy collection site early enough to allow sufficient time to set up laboratory supplies, collect relevant clinical information, and ensure rapid transport of specimens to the laboratory for placement at -80ºC (or lower) after collection.
2. Bring all necessary lab supplies including: disposable tweezers, a minimum of two 1.5-mL Sarstedt tubes (one for each whole biopsy core) pre-cooled on liquid nitrogen or dry ice/ethanol in an insulated bucket, and one pre-printed specimen label (see Section 5.4.1.1) to give to the research nurse for the patient record.
   Note: Pre-chill additional 1.5-mL Sarstedt tubes for specimen collection in case the interventional radiologist collects additional passes, or one of the other tubes is compromised prior to collection.
3. The total time elapsed between biopsy collection and placement into the pre-chilled tube is of **key importance** to biomarker analysis; biopsies should be frozen within **2 min** of

collection. The interventional radiologist will eject the biopsy onto a sterile slide (for optimal analyte recovery the slide should be pre-chilled). Start a stop watch (or note the time) at this point (Appendix E, Biopsy Collection) and immediately walk the slide to the sample preparation table.

Note: The preferred method of collection, when whole biopsies are collected, is for the interventional radiologist to eject the biopsy directly into the pre-chilled tube (next step). This minimizes the time between collection and fixation of analytes.

4. Indicate if a full or halved biopsy is prepared in the Batch Record (Appendix E, Biopsy Collection).
    a. For whole biopsies: Uncap an empty, prechilled 1.5-mL Sarstedt tube and using disposable tweezers, pick up the freshly collected needle biopsy with the tweezers at one end, and touch the opposite end of the biopsy to the inner surface of the prechilled 1.5-mL Sarstedt tube. This should attach the tissue to the tube, allowing it to be dropped into the tube while releasing the tissue from the tweezers without sticking. Dispose of the tweezers in the appropriate biohazardous waste container(s).
    b. For halved biopsies: Use 1-2 disposable tweezers and cut/shear the biopsy in half cross-wise while it is on the slide (do not pull or stretch the biopsy longitudinally). Use the tweezers to transfer the halved biopsies to sterile pre-chilled tubes as indicated above.
5. Immediately snap freeze the biopsy by placing the tube in liquid nitrogen or a dry ice/ethanol bath.
6. Calculate the total time elapsed from biopsy collection to biopsy freezing and record the total number of minutes and seconds elapsed in the Batch Record (Appendix E, Biopsy Collection).
7. If biopsy procedure details can be obtained from the interventional radiologist or research nurse, record them in the Batch Record (Appendix E, Biopsy Procedure Details). Some information may not be available until a later time from the clinical staff.
8. Transfer the frozen biopsy specimen(s) to -80ºC (or lower) for storage until shipment to the EET Biobank. Record the date and time specimens are placed at -80ºC (or lower; Appendix E, Biopsy Storage).
9. Review and finalize the Batch Record and document ANY and ALL deviations in the Batch Record (Appendix E, Notes).
10. The appropriate laboratory personnel should review the Batch Record and sign to affirm the data contained within are correct (Appendix E, Review of Batch Record).

5.3.3 Formalin-Fixed Tumor Biopsies

1. Label formalin-filled containers according to instructions in Section 5.4.1.
2. Obtain 2, 16-gauge or 18-gauge core needle biopsy specimens, and place one core in each cassette.
3. Snap the cassette lids closed and place cassettes into a formalin-filled pre-labeled container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.
4. Secure the container lids and package containers into the shipping kit according to instructions in Section 5.5. Keep tissue in formalin jars at room temperature until

shipment to the EET Biobank

5.3.4 Archival FFPE Tissues

Even when patients are able to provide a biopsy/resection specimen, a prior (archived) representative tumor tissue block may be requested. If previously-collected FFPE will be submitted, then the following criteria must be met:

- Tissue should ideally have been collected within 6 months prior to registration. Older archival material is acceptable unless otherwise specified by individual protocols.
- A copy of the original pathology report must be provided, and the tissue collection date must be recorded so the sample age can be derived.
- Formalin-fixed paraffin-embedded tumor tissue block(s) must be used to cut fresh unstained slides. The optimal block is at least 30% tumor, however less tumor content is acceptable. Preferred specimen size requirement is as follows:
    - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
    - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3

If the archival block cannot be submitted, the following can be provided

- Two (first and last cut) sectioned H&E slides (minimum of one is required), **AND**;
- Fifteen to twenty (or other number specified by each correlative study) 4 μm unstained air-dried plus slides.

5.3.5 Blood Collection and Processing

5.3.5.1 Streck Cell-Free DNA Tube (10 mL)

- Label two 10 mL Streck cfDNA BCTs (Streck catalog # 218961, 218962, or 218992), as described in Section 5.4.
- Collect 10 mL of blood into each pre-labeled tube and invert to mix. **Note: blood must be thoroughly mixed to ensure preservation of specimen.**
- After collection, blood in cfDNA Streck BCT **should never be refrigerated**, as this will compromise the specimen. Blood collected in cfDNA Streck Tubes is stable at room temperature.

5.3.5.2 EDTA Purple-Top Vacutainer Tube for Plasma (for Beumer PK laboratory at UPMC Hillman Cancer Center)

General

Blood samples to be obtained through a peripheral or central line blood draw. Samples should be drawn from the opposite arm if infusion is a peripheral infusion. Samples should NOT be drawn from the infusion line.

Drawing and Processing
Document exact start and stop times of each infusion and exact times of blood draws per Appendix K or L, respectively.

1. Collect in a 3 or 4 mL purple top tube (*e.g.* BD vacutainer 367861 plastic 13 x 75 4 mL tube).
2. Invert the vacutainer tubes several times to mix blood with EDTA anticoagulant and immediately place on ice.
3. Processing should begin within 30 minutes of collection.
4. Samples should be centrifuged for 10 min at approximately 1000 x g in a refrigerated tabletop centrifuge so as to produce plasma.
5. The resulting plasma should be aspirated from the tubes, placed into appropriately-labeled microcentrifuge tubes, and stored at -70 °C until shipment.

5.3.5.3 Red Top Vacutainer Tube for Serum (for Beumer laboratory at UPMC Hillman Cancer Center)

General
Blood samples to be obtained through a peripheral or central line blood draw. Samples should be drawn from the opposite arm if infusion is a peripheral infusion. Samples should NOT be drawn from the infusion line.

Drawing and Processing
Document exact times of blood draws per Appendix I.

1. Collect in a 3 or 4 mL red-top tube (*e.g.* BD vacutainer 367812 plastic 13 x 75 4 mL tube).
2. Allow blood to clot upright at room temperature for at least 30 minutes (maximum 60 minutes) prior to processing. If the blood is not immediately processed after the clotting period, then tubes should be stored (after the 30-60 minutes of clotting time) at 4°C for no longer than 4 hours. Process serum from red top tubes by centrifuging for 10 minutes at 1,200 x g at room temperature.
3. Using a transfer pipette**,** aliquot serum into a labeled cryovial at an aliquot volume of ≥1 mL. Avoid picking up red blood cells when aliquoting by keeping the pipet above the red blood cell layer and leaving a small amount of serum in the tube. Tightly secure the cap of the vials before storage.
4. Within 1 hour of centrifugation, store serum cryovials in a specimen box in an -70°C to -90°C or colder freezer until shipment.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions
For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in

Section 3.

- Additional Requirements:
  - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this or any other protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies without a corresponding pathology report, the radiology and operative report(s) must also be uploaded into Rave, when available. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact STS Support at STS.Support@theradex.com.

The Shipping List report **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.* formalin jar).

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (*e.g.*, P for primary or M for metastatic, or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)
- Core Number

5.4.2.2 Blood Specimen Labels

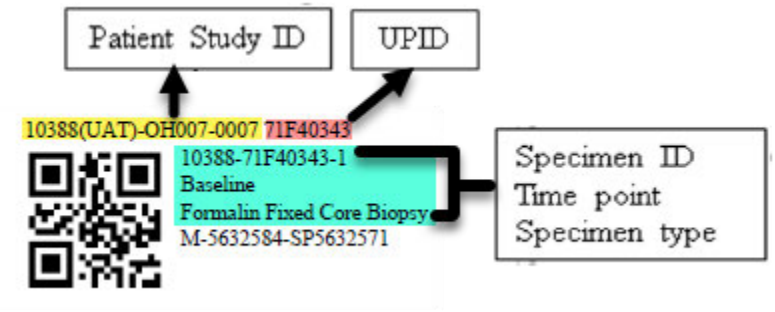
Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date (to be added by hand)

5.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time.

The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP-IAM account, then navigate to the appropriate participant.

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date on each label.
- After collection, store labeled specimens as described in Section 5.3.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), and Surgical (or Operative) reports . Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen) and/or the Tissue Biopsy Verification form (when applicable, Appendix J). Uploaded reports should have PHI data like name, date of birth, mailing address, medical record number or SSN redacted. Do not redact SPID,

block number, diagnosis or relevant dates (such as the collection date), and include the UPID and patient study ID on each document (either by label or hand writing).

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form**:** Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF**:** Enter tracking number, your contact information, recipient, number of sample containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF**:** In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.** .

Step 5: Print shipping list report and prepare to ship.

- Shipping List report is available at the site level.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Shipping Specimens from Clinical Site to Other Laboratories

5.5.1 Shipping Specimens from Clinical Site to the EET Biobank

When kits are provided, the shipping container sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

5.5.1.1 Required Forms for Specimen Submission

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	**Required Forms**
New Biopsy	1. Shipping List 2. Tissue Biopsy Verification Form 3. Diagnostic Pathology Report 4. Operative and/or Radiology Report
Blood	1. Shipping List

5.5.1.2 Specimen Shipping Instructions

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.

Frozen specimens may be shipped on Monday through Thursday.

Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

5.5.1.3 Specimen Shipping Instructions

5.5.1.3.1 Shipping Blood in an Ambient Shipper

1. Before packaging specimens verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Place specimens into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
3. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
4. Place the specimen and a copy of the shipping manifest into the shipping box. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container, to prevent specimens from freezing.
5. Close the box and attach a shipping label to the top.
6. Place an Exempt Human Specimen sticker to the side of the container.
7. Ship specimens via overnight courier to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.1.3.2 Packaging Ambient Tissue and Blood in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed. Formalin jars should be wrapped in parafilm.
2. Place the specimens in zip-lock bags. Use a separate bag for each specimen type.
3. Place specimens into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
4. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.

5. Place the specimen(s) and a copy of the shipping manifest and corresponding reports such as operative or radiology reports into the insulated shipping container. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container, to prevent specimens from freezing.
6. Place the lid on top of the container. Close the outer flaps and tape shut.
7. Attach a shipping label to the top of the shipping container.
8. Attach an Exempt Human Specimen sticker to the side of the container.
9. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.1.3.3 Packaging Frozen Specimens in a Single-Chamber Kit

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place frozen specimens in the kit compartment with dry ice. Layer the bottom of the compartment with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full. When packaging specimens, ensure that you leave enough room to include at least 5 pounds of dry ice in the shipment.
6. Insert a copy of the required forms into a plastic bag and place in the kit chamber.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
8. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
9. Complete a FedEx air bill and attach to top of shipping container.
10. Complete a dry ice label.
11. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.1.3.4 Packaging Frozen Specimens in a Dual-Chamber Kit

The Dual Chambered Specimen Procurement Kit is constructed to allow the shipment of frozen (on dry ice) and ambient (room temperature) specimens in the same container. **Dry ice may be placed in either compartment of the kit, but should not be put in both.** The dual chambered kit is only used for shipments that contain <u>both</u> frozen and ambient specimens. If formalin-fixed tissue is shipped separately (not in the same shipment as frozen specimens), then it must be shipped using institutional shipping supplies.

- **Frozen specimens** may be shipped on Monday through Thursday. Ensure that sufficient dry ice is included to completely encase the specimens to maintain specimen integrity during shipment.

- **Formalin-fixed tissue** may be shipped on Monday through Thursday.

    - Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed. If included in the shipment, formalin jar lids should be wrapped in parafilm.
    - Pre-fill one of the kit chambers about 1/3 with dry ice.
    - Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type.
    - Two biohazard envelopes are provided so that ambient and frozen specimens can be packaged separately.
- Place the zip-lock bags containing room temperature specimens in a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
- Place the zip-lock bags containing frozen specimens into the other biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
    - Put each secondary envelope into a Tyvek envelope. Expel as much air as possible and seal each envelope securely.
    - Quickly place the Tyvek envelope containing frozen specimens (*e.g*. frozen tumor, serum, etc.) in the kit compartment that is pre-filled with dry ice. Place the Tyvek envelope on top of the dry ice. Cover the specimens with additional dry ice until the compartment is almost completely full.
    - Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
    - Place the Tyvek envelope containing ambient temperature specimens (*e.g*. formalin-fixed tissue) in the other kit compartment at room temperature.
    - Insert a copy of the required forms into a plastic bag and place in the kit chamber with the ambient specimens.
    - Place the Styrofoam lid on top of the kit compartment to secure specimens during shipment. Do not tape the inner chamber shut.
    - Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
    - Complete a FedEx air bill and attach to top of shipping container.
    - Complete a dry ice label.
    - Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
    - Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.1.4 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of

specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
2200 International Street
Columbus, OH 43228
PH: (614) 722-2865
FAX: (614) 722-2897
E-mail: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred. There is no central Courier account for this study. Sites are responsible for all costs for overnight shipment per specimen shipment to the EET Biobank, utilizing the site screening and base intervention payments.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

5.5.1.5 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Phone: (614) 722-2865
E-mail: BPCBank@nationwidechildrens.org

5.5.2 Shipping Specimens from Clinical Site to the UPMC Hillman Cancer Center (Beumer PK laboratory)

1. Specimen Shipping Instructions

Preparing the shipment

1. Samples should be stored in cardboard boxes (5 1/8" x 5 1/8" x 2", L x W x H).
2. Please organize the samples by Patient and Time point in the box.
3. Do not store in plastic bags (they break on dry-ice and labels will detach).
4. A copy of each of the pharmacokinetic sample collection forms for the respective patients should be included with each shipment. To prevent problems with illegible writing on tubes, consider numbering them and numbering samples on the sample sheet.
   *Note the study number, PI, and the drugs used/to be measured.
   *A name, phone number, and email address should be included with the samples so that receipt can be acknowledged.
5. Please notify the lab by telephone (412-623-3248) or fax (412-623-1212) at least 24 hours prior to shipment.

Regulations

Shipment of samples must comply with appropriate regulations as specified by the carrier. At a minimum, all samples must be packaged within two containers with absorbent material between containers to control any spill or leakage. The outer container must be puncture-resistant (*e.g.*

cardboard mailing tube, corrugated cardboard box). A biohazard sticker must be affixed to both the inner and outer containers.

1. Shipping Address
All samples should be shipped via overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state. All specimens are to be shipped on either Monday, Tuesday, or Wednesday, and not before federal or university holidays.

Cancer Pharmacokinetics and Pharmacodynamics Facility
UPMC Hillman Cancer Center
Room G27 Hillman Research Laboratories
5117 Centre Avenue
Pittsburgh, PA 15213

2. Contact Information for Assistance
Email PK director: beumerjh@upmc.edu
Email PK lab manager: parisera@upmc.edu

5.5.3 Biomarker Plan

List of Biomarker Assays in Order of Priority

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Laboratory Performing Assay
N/A	*PIK3CA* mutations	NGS or equivalent (any local CLIA-certified assay will be accepted)	Integral To qualify for PIK3CA mutant cohort and to assess clinical benefit of trial therapies in patients with *PIK3CA* mutant and wildtype advanced solid tumors, as measured by objective response rate (CR+PR)	M	Prior to Registration	Archived tumor or Fresh tumor tissue biopsy	MD Anderson or local CLIA-certified laboratory

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Laboratory Performing Assay
N/A	*PTEN* mutations	NGS or equivalent (any local CLIA-certified assay will be accepted)	Integral To qualify for *PTEN* mutant cohort and to assess clinical benefit of trial therapies in patients with *PTEN* mutant and wildtype advanced solid tumors, as measured by objective response rate (CR+PR)	M	Prior to Registration	Archived tumor or Fresh tumor tissue biopsy.	MD Anderson or local CLIA-certified laboratory
N/A	*DDR* mutations	NGS or equivalent (any local CLIA-certified assay will be accepted)	Integral To qualify for *DDR* aberration cohort and to assess clinical benefit of trial therapies in patients with *DDR aberrant* advanced solid tumors, as measured by objective response rate (CR+PR)	M	Prior to Registration	Archived tumor or Fresh tumor tissue biopsy	MD Anderson or local CLIA-certified laboratory
1	RPPA	RPPA	Integrated To assess treatment induced changes in PI3K pathway signaling (*e.g.*, pAKT, pS6, p4EBP1); to correlate with treatment response and progression	M/O *	Baseline, C1D15, C2D15, and at C24	Frozen tumor tissue	Yiling Lu RPPA Core Laboratory/ MD Anderson
2	WES	NGS	Exploratory To correlate SNV and CNV profiles with treatment response	M/O *	Baseline and C24	Fresh tumor tissue biopsy	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Laboratory Performing Assay
3	RNA Seq	RNA sequencing	Exploratory To correlate gene expression profiles with treatment response	M/O *	Baseline, C1D15, C2D15, and at C24	Fresh tumor tissue biopsy	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich
4	Copanlisib PK Olaparib PK	MS	Integrated To assess PK of copanlisib and olaparib	M**,•	1. C1D8 (baseline [pre-dose], 30 minutes, 55 min [5 min pre-end infusion], 1hr, 3h, 5h, 7hr and 23hr after copanlisib infusion). 2. C1D15 (baseline [pre-dose], 30 min, 55 min [5 min pre-end infusion])	Plasma (from blood)	Beumer / NorthEast Biolabs

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Laboratory Performing Assay
5	Durvalumab PK (Triplet combination only)	electrochemiluminescence	Integrated To assess PK effects of durvalumab.	M•	3. C2D1 (baseline [pre-dose], 50 min [10 min pre-end infusion]) 4. C3D1 (baseline [pre-dose], 50 min [10 min pre-end infusion]) 5. C4D1 (baseline [pre-dose], 50 min [10 min pre-end infusion]) 6. C5D1 (baseline [pre-dose], 50 min [10 min pre-end infusion]) relative to durvalumab infusion	Serum (from blood)	Beumer / MedImmune

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Laboratory Performing Assay
6	ctDNA sequencing	NGS	Exploratory To correlate ctDNA mutation profiles with tumor sequencing, correlate baseline ctDNA mutations, particularly in components of the PI3K pathway with treatment response, and correlate changes in ctDNA variant allele frequencies with responses, assess emergent resistant mutations at progression, including *BRCA* reversion	M	Baseline, C1D15, C2D15, each restaging, and C24/DP	Blood	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich
7	WES	NGS	Exploratory To remove patient-specific germline polymorphisms and improve the detection of somatic tumor mutations	M	Baseline	Blood	MoCha, Frederick National Laboratory for Cancer Research (FNLCR) Chris Karlovich

PIK3CA = p110 catalytic subunit of phosphatidylinositol-3 kinase; CLIA = clinical laboratory improvement amendments; NGS = next generation sequencing; CR = complete response; PR = partial response; M = mandatory; FFPE = formalin fixed, paraffin embedded; PTEN = phosphate and tensin homolog; DDR = DNA Damage response; RRPA = reverse phase protein assay; C1D8 = cycle 1, day 8; C1D15 = cycle 1, day 15; C1D22 = cycle 1, day 22; C2D1 = cycle 2, day 1; C2D22 = cycle 2, day 22; C3D1 = cycle 3, day 1; C4D1 = cycle 4, day 1; C5D1 = cycle 5, day 1; C24 = cycle 24; DP = disease progression; WES = whole exome sequencing; pAKT = phosphorylated protein kinase B; SNV = single nucleotide variants; CNV = copy number variants; PD-L1 = programmed death ligand 1; RNA Seq = RNA sequencing; PK = pharmacokinetics; MS = mass spectrometry; C1D1 = cycle 1, day 1; O = optional; C2D15 = cycle 2, day 15, C4D1 = cycle 4, day 1; ctDNA = circulating tumor DNA; cfDNA = cell free DNA; C1D8 = cycle 1, day 8.

* Tissue such as small biopsies (mostly core needle biopsies, but includes endoscopy and punch biopsies) and surgical resections will be collected at baseline, Cycle 1 Day 15, and optional biopsy at Cycle 24 or disease progression (whichever comes first) for the doublet combination. For the triplet combination, biopsies will be collected at baseline, Cycle 1 Day 15, optional biopsies at Cycle 2 Day 15 and Cycle 24 or disease progression (whichever comes first).

**Patients treated at Dose Level 3a in Step 1 and those treated in Step 2 will not undergo the Cycle 1 Day 8 PK sample collection. Time points for the Cycle 1 Day 15 collection are as follows: baseline (pre-dose), 30 min post start of copanlisib infusion, 55 min post start of copanlisib infusion (5 min pre-end infusion), and 1 h, 3 h, 5 h, 7 h, and 23 h post end of copanlisib infusion.

• PK samples will not be collected from patients treated in Step 3.

5.6 Integral Laboratory Studies

5.6.1 PIK3CA Mutations

PIK3CA mutation status evaluation will be performed prior to registration. Eligibility will be based on the presence of hotspot PIK3CA mutations such in E542, E545, and H1047 only. Hotspot PIK3CA mutations will be determined by the PODS group at MD Anderson.

5.6.1.1 Sites Performing Correlative Study

A local CLIA-certified laboratory or Dr. Timothy Yap at MD Anderson will analyze samples.

5.6.2 PTEN Mutations

PTEN mutation status evaluation will be performed prior to registration. Eligibility will be based on the presence of actionable PTEN mutations. Actionability will be assessed by the PODS group at MD Anderson.

5.6.2.1 Sites Performing Correlative Study

A local CLIA-certified laboratory or Dr. Timothy Yap at MD Anderson will analyze samples.

5.6.3 DDR Mutations

DDR mutation status evaluation will be performed prior to registration. Eligible genes include: BARD1, BRCA1, BRCA2, BRIP1, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, and RAD51D. Actionability will be assessed by the PODS group at MD Anderson.

5.6.3.1 Sites Performing Correlative Study

A local CLIA-certified laboratory or Dr. Timothy Yap at MD Anderson will analyze samples.

5.7 Integrated Correlative Studies

5.7.1 RPPA

RPPA-based proteomic analysis will be performed using 181 high-quality antibodies that target total (n=128), cleaved (n=1), acetylated (n=1) and phosphorylated forms (n=51) of proteins in patient samples. The function space covered by the antibodies used in the RPPA analysis encompasses major functional and signaling pathways of relevance to human cancer. Different batches of RPPA data will be merged using an algorithm, called Replicates Based Normalization (RBN), which mitigates batch effects facilitating creation of a single protein dataset merging samples across different batches. Two-way unsupervised hierarchical clustering analysis will be used to discover the groups of biological objects sharing common characteristics, and a two-dimensional heat map to visualize protein expression patterns. To detect the discriminating

biomarkers for each cluster (obtained by hierarchical clustering using the RPPA data normalized by RBN), LIMMA will be used to select biomarkers by comparing samples in each cluster with samples in all the other clusters together. In addition, pathway activity scores will be computed using a series of pathway predictors developed based on member proteins selected by literature review.

5.7.1.1 Specimens Receipt and Processing at the EET Biobank

Frozen tissue specimens received from the collection site should be stored at -80 or lower.

5.7.1.2 Sites Performing RPPA

This assay will be performed at the MD Anderson RPPA Core Laboratory (Lab PI: Yiling Lu). All of the samples from this study collected for this assay will be stored at the EET Biobank at the Nationwide Children's Hospital and will be shipped later to MD Anderson RPPA Core laboratory for batch analysis.

5.7.1.3 Shipment of specimens from the EET Biobank to Site Performing Correlative Study
Specimens will be shipped from the EET Biobank to:
Functional Proteomics RPPA Core Facility
Attn: Doris Siwak, PhD
6565 MD Anderson Blvd., Room Z4.2040
Houston, TX 77030

5.7.1.4 Contact Information for Notification of Shipment
Email Dr. Lu at yilinglu@mdanderson.org

5.7.2 Whole Exome Sequencing (WES)

5.7.2.1 Specimens Receipt and Processing at the EET Biobank

Tumor tissue received in formalin will be paraffin-embedded. DNA and RNA will be co-extracted from tumor tissue. The nucleic acids will be analyzed to determine concentration and quality. Aliquots of DNA and RNA will be shipped to the central sequencing laboratory for analysis.

5.7.2.2 Sites Performing Correlative Study

WES will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the leadership of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.7.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study
Specimens will be shipped from the EET Biobank to:

Specimens will be shipped from the EET Biobank to:
MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.7.2.4 Contact information for notification of specimen shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.7.3 Olaparib PK

5.7.3.1 Specimens Receipt and Processing at the Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center
Fresh/Frozen plasma aliquots will be received at the Beumer laboratory for processing and storage.

5.7.3.2 Site Performing Olaparib PK
This assay will be performed at the Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center. An assay is being implemented following a published method (Nijenhuis et al. Journal of Chromatography B, 940 (2013) 121– 125). The PK laboratory will take aliquots of these samples and ship to NorthEast Biolabs for analysis of copanlisib (contracted by Bayer).

5.7.3.3 Contact information for notification of specimen shipment:
See Section 5.5.2.

5.7.4 Copanlisib PK

5.7.4.1 Specimens Receipt and Processing at the Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center
Fresh/Frozen plasma aliquots will be received at the Beumer laboratory for processing and storage.

5.7.4.2 Site Performing Copanlisib PK
This assay will be performed at NorthEast Biolabs. All of the samples from this study collected for this assay will be stored at the Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center and will be shipped later to NorthEast Biolabs for batch analysis.

5.7.4.3 Contact information for notification of specimen shipment:
See Section 5.5.2.

5.7.5 Durvalumab PK

5.7.5.1 Specimens Receipt and Processing at the Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center

Fresh/Frozen serum aliquots will be received at the Beumer laboratory for processing and storage.

5.7.5.2 Site Performing Durvalumab PK

The assay for durvalumab, anti-drug antibody, and s-PD-L1 will be performed at MedImmune. All of the samples from this study collected for this assay will be stored at the Cancer Pharmacokinetics and Pharmacodynamics Facility, UPMC Hillman Cancer Center and will be shipped later to MedImmune or contracted designee for batch analysis.

5.7.5.3 Contact information for notification of specimen shipment:

See Section 5.5.2.

5.8 Exploratory/Ancillary Correlative Studies

5.8.1 Whole Transcriptome Sequencing (RNASeq)

5.8.1.1 Specimens Receipt and Processing at the EET Biobank

See Section 5.8.2.1

5.8.1.2 Sites Performing Correlative Study

RNA Seq will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.8.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.8.1.4 Contact Information for Notification of Specimen Shipment

Thomas Forbes (mochasamplereceiving@nih.gov)

5.8.2 ctDNA Sequencing

5.8.2.1 Specimens Receipt and Processing at the EET Biobank

Upon receiving the Streck cfDNA Tube from the collection site, the Biorepository should prepare Plasma and PBMCs.

- For each 10 mL Streck tube, create 4 plasma vials of 1 mL aliquots and store at -80°C.
- Create at least one PBMC vial (~5 x 10^6 cells/mL depending on blood volume and study need). Typical recovery can expect 1 x 10^7 cells from 10 mL tube.
- Slow-freeze aliquots at -80°C in a freezing container for 24 hours (up to 14 days) followed by long-term cryopreservation in the vapor phase of a LN2 tank.

5.8.2.2 Site Performing Correlative Study

ctDNA sequencing will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.9.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.9.2.4 Contact Information for Notification of Specimen Shipment
Thomas Forbes (mochasamplereceiving@nih.gov)

6. TREATMENT PLAN

6.1 Agent Administration

In Step 1, the doublet combination of copanlisib and olaparib will be investigated. Dose escalation will be undertaken in patients with advanced solid tumors, with the population enriched for those with both PI3K-AKT pathway and DDR aberrations. If a DLT is observed at dosing Level 3 and the dose escalation has completed, a maximum of 6 patients will be treated with a less intense schedule of copanlisib 60 mg Day 1 and 15 and olaparib 300 mg BID (dose level 3a) to improve the safety profile.

Step 2 will not commence until safety data from Step 1 has been formally reviewed and discussed by the study team and with CTEP.

In Step 2, the RP2D of the copanlisib/olaparib doublet combination is copanlisib 60 mg Days 1 and 15 and olaparib 300 mg BID of each 28-day cycle. Durvalumab (MEDI4736) at 1500 mg Day 1 of each 28-day cycle will be added to form a novel triplet combination. Patients will start treatment in Cycle 1 with copanlisib and olaparib alone. Durvalumab (MEDI4736) will be added on Cycle 2 Day 1 (C2D1). The dose escalation phase will involve patients with advanced solid tumors, with the population enriched for those with both PI3K-AKT pathway and DDR aberrations. A protocol amendment will be required before the initiation of Step 2.

In Step 3, dose expansion for the copanlisib/olaparib doublet combination can proceed upon completion of Step 1 and can proceed simultaneously with Step 2. The dose expansion for the copanlisib/olaparib/durvalumab (MEDI4736) triplet combination can proceed upon completion of Step 2 and can proceed simultaneously with dose expansion for copanlisib/olaparib doublet combination. Patient assignment to the doublet or triplet combinations will be based on slot availability. During cohort expansion, patients to be assessed include: those with germline DDR aberrations (3A and 3C dose expansion cohorts), those with cancers with somatic DDR aberrations (3A and 3C dose expansion cohorts), patients with PIK3CA mutant cancers (3B and 3D dose expansion cohorts), and those with PTEN mutations (3B and 3D dose expansion cohorts). 15 patients will be recruited to each of the 4 molecular dose expansion cohorts (3A, 3B, 3C, 3D), for a total of 60 patients in dose expansion.

Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose escalation schema for the doublet combination of copanlisib and olaparib (Step 1)

Dose Escalation Schedule		
	Copanlisib*	Olaparib*
Level -1**	45 mg (D1, D15), 28-day cycle	200 mg BID
Level 1***	45 mg QW, D1, D8, D15, 28-day cycle	200 mg BID
Level 2	45 mg QW, D1, D8, D15, 28-day cycle	300 mg BID
Level 3****	60 mg QW, D1, D8, D15, 28-day cycle	300 mg BID
Level 3a	60 mg D1 and D15, 28-day cycle	300 mg BID
*Alternative schedules may be pursued depending on toxicities, pharmacokinetic and pharmacodynamic data generated from this and other trials. **Doses to pursue at dose level -1 will depend on the dose-limiting toxicities observed at dose level 1. ***Starting dose level.		

**** If DLT is observed at dosing Level 3, and the dose escalation is complete, a maximum of 6 patients will be treated with a less intensive schedule of copanlisib 60 mg Day 1 and 15 and olaparib 300 mg BID (dose level 3a) to improve the safety profile.

D = Day; BID = twice a day; QW = once a week.

Dose escalation schema for the triplet combination of copanlisib, olaparib, and durvalumab (MEDI4736 (Step 2)

Dose Escalation Schedule			
	Copanlisib	Olaparib	Durvalumab (MEDI4736)
Level -1*	45 mg (D1, D15), 28-day cycle	200 mg BID	1500 mg D1 28-day cycle (Starting Cycle 2, Day 1)
Level 1	60 mg (D1, D15), 28-day cycle	300 mg BID	1500 mg D1 28-day cycle (Starting Cycle 2, Day 1)
*Doses to pursue at dose level -1 will depend on the dose-limiting toxicities observed at dose level 1.			

D = Day; BID = twice a day
RP2D = recommended phase 2 dose; MTD = maximum tolerated dose

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Copanlisib	No IV glucose preparations should be administered on the days of infusion. Thirty mins prior to copanlisib infusions give 4 mg IV or PO dexamethasone and 25 mg diphenhydramine IV or PO for prevention of rash.	**45 mg	IV over 1 hour	**D1, D8, and D15 (or on D1 and D15 for dose level 3a)	28 days (4 weeks)
Olaparib	Not Applicable	**200 mg	PO BID	BID	
Durvalumab (MEDI4736)*	Not Applicable	***1500 mg	IV over 1 hour	Q28D	
*Durvalumab (*MEDI4736) should be administered before copanlisib for the triplet combination.* **Doses and schedule as appropriate for assigned dose level.*					

Regimen Description					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
****Refer to Section 6.1.3 for weight ≤30kg.*					

IV = intravenously ; D = day; QW; once every week; BID = twice a day;
Q28D = once every 28 days

The patient will be requested to maintain a medication diary of each dose of olaparib. The medication diary (Appendix F) will be returned to clinic staff at the end of each course.

6.1.1 Copanlisib

Based on the company-sponsored studies with copanlisib in patients with oncologic malignancies, the RP2D of copanlisib monotherapy is 60 mg and will be administered by IV for 1 hour on Days 1, 8, and 15 of every 28-day cycle. A copanlisib dose reduction to 45 mg has been allowed for toxicities (Copanlisib Investigator's Brochure, 2017). The starting dose for this combination trial is 45 mg. For patients treated at dose level 3a, dose level 1 of the triplet dose escalation, and dose expansion for both the doublet and triplet combinations, copanlisib 60 mg will be administered by IV for 1 hour on Days 1 and 15 of every 28-day cycle.

6.1.1.1 Agent Administration

Use of antiemetics prior to copanlisib administration is not allowed. Use of antiemetics should not be needed since each patient will receive 25 mg diphephydramine (IV or PO) and 4 mg dexamethasone (IV or PO) to prevent copanlisib-induced rash. Should a patient require antiemetics after the first infusion, use of additional corticosteroids is not allowed. Administer copanlisib as an IV infusion over one hour (+/-10 minutes). After administration, flush the line with 0.9 % sodium chloride to ensure complete dose is given. No IV glucose preparations should be administered on the days of infusion.

On days both copanlisib and olaparib are given, follow the treatment order below:

1.) Premedication with 25 mg diphenhydramine (IV or PO) and 4 mg dexamethasone (IV or PO)
2.) Olaparib dose (can be given at the same time as the premedications)
3.) Copanlisib infusion over 60 minutes (+/-10 minutes) will begin at least 30 minutes AFTER Olaparib dose

Note: If the Olaparib dose is held, there is no window between the premedication and copanlisib infusion.

Recommendations on meal timing on copanlisib infusion days

Because of an inhibitory effect on PI3Kα-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporarily increase in blood glucose. Consuming meal in close proximity to copanlisib infusion may exacerbate a glucose level increase. It is

recommended that timing and content of caloric intake on infusion days is monitored by the investigators. Consultation with diabetologist or endocrinologist is advised**.**

The investigator may manage the timing of post-infusion meals based on the glucose profile during prior infusion days to minimize glucose increases. This is in addition to glucose lowering medication. On infusion days a low carbohydrate diet is recommended, the timing and content of meal intake and additional glucose testing (if clinically indicated) is managed and monitored by the investigators based on glucose response patterns during prior treatment days. However, caloric restriction is not intended for the population under study. Refer to Appendix D for glycemic indices of common foods.

NOTE: If patient needs to take a low glycemic meal, then glucose test should be taken prior to meal intake and at 1 and/or 2 hours after the meal. All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, and meal timing will be collected as part of the clinical source documentation.

NOTE: Caloric intake and timing recommendations for diabetic patients who require insulin treatment prior to the infusion at any cycle visit should be managed by the investigator based on consultation with treating physician or diabetes/endocrinologist physician.

Pre-dose glucose levels

Period	**Pre-dose glucose levels (first glucose measurement)**
Day 1 of cycle 1	<160 mg/dL (fasting*) < 200 mg/dL (non-fasting**)
Subsequent infusions after Cycle 1 Day 1	<160 mg/dL (fasting*) < 200 mg/dL (non-fasting**)

*Fasting refers to a ≥ 8 h fast.
**Non-fasting status includes any caloric intake such as meals and also juice, snacks, and other caloric intake not consistently called a meal.

From Cycle 1 Day 1 onwards, glucose measurements at the site may be done either by laboratory analysis or in capillary blood.

Post-dose glucose monitoring after C1D1 is performed as clinically indicated at the investigator's discretion.

All glucose measurements done at the site, oral glucose lowering medication and/or insulin administration, if applicable, fasting/non-fasting status and meal intake timing on infusion days will be collected as part of the clinical source documentation.

6.1.2 Olaparib

6.1.2.1 Agent Administration

Patients will be administered olaparib BID. 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. Consumption of grapefruit, grapefruit juice, or Seville oranges while on olaparib therapy is prohibited. On days that both copanlisib and olaparib are given, follow the treatment order below:

1.) Premedication with 25 mg diphenhydramine (IV or PO) and 4 mg dexamethasone (IV or PO)
2.) Olaparib dose (can be given at the same time as the premedications)
3.) Copanlisib infusion over 60 minutes (+/-10 minutes) will begin at least 30 minutes AFTER Olaparib dose

Note: If the Olaparib dose is held, there is no window between the premedication and copanlisib infusion.

If vomiting occurs shortly after the olaparib 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 will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose is not to be taken and the patient should take their allotted dose at the next scheduled time.

6.1.3 Durvalumab (MEDI4736)

6.1.3.1 Agent Administration

Durvalumab (MEDI4736) will only be administered for the triplet combination. Durvalumab (MEDI4736) should be administered before copanlisib starting on Cycle 2 Day 1 of the triplet combination therapy. For patients >30 kg, use flat dosing: 1500 mg durvalumab (MEDI4736) via IV infusion D1 Q28D for a maximum of 24 months or until disease progression (whichever is earlier), unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

If a patient's weight falls to ≤30 kg, the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab (MEDI4736) Q4W until the weight improves to >30 kg, at which point, the patient should start receiving the fixed dosing of durvalumab (MEDI4736) at 1500 mg Q4W.

Standard infusion time is 60 minutes (± 10 minutes). In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

On days when olaparib, copanlisib, and durvalumb are to be administered, follow the treatment order below:

1.) Durvalumab will be administered over 60 minutues (± 10 minutes)
2.) Premedication with 25 mg diphenhydramine (IV or PO) and 4 mg dexamethasone (IV or PO) AFTER durvalumab infusion is completed
3.) Olaparib dose (can be given at the same time as the premedications)
4.) Copanlisib infusion over 60 minutes (+/- 10 minutes) will begin at least 30 minutes AFTER Olaparib dose

In the event olaparib is held, follow the treatment order below:

1.) Durvalumab will be administered over 60 minutues (± 10 minutes)
2.) Premedication with 25 mg diphenhydramine (IV or PO) and 4 mg dexamethasone (IV or PO) AFTER durvalumab infusion is complete
3.) Copanlisib infusion over 60 minutes (+/-10 minutes) AFTER premedications are administered

In the event copanlisb is held, follow the treatment order below:

1.) Durvalumab will be administered over 60 minutues (± 10 minutes)
2.) Olaparib dose AFTER durvalumab infusion is complete

Note: If the Copanlisib dose is held, there is no need to administer the premedications.

6.1.3.2 Supportive Care

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

- In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.
- If the infusion related reaction is ≥Grade 3 or higher in severity, study drug will be discontinued. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Section 7.

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

addition to the ability to admit patients to an intensive care unit if necessary.

6.2 Definition of Dose-Limiting Toxicity

6.2.1 DLTs for Steps 1 and 2

Severity of AEs will be graded according to CTCAE v5. Any of the following AEs occurring during the DLT observation period (Cycle 1 through Cycle 2 Day 1 for the doublet combination; Cycle 1 through Cycle 3 Day 1 for the triplet combination), which are attributable to at least one of the investigational products will be classified as DLTs:

- Any Grade 2 toxicity that requires permanent discontinuation durvalumab (MEDI4736) or combination during the first 4 weeks.
- Any Grade 5 toxicity.

Hematological:

- Grade 4 neutropenia (absolute neutrophil count [ANC] <0.5 x 109/L) lasting >7 days
- Febrile neutropenia, defined as ANC <1000/mm^3 with a single temperature of >38.3ºC (>101ºF) or a sustained temperature of ≥38ºC (100.4ºF) for more than 1 hour
- Neutropenic infection (ANC <1,000/mm3 or <1.0 x 109/L, and Grade >3 infection
- Grade ≥3 thrombocytopenia (platelet count <50.0 × 109/L) with bleeding
- Grade 4 thrombocytopenia (platelet count <25.0 x 109/L)
- Grade 4 anemia (life-threatening consequences; urgent intervention indicated)

Non-hematological:

- Non-hematological toxicities:
    - Grade ≥4 toxicities
    - Confirmation of QTc prolongation (>500 msec) or QTc increase >60 msec from baseline
    - Grade ≥ 3AE hyperglycemia or hypertension lasting ≤ 7 days (transient, intermittent, or reversible hyperglycemia and/or hypertension that can be optimally controlled with our without intervention will not be considered a DLT)
    - Grade 3 skin rash despite optimal medical intervention (*e.g.*, IV steroids)
    - Grade 3 diarrhea despite maximal medical intervention (*e.g.*, IV steroids).
- Any other toxicity that is greater than that at baseline, is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of dosing schedule of more than 14 days
- Any event, including significant dose reductions or omissions, judged to be a DLT by the Safety Review Committee
- Any other toxicity in any course of treatment that in the opinion of the investigators and medical monitors is dose-limiting

Please see Section 7 for the management of DLTs.

The following toxicities will not be considered DLTs:

- Alopecia of any grade
- Isolated laboratory changes of any grade without clinical sequelae or clinical significance

Evaluability criteria:

To be considered evaluable for the specified DLT period in Steps 1/2 escalation cohorts or evaluable in Step 3 expansion cohorts, patients must have received at least 75% of Olaparib doses and have no missed Copanlisib doses. There will be an allowance for a 1 week delay within C1 for Copanlisib as long as all doses are administered

6.2.2 DLTs for Step 2 only

The following toxicities will not be considered DLTs:

- Vitiligo of any grade
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the patient is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (*e.g.*, inflammatory reaction at sites of metastatic disease, lymph nodes, *etc.*)
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

Management and dose modifications associated with the above adverse events are outlined in Section 7.

6.3 Dose Expansion Cohorts:

Once the RP2D is reached for the doublet and/or triplet combinations, an additional 15 patients will be enrolled in each of 4 cohorts, namely, patients with germline or somatic DDR aberrations treated with the doublet combination (3A); patients with PIK3CA or PTEN mutations treated with the doublet combination (3B); patients with germline or somatic DDR aberrations treated with the triplet combination (3C); and patients with PIK3CA or PTEN mutations treated with the triplet combination (3D), for a total of 60 patients in the dose expansion who will be treated at either the RP2D/MTD of the doublet or triplet combination. Monitoring of all safety and toxicity data is done by the PI and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred according to the AEs summarized in section 6.2.1.

6.4 General Concomitant Medication and Supportive Care Guidelines

6.4.1 Copanlisib

Because there is a potential for interaction of copanlisib with other concomitantly administered drugs, the case report form (CRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The known potential targets for drug interaction are CYP3A4 inducers or inhibitors, as well as drugs modulating glucuronidation, P-gp, BCRP, and MATE2K function. Concomitant use of medications listed in Appendix B is prohibited while on copanlisib. Appendix C should be provided to patients if available.

6.4.1.1 Substrates with narrow therapeutic indices

Substrates of P-gp and/or BCRP with narrow therapeutic index should be used with caution and patients monitored for any sign of toxicity. Furthermore, sensitive substrates of the renal drug transporter MATE2K (*e.g*. metformin) need to be used with caution. Metformin should be interrupted for 48 hours after receiving iodinated contrast media. Please see prescribing information for further information.

6.4.1.2 Monitoring

Patients taking medications with narrow therapeutic index should be proactively monitored if these medications cannot be avoided. These medications may include quinidine, cyclosporine, and digoxin.

6.4.1.3 Systemic corticosteroid therapy

Systemic corticosteroid therapy at a daily dose higher than 10 mg prednisone or equivalent is not permitted while on study. Previous corticosteroid therapy must be stopped or reduced to the allowed dose at least 14 days prior to the CT/MRI screening. If a patient is on chronic corticosteroid therapy, corticosteroids should be de-escalated to the maximum allowed dose before the screening. Patients may be using topical or inhaled corticosteroids. Short-term (up to 7 days) systemic corticosteroids above 10 mg prednisolone or equivalent will be allowed for the management of acute conditions (*e.g.,* treatment of non-infectious pneumonitis). The use of corticosteroids as antiemetics prior to copanlisib administration will not be allowed.

6.4.1.4 Herbal Medications

Patients should stop using herbal medications at least 7 days prior to the first dose of copanlisib. Herbal medications include, but are not limited to: St. John’s Wort, Kava, ephedra, gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, black cohosh and ginseng.

6.4.2 Olaparib

Because there is a potential for interaction of olaparib with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter

medications, vitamins, nutritional supplements, or alternative therapies at the time of enrollment and throughout the study. The CRF should capture the dates of administration (including start/end dates if known), dosage (including dosing frequency/schedule), and reason for use. The PI should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendices C and D should be provided to patients if available.

6.4.2.1 Dietary Restrictions and Over-the-Counter/Self-Medication

It is prohibited to consume grapefruit, grapefruit juice, Seville oranges, or Seville orange juice while on olaparib therapy. The use of any natural/herbal products or other traditional remedies should be discouraged.

6.4.2.2 Medications that May NOT be Administered

No other anti-cancer therapy (chemotherapy, immunotherapy, hormonal therapy (hormone replacement therapy [HRT] is acceptable), radiotherapy (except palliative), 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 30 days prior to dosing study agents, while the patient is receiving study agents, and for 100 days after the last dose of study agents. Inactivated vaccines are permitted. 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.

6.4.2.3 Restricted Concomitant Medications

6.4.2.3.1 Strong or Moderate CYP3A Inhibitors

Known strong CYP3A inhibitors (*e.g.*, itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) should not be taken with olaparib.

If there is no suitable alternative concomitant medication, the dose of olaparib should be reduced for the period of concomitant administration (please refer to Section 7.2.2). The dose reduction of olaparib should be recorded on the CRF with the reason documented as concomitant CYP3A inhibitor use. Monitor the patient carefully for any change in efficacy of olaparib.

- Strong CYP3A inhibitors – reduce the dose of olaparib to 100 mg BID for the duration of concomitant therapy with the strong inhibitor and for 5 half-lives afterwards.
- Moderate CYP3A inhibitors - reduce the dose of olaparib to 150 mg BID for the duration of concomitant therapy with the moderate inhibitor and for 3 half-lives afterwards.
- After the washout of the inhibitor is complete, the olaparib dose can be re-escalated.

6.4.2.3.2 Strong or Moderate CYP3A Inducers

Strong (*e.g.*, phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) and moderate CYP3A inducers (*e.g.*, bosentan, efavirenz, modafinil) of CYP3A should not be taken with olaparib.

If the use of any strong or moderate CYP3A inducers are considered necessary for the patient's safety and welfare, this could diminish the clinical efficacy of olaparib.

If a patient requires use of a strong or moderate CYP3A inducer or inhibitor, then they must be monitored carefully for any change in efficacy of olaparib.

6.4.2.3.3 P-gp inhibitors

It is possible that co-administration of P-gp inhibitors (*e.g.*, amiodarone, azithromycin) may increase exposure to olaparib. Caution should therefore be exercised.

6.4.2.3.4 Effect of olaparib on other drugs

The efficacy of hormonal contraceptives may be reduced if co-administered with olaparib.

Based on limited *in vitro* data, olaparib may increase the exposure to substrates of CYP3A4, or organic transporting polypeptides 1B1 (OATP1B1), organic cation transporter 1 (OCT1), OCT2, organic anion transporter 3 (OAT3), MATE1, and MATE2K.

Based on limited *in vitro* data, olaparib may reduce the exposure to substrates of CYP2B6.

Caution should therefore be exercised if substrates of these isoenzymes or transporter proteins are co-administered.

Examples of substrates include (check a frequently-updated resource for more comprehensive lists):

- CYP3A4 – hormonal contraceptive, simvastatin, cisapride, cyclosporine, ergot alkaloids, fentanyl, pimozide, sirolimus, tacrolimus, and quetiapine
- CYP2B6 – bupropion, efavirenz
- OATP1B1 – bosentan, glibenclamide, repaglinide, statins, and valsartan
- OCT1, MATE1, MATE2K – metformin
- OCT2 – serum creatinine
- OAT3 – furosemide, methotrexate

6.4.2.4 Anticoagulant Therapy

Patients who are taking warfarin may participate in this trial; however, it is recommended that the INR be monitored carefully at least once per week for the first month, then monthly if the

INR is stable. Subcutaneous heparin and low molecular weight heparin are permitted.

6.4.2.5 Anti-emetics/Anti-diarrheals

If a patient develops nausea, vomiting, and/or diarrhea, then these symptoms should be reported as AEs and appropriate treatment of the event given. Diarrhea is a common problem experienced by many patients and is a risk with olaparib. If it is not controlled quickly, it can lead to dehydration.

6.4.2.5.1 When to call your doctor to report diarrhea

- Fever of 100.5°C (212°F) or higher with diarrhea.
- If you are experiencing diarrhea for the first time after starting therapy. Based on questions answered during that phone call, we will advise starting with 2 milligrams (mg) of loperamide (Imodium) if it seems the symptoms are related to the treatment.
- If you still have diarrhea 24 hours, or more than 6 loose bowel movements after starting Imodium (your doctor may advise additional medications or want to evaluate you in person if there is a concern that you are becoming dehydrated).

6.4.2.5.2 Over the counter medication management of diarrhea

- For diarrhea that occurs more than 2 episodes a day, use Imodium. We recommend that the patient have Imodium on hand at home before starting therapy.
    - 1st episode of diarrhea: Take 2 caplets (4 mg).
    - During day 1: Take 1 caplet (2 mg) after each episode of diarrhea
    - During the night: Take 2 caplets (4 mg) at bedtime if the patient still has diarrhea.
    - Do not take more than 8 tablets (8 mg) of loperamide in 24 hours.

6.4.2.5.3 Drink plenty of fluids

- Drink 8 to 19 large glasses of liquid a day to replace those lost by diarrhea. Drink small quantities at a time slowly.
- Avoid caffeinated, very hot, or very cold fluids. Examples of acceptable fluids are:
    - Water (should only be part of the 8 to 10 glasses a day)
    - Jell-O / gelatin
    - Gatorade
    - Clear soup or broth
    - Other non-caffeinated fluid.

6.4.2.5.4 Eat small meals often

- A good choice of foods for diarrhea is the BRAT diet:
    - B – bananas
    - R – rice
    - A – applesauce
    - T – toast

- When these foods are being well tolerated, than you can add other bland low fiber foods such as:
    - Chicken (white meat without skin), steamed rice, crackers, white bread, pasta noodles without sauce, and canned or cooked fruits without skins.
    - Foods high in potassium: bananas, apricots without skin, peach nectar, potatoes without skin, broccoli, halibut, mushrooms, asparagus, and non-fat milk.
- Foods that can make diarrhea and cramping worse:
    - Fatty, fried, grease, or spicy foods can cause more problems and discomfort.
    - High-fiber foods: bran, whole grain cereals, dried fruit, fruit skins, popcorn, nuts, and vegetables.
    - Foods that cause gas: beer, beans, cabbage, and carbonated drinks.

6.4.2.6 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.

6.4.2.7 Administration of other Anti-Cancer Agents

Patients must not receive any other concurrent anti-cancer therapy, except the study drugs, while on study treatment. Patients may continue the use of bisphosphonates, luteinizing hormone releasing hormone (LHRH) agonists, 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 the agents were started at least 4 weeks prior to beginning study treatment.

6.4.3 Durvalumab (MEDI4736)

The PI must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to Sections 6.4.3.1 and 6.4.3.2.

6.4.3.1 Permitted concomitant medications

Supportive medications

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

6.4.3.2 Excluded concomitant medications

Prohibited concomitant medications

Prohibited medication/class of drug:	**Usage:**
Any concurrent anticancer drugs other than those under investigation in this study.	Should not be given concomitantly whilst the patient is on study treatment.
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the durvalumab (MEDI4736) infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs. • The use of corticosteroids as antiemetics prior to copanlisib administration will not be allowed • Use in patients with contrast allergies. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (*e.g.,* chronic obstructive pulmonary disease, radiation, nausea, *etc*.).
Live attenuated vaccines	Prohibited for 30 days prior to study agents, during the study, and for 100 days after the last dose of study drugs. Inactivated vaccines are permitted.
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

6.4.4 Monitoring for HIV-Infected Patients

Monitoring for HIV-infected patients should include:

- Viral load and CD4 count every 12 weeks.
- If CD4 count drops to less than 200 cells/mcL while on study, initiate viral load test. If viral load proves undetectable at this time, continue CD4 and viral load checks every 8 weeks. If 2 consecutive viral load tests are undetectable, revert to every 12 week testing for CD4 and viral load testing.
    - If an opportunistic infection occurs with a CD4 count of <200 cells/mcL, hold study treatment. Initiate treatment of the infection and continue to hold study treatment; once clinically stable, CD4 count is >200 cells/mcL and viral load has remained undetectable, reinitiate study treatment.

6.5 Restrictions During the Study

The following restrictions apply while the patient is receiving study treatment and for the specified times before and after:

Female patient of child-bearing potential (For Steps 1, 2, and 3)

- Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least two **highly** effective method of contraception (See the Highly effective methods of contraception table below and Appendix G) from signing the informed consent and continue throughout this period of taking study treatment and for at least **six (6) months after the last dose of durvalumab (MEDI4736) + copanlisib + olaparib** combination therapy or must totally abstain from any form of sexual intercourse (as described in Appendix G). Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential (For Steps 1, 2, and 3)

- Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through **6 months after receipt of the final dose of durvalumab (MEDI4736) + copanlisib + olaparib** combination therapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation for 3 months following the last dose of olaparib.

  Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Highly effective methods of contraception Table below and Appendix G).

Female patients of child-bearing potential (For Steps 1, 2, and 3)

- Females of childbearing potential are defined as those who are not surgically sterile (*i.e.*, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (*i.e.*, less than 1% per year) when used consistently and correctly are described in the Highly effective methods of contraception Table. Note that some contraception methods are not considered highly effective (*e.g.*, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Highly effective methods of contraception (<1% failure rate)

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: *e.g.*, Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: *e.g.*, NuvaRing® • Injection: Medroxyprogesterone injection: *e.g.*, Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: *e.g.*, Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

Blood donation (For Steps 2 and 3 only)

Patients should not donate blood while participating in this study or for at least 120 days following the last infusion of durvalumab (MEDI4736).

6.6 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 24 months, as long as patients are gaining antitumor benefit as defined by PR or CR by RECIST v1.1, or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Bone marrow findings consistent with MDS or AML, treatment with all agents will be stopped
- Grade ≥3 infusion reaction
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Initiation of alternative anticancer therapy including other investigational agent
- Pregnancy or intent to become pregnant
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.7 Treatment Beyond Progression with Copanlisib + Olaparib or Copanlisib + Olaparib + Durvalumab (MEDI4736) + Combination

If progression occurs after confirmed response (CR or PR as defined by RECIST 1.1), continued therapy should not be permitted in the following cases:

- Patients with rapid progression of disease at critical anatomical sites (e.g. cord compression) requiring urgent alternative medical intervention.
- Patients who have clinically relevant worsening of laboratory values.
- Patients who have a clinically significant decline in performance status at time of progression.

Additionally, at the time that progression occurs, patients will be re-consented using a written informed consent document that details FDA-approved therapy, and its clinical benefit(s), that the patient will be foregoing in order to continue receiving the investigational products of the study.

New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm). Any new lesion considered non-measurable at the time of initial progression may become measurable and therefore included in the tumor burden measurement.

Patients should follow the same treatment guidelines as stipulated in the protocol, including the same dose and frequency of treatments and the same schedule of assessments, and off-treatment criteria. If PD is confirmed with subsequent staging scans, patient should be removed from the therapy.

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥4 weeks to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR, or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

6.8 Duration of Follow Up

The study is expected to last between 18-24 months. Thirty (30) days (± 7 days) after administration of the last dose of study drug, patients will return to the clinic for a final end-of-study evaluation. Any patient who prematurely discontinues the study for any reason will be instructed to return to the clinic and all procedures to be performed at the final end-of-study visit should be performed at this time. Patients who discontinue the study prematurely due to an AE will be followed by the investigator until the AE is resolved or until the medical condition of the patient becomes stable. After the end-of-study visit, patients will remain in long-term follow up until disease progression, start of a new cancer therapy, or for up to two years after the last dose of study drugs, whichever comes first. During this time, the study staff will contact patients every 3 months (± 7 days) via telephone for an AE assessment. Each call should last approximately 5 minutes. Patients will be monitored over the phone with local labs after 90 days and SAEs will only be reported if it is believed that there is a possibility they are related to treatment. Depending on the findings of the telephone call, a follow up physical examination may be needed.

The safety follow-up period will be at least 90 days after the administration of the last study drug for all patients, regardless of initiation of subsequent anticancer therapy. AEs and SAEs will be recorded from time of signature of informed consent, throughout the treatment period, up to 90 days after the administration of the last dose of study drug.

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

7. DOSING DELAYS/DOSE MODIFICATIONS FOR TREATMENT-RELATED TOXICITY

7.1 Copanlisib-Related Toxicity

Recommended dose reductions for copanlisib:

Any toxicity observed during the course of the study may be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. Patients requiring a delay of >4 weeks should be taken off protocol therapy. If the interruption is any longer than 4 weeks, the lead study team must be informed. Patients requiring > 2 dose reductions should be taken off protocol therapy.

The lead study team must be informed if copanlisib is discontinued to determine if the patient may continue treatment on remaining therapies if continuing to receive clinical benefit.

Copanlisib dose reductions for study treatment

Initial copanlisib dose	Dose reduction 1	Dose reduction 2
60 mg IV, Days 1 and 15	45 mg IV, Days 1 and 15	30 mg IV, Days 1 and 15

Dose delays/modifications for copanlisib-related toxicity:

Nausea	**Management/Next Dose for Copanlisib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Vomiting	**Management/Next Dose for Copanlisib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: antiemetics.	

Diarrhea	**Management/Next Dose for Copanlisib**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	
Recommended management: Loperamide antidiarrheal therapy Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

Neutropenia	**Management/Next Dose for Copanlisib**
≤ Grade 1	No change in dose
Grade 2	Investigator judgement to continue treatment or dose interruption; appropriate supportive treatment and causality investigation. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

Thrombocytopenia	**Management/Next Dose for Copanlisib**
≤ Grade 1	No change in dose
Grade 2	Investigator judgement to continue treatment or dose interruption; appropriate supportive treatment and causality investigation.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy
*Patients requiring a delay of >4 weeks should go off protocol therapy. **Patients requiring > two dose reductions should go off protocol therapy.	

7.1.1 Dose Modification Rules for Transient Post-Infusion Hyperglycemia

Patients who develop transient post-infusion glucose >250 mg/dL after study drug administration may continue treatment. However, the next infusion must be delayed until the patient's pre-infusion glucose levels return to <160 mg/dL (fasting) or <200 mg/dL (non-fasting). Guidelines for the management of transient glucose increases are given in the tables below. Continuing occurrence of post-infusion blood glucose >500 mg/dL, based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of copanlisib, will require dose reduction by one dose level.

- Further dose reduction **(where appropriate per study design/population)** is allowed as long as discontinuation criteria was not met.
- Dose re-escalation is allowed when a patient has achieved controlled glucose levels per investigator's judgment.
- Persistent occurrence of post-infusion blood glucose >500 mg/dL based on laboratory analysis which occurred at the lowest dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) with consultation of a diabetes specialist requires permanent discontinuation of the study drug.

Management of post-infusion glucose increases

• Criteria	• Recommendation
• **Glucose increases of** • **CTCAE grade 1**	• Continue study treatment
• **Glucose increases of** • **CTCAE grade 2**	• Hydration as clinically indicated • When planning next infusion prophylaxis with oral glucose lowering medication per local SOC is recommended • Consultation with endocrinologist for diabetic patients is recommended
• **Glucose increases of** • **CTCAE ≥ grade 3**	• Hydration as clinically indicated (orally, IV) • Insulin therapy per local SOC • When planning next infusion consider prophylaxis with oral glucose lowering medication per local SOC • Consultation with endocrinologist is recommended

Management of Transient Glucose Increase on the Day of Copanlisib Infusion

Criteria	Recommendation	Suggested Treatment
Asymptomatic glucose increases to a value ≤250 mg/dL	Does not generally require treatment with glucose lowering medication.	None
Asymptomatic glucose increase to value >250 mg/dL	• Should have repeated laboratory glucose determination. • If the repeated glucose value is decreasing, the glucose may be followed without glucose lowering medication treatment if hydration status is normal as	• Hydration if appropriate. • When planning next infusion consider prophylaxis with oral glucose lowering medication.

	clinically assessed. • Consultation with endocrinologist is recommended.	
Symptomatic or persisting glucose increases to a value >250 mg/dL	• Hydration status should be clinically assessed. • If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or intravenously [IV]). • Laboratory test confirming increase should be repeated. If the repeated glucose value is persistent and/or patient is symptomatic and/or the hydration status indicates the need for hydration, glucose lowering medication should be administered. • Prompt input from a diabetes specialist should be obtained.	• Hydration if appropriate • Rapid/ short acting insulin may be given for glucose persisting at >250 mg/dL, or if the patient is symptomatic during the infusion day. • Rapid/short acting insulin. • According to the institution sliding scale coverage of glucose persisting at >250 mg/dL is recommended, with oral or IV hydration as clinically appropriate. When planning next infusion, consider prophylaxis with oral glucose lowering medication.

Management of Transient Glucose Increase on Subsequent Days Following Copanlisib Infusion

Criteria	Recommendation	Suggested Treatment
Grade 2 Max post infusion glucose >200 mg/dL noted on subsequent days	• Oral glucose lowering medication recommended on subsequent days. • Consultation with endocrinologist is recommended.	• The use of sulphonylurea/metaglinides, insulin secretagogues medications to manage increased glucose levels post drug infusions is not recommended. • Treatment with glucose lowering medication suggested according to the local standards of practice. • Based on the mechanisms of action and decreased risk of hypoglycemia; metformin, sodium-glucose co-transporter-2 (SGLT-2) inhibitor or dipeptidyl

		peptidase-4 (DPP-4) inhibitor might be useful treatment options.

The need for glucose monitoring at home should be determined by the investigator based on post-infusion glucose profile and clinical status of the patient.

7.1.1.1 Monitoring of diabetic patients

If the patient already monitors his/her blood glucose as part of routine anti-diabetic care, the routine measurements should not be replaced by the study specific measurements.

7.1.2 Treatment of Blood Pressure Increases Associated with Copanlisib

It is important that patients with pre-existing arterial hypertension adhere to their regular medication schedule and take their usual doses on the days of study drug infusion.

The management of acute BP increases following copanlisib will need to be individualized for each patient, but experience from a Bayer-sponsored phase 1 study with copanlisib has suggested the benefit of dihydropyridine calcium channel blockers (*i.e.,* amlodipine, felodipine). Topical nitrates should also be considered. Verapamil and diltiazem (non-dihydropyridine calcium channel blockers and moderate inhibitors of CYP3A4) should be used with caution due to a potential CYP3A4 interaction. In general, it is advisable for sites to be prepared, so that anti-hypertensive medication is readily available in case of need.

In the event of the occurrence of arterial hypertension ≥150/90 mmHg during infusion of copanlisib at any cycle, antihypertensive treatment is suggested as indicated in the Dose Modification of Copanlisib for Arterial Hypertension Table below. In the event of the occurrence of grade 3 arterial hypertension (≥160/100 mmHg) during infusion of copanlisib, the infusion should be interrupted and anti-hypertensive treatment as suggested above is administered. Infusion can be resumed when BP has returned to <150/90 mmHg.

Dose Modification of Copanlisib for Arterial Hypertension Table below

Toxicity (CTCAE)	**Study drug action**	**Recommendation**
Pre-dose measurements BP ≥150/90 mmHg	No dose should be given until recovery to <150/90 mmHg	Consider BP lowering medication. Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to <150/90 mmHg. If BP doesn't return to <150/90 mmHg, delay dosing until next visit.
During infusion: CTCAE hypertension of grade 3 or ≥160/100 mmHg	Infusion can be interrupted or slowed down and administration of BP lowering therapy	Infusion may be resumed when BP has returned to <150/90 mmHg at the investigator's discretion or skipped. Subsequent study drug

	should be initiated.	administrations may be reduced by 1 dose level at the investigator's discretion.[a]
Post-dose: Drug-related CTCAE hypertension of grade 3 or ≥160/100 mmHg [b]	–	Administration of BP lowering therapy should be initiated according to local standard of care. Additional measurements to be performed as clinically indicated until recovery to <150/90 mmHg. Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion.[b]
CTCAE hypertension of grade 4	Permanent discontinuation	–

[a]: The lowest dose level is 30 mg.
[b]: Not manageable despite optimal antihypertensive treatment.
CTCAE = Common Terminology Criteria for Adverse Events; BP = blood pressure,

Blood pressure measurement on treatment days

BP will be measured every 5-10 minutes prior to each copanlisib dose (no more than 4 measurements) until there are two consecutive results <150/90 mmHg. If BP is ≥150/90 mmHg, the investigator can consider a medical intervention or delaying the infusion of study drug. The patient should rest for 5-10 min before blood pressure is recorded.

On infusion days, BP will be measured at 0 hour (pre-dose), 30 minutes (mid-infusion), 60 minutes (end of infusion), and 1 hour after the end of infusion

NOTE: A window of ±10 minutes is allowed for all BP measurements, except for pre-dose (0 hour) measurement, which may apply a window of ±5 minutes.

7.1.3 Non-Infectious Pneumonitis

The investigator is requested to differentiate between non-infectious pneumonitis, and infectious pneumonitis (viral, bacterial, or fungal), aspiration pneumonitis, or other pneumonitis clearly not due to a potential hypersensitivity reaction to the copanlisib infusion; and provide the basis for his/her assessment that it is infectious or other, as appropriate. The investigator is requested to report with the most specific clinical terms to describe the condition, not simple "pneumonitis".

In the event of suspected non-infectious pneumonitis, modify copanlisib treatment as per table below.

Dose adjustment for non-infectious pneumonitis

Suspected or confirmed NIP per	Action Taken	Re-treatment dose after recovery

CTCAE		
Grade 1	No Change	NA
Grade 2	Dose Interruption Until recovery to ≤grade 1	Decrease dose to the next lowest dose level [a]
Grade 2 second re-occurrence	Permanent Discontinuation	NA
Grade 3	Permanent Discontinuation	NA
Grade 4	Permanent Discontinuation	NA

NA = Not applicable; NIP = Non-infectious pneumonitis; CTCAE = Common Terminology Criteria for Adverse Events.
a: Not applicable for 45 mg dose level. No re-escalation is allowed after the dose reduction.
The lowest dose level is 45 mg; if a patient is already on the 45 mg dose level and cannot tolerate treatment study treatment will be discontinued permanently.

7.2 Olaparib-Related Toxicity

Except where otherwise specified, the table below provides olaparib dose reduction recommendations from an assumed initial dose of 300 mg BID (the single-agent RP2D for olaparib).

Any toxicity observed during the course of the study could be managed by interruption of the dose of study treatment or dose reductions. Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is any longer, the study team must be informed. Study treatment can be dose reduced to 250 mg twice daily as a first step and to 200 mg twice daily as a second step. If the reduced dose of 200 mg twice daily is not tolerable, further dose modifications can be discussed and approved by the PI and CTEP Medical Monitor and documented in writing.

Once dose is reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors).

The lead study team must be informed if olaparib is discontinued to determine if the patient may continue treatment on remaining therapies if continuing to receive clinical benefit.

Olaparib dose reductions for study treatment

Initial Olaparib Dose	**Following re-challenge post interruption: Dose reduction 1**	**Dose reduction 2**
300 mg BID	250 mg BID	200 mg BID

7.2.1 Dose Reduction/Discontinuation for Organ Dysfunction

7.2.1.1 Hepatic Impairment

The effect of mild or moderate hepatic impairment (Child-Pugh classification A or B) on single dose PK of olaparib has been characterized and no olaparib dose adjustment in patients with mild or moderate hepatic impairment is required.

Olaparib is not recommended for use in patients with severe hepatic impairment as the PK and safety of olaparib in patients with severe hepatic impairment has not been studied.

7.2.1.2 Renal Impairment

If, subsequent to study entry and while still on study therapy, a patient's Cockcroft-Gault estimated CrCl falls below the threshold for study inclusion (≥51 mL/min), retesting should be performed promptly.

A dose reduction is recommended for patients who develop moderate renal impairment (CrCl between 31 and 50 mL/min, as estimated by Cockcroft-Gault or based on a 24-hour urine test) for any reason during the course of the study: the dose of olaparib should be reduced to 200 mg BID.

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

The effect of mild and moderate renal impairment on the single dose PK of olaparib has been evaluated in a formal renal impairment study. Olaparib has not been studied in patients with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease; if patients develop severe impairment or end stage disease, is it recommended that olaparib be discontinued.

Olaparib dose reduction if patient develops moderate renal impairment

Initial Olaparib Dose	**Moderate renal impairment (calculated creatinine clearance by Cockcroft-Gault equation or based on a 24 hour urine test between 31 and 50 mL/min): Dose reduction**
300 mg BID	200 mg BID

7.2.2 Dose Reductions for Patients Receiving a Strong or Moderate CYP3A4 Inhibitor

As noted in Sections 6.4.2.3.1 and 6.4.2.3.2, patients should avoid taking strong or moderate CYP3A4 inhibitors while receiving olaparib. If there is no suitable alternative concomitant medication, the dose of olaparib should be reduced for the period of concomitant administration. The dose reduction of olaparib should be recorded on the CRF with the reason documented as concomitant CYP3A inhibitor use.

Olaparib dose reductions if patient must take a strong or moderate CYP3A inhibitor

Initial Olaparib Dose	**Olaparib Dose if Receiving a Strong CYP3A inhibitor**	**Olaparib Dose if Receiving a Moderate CYP3A inhibitor**
300 mg BID	100 mg BID	150 mg BID

7.2.3 Management of Hematological Toxicity

7.2.3.1 Management of Anemia

Management of Anemia

Hemoglobin (Hb)	Action to be taken
Hb <10 *but* ≥8 g/dL (CTCAE Grade 2)	**First occurrence:** Give appropriate supportive treatment and investigate causality. Investigator judgement to continue olaparib with supportive treatment (*e.g.* transfusion) *or* interrupt dose for a maximum of 4 weeks. Study treatment can be restarted if Hb has recovered to >9 g/dL. **Subsequent occurrences:** If Hb **<10** *but* **≥9 g/dL**, investigator judgement to continue olaparib with supporting treatment (*e.g.* transfusion) *or* dose interrupt (for max of 4 weeks) and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step). If Hb **<9** *but* **≥8 g/dL**, dose interrupt (for max of 4 weeks) until Hb ≥9 g/dL and upon recovery dose reduction may be considered (to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step).
Hb <8 g/dL (CTCAE Grade 3)	Give appropriate supportive treatment (*e.g.* transfusion) and investigate causality. Interrupt olaparib for a maximum of 4 weeks until improved to Hb ≥9 g/dL. Upon recovery dose reduce to **250 mg twice daily** as a first step and to **200 mg twice daily** as a second step in the case of repeat Hb decrease.

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. For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence), refer to Section 7.2.3.3 for the management of this.

7.2.3.2 Management of Neutropenia, Leukopenia and Thrombocytopenia

Management of Neutropenia, Leukopenia and Thrombocytopenia

Toxicity	Study treatment dose adjustment
CTCAE Grade 1-2	Investigator judgement to continue treatment or if dose interruption, this should be for a maximum of 4 weeks; appropriate supportive treatment and causality investigation
CTCAE Grade 3-4	Dose interruption until recovered to CTCAE grade 1 or better for a maximum of 4 weeks. If repeat CTCAE grade 3-4 occurrence, dose reduce olaparib to **250 mg twice daily** as a first step and **200 mg twice daily** as a second step

AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study drug if CTCAE grade 3 or worse neutropenia occurs.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not recommended; however, if a patient develops febrile neutropenia, study treatment 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 (7 days for pegylated G-CSF) of the last dose of study treatment unless absolutely necessary.

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

For cases where patients develop prolonged hematological toxicity (≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse), refer to the next section.

7.2.3.3 Management of Prolonged Hematological Toxicities While on Study Treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse neutropenia (ANC $<1\times10^9$/L)
- ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets $<50\times10^9$/L)

Check weekly differential blood counts including reticulocytes and peripheral blood smear. Study treatment should be discontinued if blood counts do not recover to CTCAE grade 1 or better within 4 weeks of dose interruption. Refer to a hematologist.

If any blood parameters remain clinically abnormal after 4 weeks of dose interruption, the patient should be referred to hematologist for further investigations. Patients with laboratory findings consistent with AML or MDS should receive a full work up as per the local standard of care for evaluation of a suspected hematological malignancy including, but not limited to, bone marrow aspirate/smear, flow cytometric evaluation of the marrow, and evaluation of cytogenetics. 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.

Development of a confirmed MDS, AML, or other clonal blood disorder should be reported as an SAE via CTEP-AERS and full reports must be provided by the investigator to the CTEP Medical Officer. Olaparib treatment should be discontinued if the patient's diagnosis of MDS and/or AML is confirmed.

7.2.4 Management of Non-Hematological Toxicity

Repeat dose interruptions are allowed as required, for a maximum of 4 weeks on each occasion. If the interruption is longer than 4 weeks, the CTEP Medical Monitor must be informed. Where toxicity reoccurs following re-challenge with study treatment, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction or must permanently discontinue study treatment.

Study treatment can be dose reduced to 250 mg BID as a first step and to 200 mg BID as a second step. Treatment must be interrupted if any NCI-CTCAE grade 3 or 4 AE occurs which the investigator considers to be related to administration of study treatment.

7.2.4.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (*e.g.*, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study treatment dosing is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis. Guidance for immune-mediated pneumonitis is provided in the durvalumab toxicity management guidelines (Section 7.3).

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

7.2.4.2 Management of Nausea and Vomiting

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

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

As per international guidance on anti-emetic use in cancer patients (European Society for Medical Oncology [ESMO], National Comprehensive Cancer Network [NCCN]), generally a single agent antiemetic should be considered, such as a dopamine receptor antagonist, antihistamine, or dexamethasone.

7.2.4.3 Interruptions for Intercurrent Non-Toxicity Related Events

Study treatment dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart study treatment within 4 weeks for resolution of

intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the CTEP Medical Monitor.

All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions are to be recorded in the electronic CRF (eCRF).

Study treatment should be stopped at least 3 days prior to planned surgery. After surgery study treatment can be restarted when the wound has healed. No stoppage of study treatment is required for any needle biopsy procedure.

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

Because the AEs related to olaparib may include asthenia, fatigue, and dizziness, patients should be advised to use caution while driving or using machinery if these symptoms occur.

7.3 Durvalumab (MEDI4736)-Related Toxicity

Guidelines for the management and dosing modifications for immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for MEDI4736 (durvalumab) monotherapy are provided in the subsections below as follows:

- General guidelines for toxicity management and dosing modifications
- Toxicity management and dosing modification guidelines for specific immune-related adverse events (irAEs)/immune-mediated AEs (imAEs) and other irAEs/imAEs not specified
- Toxicity management and dosing modification guidelines for infusion-related reactions
- Toxicity management and dosing modifications guidelines for non-immune-mediated AEs

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

The lead study team must be informed if durvalumab (MEDI4736) is discontinued to determine if the patient may continue treatment on remaining therapies if continuing to receive clinical benefit.

TABLE 5a: General Guidelines for Toxicity Management and Dosing Modifications for Durvalumab and/or Tremelimumab (Note – this guideline is consistent with TMG version October 2022 from Astra-Zeneca)

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the AstraZeneca toxicity management guidelines (TMGs). Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, *et al*. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother Cancer* 2021;9:e002435.

2. Brahmer JR, *et al*. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2018;36(17):1714-1768.

3. Haanen JBAG, *et al*. Management of toxicities for immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. *Annals Oncol* 2017;28(Suppl4):i119-i1142.

4. Sangro B, *et al*. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. *J Hepatol* 2020;72(2):320-341.

5. Thompson JA, *et al*. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 1.2022. Published February 28, 2022.

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 should be withheld and corticosteroids administered. Upon improvement to Grade ≤1, **corticosteroid should be tapered over ≥28 days.** More potent immunosuppressive agents such as tumor necrosis factor (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 glucose monitoring and other prophylaxis considerations for long-term steroid use with immune checkpoint inhibitor therapy:
    - **Infection Prophylaxis:** Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation.
    - **Gastritis:** Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy.
    - Osteoporosis: Consider measures for prevention and mitigation of osteoporosis.
- 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 PI.

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

Pediatric Considerations Regarding Immune-Mediated Reactions	
Dose Modifications	**Toxicity Management**
The criteria for permanent discontinuation of MEDI4736 (durvalumab)/tremelimumab is the same for pediatric patients as it is for adult patients, based on grade and type of the imAEs, and ability to reduce corticosteroid below a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after of initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for dosing of steroids (*i.e.*, mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for intravenous immunoglobulin (IV Ig) and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Table 5b: Durvalumab or Tremelimumab Dose Delays and Toxicity Management for immune-mediated AEs (imAEs)

Adverse Events	Severity Grade of the Event (NCI CTCAE v 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	For Any Grade: – Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease). – Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. – Initial workup may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (CT) scan. – Consider Pulmonary and Infectious Diseases consults.		
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study	**For Grade 2** – Monitor symptoms daily and consider hospitalization, as clinically indicated. – Consider Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study PI.

		regimen will be based upon treating physician's discretion and after completion of steroid taper (<10 mg prednisone or equivalent).	− Promptly start systemic steroids (*e.g.*, prednisone 1 to 2 mg/kg/day PO or IV equivalent). − Consider HRCT or chest CT with contrast, Repeat imaging study, as clinically indicated. − If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day − If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive agent such as tumor necrosis factor (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 or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. − Consider discussing with study PI.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** − Hospitalize the patient. − Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. − Obtain Pulmonary and Infectious Disease Consults; consider discussing with study PI, as needed. − Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results. − Supportive care (e.g., oxygen). − If no improvement within 2 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, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.

<table>
<tr><td rowspan="4">Diarrhea/ Colitis</td><td colspan="3">For Any Grade:
− 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.
− 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 AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.
− PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.
− Consider further evaluation with imaging study with contrast.
− Consult a gastrointestinal (GI) specialist for consideration of further workup.
− 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 events, including intestinal perforation.
− Use analgesics carefully; they can mask symptoms of perforation and peritonitis.</td></tr>
<tr><td>Grade 1</td><td>No dose modifications.</td><td>For Grade 1:
− Monitor closely for worsening symptoms.
− Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures.
− If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.</td></tr>
<tr><td>Grade 2</td><td>Hold study drug/study regimen until resolution to Grade ≤1
• If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone, or equivalent).</td><td>For Grade 2:
− Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide.
− Consider further evaluation with imaging study with contrast.
− Consider consult of a gastrointestinal (GI) specialist for consideration of further workup.
− 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 no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV (may be</td></tr>
</table>

			repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines)[a]. **Caution:** it is important 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**. − Consider, as necessary, discussing with study PI if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	Grade 3 For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone per day, or equivalent). For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study investigator, in discussion with study PI. **<u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy,</u>** **Permanently discontinue both durvalumab and tremelimumab for 1) Grade 3 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Urgent GI consult and imaging and/or colonoscopy as appropriate. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − Monitor stool frequency and volume and maintain hydration. − If still no improvement within 2 days, continue steroids and promptly add further immunosuppressant agents (*e.g.*, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **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.**
Hepatitis (elevated LFTs) ***Infliximab should not be used for management of immune-related hepatitis.*** **PLEASE SEE**	**For Any Grade:** − Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin. − Patients should be thoroughly evaluated to rule out any alternative etiology (*e.g.*, viral hepatitis, disease progression, concomitant medications).**Infliximab should not be used for immune-mediated hepatitis.**		
	Grade 1 ALT or AST ≤3×ULN or	− No dose modifications. − If it worsens, then consider holding therapy.	**For Grade 1:** − Continue transaminase and total bilirubin monitoring per protocol.

shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients (or secondary tumor involvement of the liver with abnormal baseline values [BLV])	total bilirubin ≤1.5×ULN		
	Grade 2 ALT or AST >3× to ≤5×ULN or total bilirubin >1.5× to ≤3×ULN	• Hold study drug/study regimen dose until Grade ≤1. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST and/or ALT >3×ULN + bilirubin >2×ULN without initial findings of cholestasis (*i.e.*, elevated ALP) and in the absence of any alternative cause.	**For Grade 2:** − Regular and frequent checking of transaminases and total bilirubin (*e.g.*, every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. − If no resolution to Grade ≤1 in 1 to 2 days, consider, as necessary, discussing with study PI. − If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3 (ALT or AST >5× to ≤10×UL)	• Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to Grade ≤1 after completion of steroid taper (<10 mg prednisone, or equivalent). • **If in combination with tremelimumab, do not restart tremelimumab.**	**For Grade 3:** • Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. • Perform Hepatology Consult, abdominal workup, and imaging as appropriate. If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant (*i.e.*, mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Study PI if mycophenolate is not available. **Infliximab should NOT be used.**
	Grade 4 ALT or AST >10×ULN OR total bilirubin >3×ULN **Hy's Law criteria** Concurrent ALT or AST >3×ULN AND total bilirubin >2×ULN	• Permanently discontinue study drug/study regimen.	**For Grade 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 an additional immunosuppressant (*i.e.*, mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Study PI if mycophenolate is not available. **Infliximab should NOT be used.** Perform Hepatology Consult, abdominal workup, and imaging as appropriate.

<table>
<tr><td rowspan="3">Hepatitis (elevated LFTs)

THIS shaded area is guidance only for management of “Hepatitis (elevated LFTs)” in HCC patients
See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation</td><td colspan="3">For Any Grade:
– Monitor and evaluate liver function test: AST, ALT, ALP, and TB.
– Thoroughly evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]).
– For HBV+ patients: evaluate quantitative HBV viral load, quantitative HB surface antigen (HBsAg), or HB envelope antigen (HBeAg).
– For HCV+ patients: evaluate quantitative HCV viral load.
– Consider consulting Hepatology/Infectious Disease specialists regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/mL.
– Consider consulting Hepatology/Infectious Disease specialists regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold.
– For HCV+ with HB core antibody (HBcAB)+: Evaluate for both HBV and HCV as above.
– Infliximab should not be used for management of immune-related hepatitis.</td></tr>
<tr><td>(Isolated AST or ALT >ULN and ≤2.5×BLV)</td><td>• No dose modifications.</td><td>• If ALT/AST elevations represent significant worsening based on investigator assessment, then treat as Grade 2 event.
• For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation</td></tr>
<tr><td>(ALT or AST > 2.5-≤ 5×BLV and ≤ 20×ULN)</td><td>• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 or baseline.
• If toxicity worsens, then treat as Grade 3 or Grade 4.
• If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent).</td><td>For Grade 2:
– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved.
– Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion.
– Consider, as necessary, discussing with study PI.
– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an immune-mediated AE, recommend to 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 workup and treatment with IV methylprednisolone 2 mg/kg/day.
– If still no improvement within 2 to 3 days despite 2 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult).[a] Discuss with study PI if mycophenolate mofetil is not available. Infliximab should NOT be used.</td></tr>
</table>

	(ALT or AST >5-7× BLV and ≤ 20× ULN OR concurrent 2.5-5×BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2×ULN)	• Withhold durvalumab and permanently discontinue tremelimumab • Resume study drug/study regimen if elevations downgrade to Grade ≤1 and after completion of steroid taper (<10 mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 within 14 days.	**For Grade 3:** – Regular and frequent checking of LFTs (*e.g.*, every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study PI. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with study PI if mycophenolate is not available. **Infliximab should NOT be used.**
	(ALT or AST > 7×BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN)	Permanently discontinue study drug/study regimen.	**For Grade 4:** **Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (*e.g.*, fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise.** - **For example, manage dosing for second level of transaminase rise (*i.e.*, AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (*i.e.*, AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline).** - **For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen.**		

Nephritis and/or renal dysfunction (elevated serum creatinine)	**Any Grade:** − Consider consulting a nephrologist. − Consider imaging studies to rule out any alternative etiology. − 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). Follow urine protein/creatinine ratio every 3-7 days. − 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	No dose modifications.	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. − Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. − Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated.
	Grade 2	Hold study drug/ study regimen until resolution to Grade ≤1 or baseline. − If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2:** − Consider including hydration, electrolyte replacement, and diuretics, as clinically indicated. − Follow urine protein/creatinine ratio every 3-7 days. − Carefully monitor serum creatinine as clinically warranted. − Consult nephrologist and consider renal biopsy if clinically indicated. − Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out. − If event is persistent (beyond 5 days) or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. − If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO/IV equivalent, consider additional workup. − When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Carefully monitor serum creatinine daily. − Follow urine protein/creatinine ratio every 3-7 days. − 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 of steroids or worsens despite prednisone at

			1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant.
Rash or Dermatitis	General Guidance **For Any Grade:** − Patients should be thoroughly evaluated to rule out any alternative etiology. − Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)1 IS SUSPECTED.** − **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPHIGOID 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 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, resume drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent).	**For Grade 2:** − Consider dermatology consult and skin biopsy, as indicated. − 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 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with study PI and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 3:** − Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − Consider hospitalization. − Monitor extent of rash [Rule of Nines]. − Consider, as necessary, discussing with study PI.
	Grade 4	Permanently discontinue study drug.	**For Grade 4:** Same as grade 3.

<table>
<tr><td rowspan="4">Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)</td><td colspan="3">Any Grade
(Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity.)
<u>General Guidance</u>
For Any Grade:
− Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections).
− Consider consulting an endocrinologist for endocrine events.
− Consider discussing with study PI, as needed.
− Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behavior changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.)
− Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin H1c (HgA1c)). 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.
− 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.</td></tr>
<tr><td>Grade 1</td><td>No dose modifications.</td><td>For Grade 1 (including asymptomatic TSH elevation):
− Monitor patient with appropriate endocrine function tests.
− For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency).
− If TSH <0.5 × LLN, or TSH >2 × ULN or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.</td></tr>
<tr><td>Grade 2, 3 or 4</td><td>− For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve.
− Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or</td><td>For Grade 2, 3 and 4:
− 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 work-up, except those with isolated hypothyroidism or T1DM, 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</td></tr>
</table>

		equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	relevant hormone replacement. – **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, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis</u>.** – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/ Lipase Increased	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology. – 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.	See guidance above.
	Grade 2, 3, or 4	In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	See guidance above.
Acute Pancreatitis	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral.		
	Grade 2	**Consider holding study drug/regimen.**	- Consider IV hydration. - Consider Gastroenterology referral.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings. If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4:** Permanently discontinue study drug/study regimen.	- Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - IV hydration.

Nervous System Disorders (for specific neurological AEs below, refer to **separate management guidelines in subsequent rows:** • aseptic meningitis, • encephalitis, • transverse myelitis, • peripheral neuropathy, • myasthenia gravis, and • Guillain-Barré)	General Guidance **For Any Grade:** − Patients should be evaluated to rule out any alternative etiology (*e.g.*, disease progression, infections, metabolic syndromes, or medications). − Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). − Consider appropriate diagnostic testing (*e.g.*, electromyogram and nerve conduction investigations). − Perform symptomatic treatment with neurological consult as appropriate.		
	Grade 1	No dose modifications.	**For Grade 1:** − See "Any Grade" recommendations above. − 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/study regimen 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/ tremelimumab 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 PI. − 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 PI. − 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.

Aseptic meningitis	**Any Grade**	Permanently discontinue study drug.	**For Any Grade:** − Consider neurology consult. − Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for − diagnosis. − Exclude bacterial and viral infections. (*i.e.*, HSV). − Consider IV acyclovir until polymerase chain reactions are available. − Consider, as necessary, discussing with study PI. − Consider hospitalization.
Encephalitis	**General Guidance** − Symptoms may include confusion, altered behavior, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. **For Any Grade:** − Consider neurology consult. − Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. − Exclude bacterial and viral infections. (*i.e.*, HSV) − Consider IV acyclovir until polymerase chain reactions are available.		
	Grade 2	Permanently discontinue study drug/study regimen.	− Consider, as necessary, discussing with study PI. − Once infection is ruled out, start methylprednisolone 1-2 mg/kg/day. − For progressive symptoms or if oligoclonal bands are present, consider methylprednisolone 1 g IV daily for 3-5 days plus IV Ig or plasmapheresis.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Consider, as necessary, discussing with study PI. − Consider hospitalization. − Once infection is ruled out, start methylprednisolone 1 g IV daily for 3-5 days. For progressive symptoms, consider adding IV Ig or plasmapheresis.
Transverse myelitis	**Any Grade**	− Permanently discontinue study drug/study regimen. − Consider MRI of the spine and brain.	**For Any Grade:** − Consider neurology consult. − Inpatient care. − Consider prompt initiation of high methylprednisolone pulse dosing. − Strongly consider IV Ig or plasmapheresis.

<table>
<tr><td>Peripheral neuropathy</td><td colspan="3">For Any Grade:
− 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.</td></tr>
<tr><td></td><td>Grade 1</td><td>No dose modifications.</td><td>For Grade 1:
− Consider, as necessary, discussing with the study PI.
− Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.
− Monitor symptoms for interference with ADLS, gait difficulties, imblanace, or autonomic dysfunction.</td></tr>
<tr><td></td><td>Grade 2</td><td>Hold study drug/study regimen dose until resolution to Grade ≤1.</td><td>For Grade 2:
− Obtain a neurology consult.
− Consider electromyography (EMG)/ nerve conduction studies (NCS).
− Observation for additional symptoms or consider initiating prednisone 0.5-1 mg/kg orally.
− If progression, initiate methylprednisolone 2-4 mg/kg/day and treat per Guillain-Barré Syndrome (GBS) guidelines below.
− Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).</td></tr>
<tr><td></td><td>Grade 3 or 4</td><td>For Grade 3 or 4:
Permanently discontinue study drug/study regimen.</td><td>For Grade 3 or 4 (severe or life-threatening events):
− Consider, as necessary, discussing with study PI.
− Recommend hospitalization.
− Monitor symptoms and obtain neurological consult.
− Treat per Guillain-Barré Syndrome (GBS) guidelines below.</td></tr>
<tr><td>Guillain-Barré Syndrome (GBS)</td><td colspan="3">General Guidance
For Any Grade:
− Recommend hospitalization.
− Obtain neurology consult.
− Obtain MRI of spine to rule out compression lesion.
− Obtain lumbar puncture.
− Antibody tests for GBS variants.
− Perform pulmonary function tests (PFT).
− Obtain electromyography (EMG) and nerve conduction studies (NCS).
− Frequently monitor PFTs and neurologic evaluations.
− Monitor for concurrent autonomic dysfunction.
− Initiate medication as needed for neuropathic pain.</td></tr>
</table>

	Grade 2-4	Permanently discontinue.	− See general guidelines above. − **Start IV Ig or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis	General Guidance **For Any Grade:** − Obtain neurology consult. − Recommend hospitalization. − Perform pulmonary function tests (PFT). − Obtain labs: ESR, CRP, creatinine phosphokinase (CPK), aldolase, and anti-striational antibodies. − Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis. − Obtain electromyography (EMG) and nerve conduction studies (NCS). − Consider MRI of brain/spine to rule out CNS involvement by disease. − Avoid medications that might exacerbate MG (*e.g.* beta blockers, some antibiotics, IV magnesium).		
	Grade 2	Permanently discontinue.	− Consider pyridostigmine 30 mg three times daily and gradually increase based on symptoms (max dose 120 mg four times daily). − Consider starting low dose prednisone 20 mg daily and increase every 3-5 days. (Target dose 1 mg/kg/day. Max dose 100 mg daily.)
	Grade 3-4	Permanently discontinue.	− Start methylprednisolone 1-2 mg/kg/day. Taper steroids based on symptom improvement. − Start plasmapheresis or IV Ig. − Consider rituximab if refractory to plasmapheresis or IV Ig. − Frequent PFT assessments. − Daily neurologic evaluations.
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 discussing with the study PI. − 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). Consult a cardiologist early, to promptly assess 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.**		
	Any grade (Grade 2-4)	Permanently discontinue study drug/study regimen.	**For Grade 2-4 (any grade):** − Monitor symptoms daily, hospitalize. − Consider cardiology consultation and prompt start of high-dose/pulse corticosteroid therapy.

			– Supportive care (*e.g.*, oxygen). – If no improvement, consider additional immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab), IV Ig or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant or relevant practice guidelines. **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.**
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, and ; 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 Clinical Study Lead. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (*i.e.*, consider whether a Rheumatology 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.		
	Grade 1	- 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 PI.
	Grade 2	Hold study drug/study regimen dose until 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.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study PI. – 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 2 to 3 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 3 days, consider additional immunosuppressive therapy such as TNF inhibitors (*e.g.*, infliximab), IV Ig or plasmapheresis, or other therapies based on at the discretion of the treating specialist consultant or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. **Permanently discontinue** study drug/study regimen 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 drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommended hospitalization. – Consider Rheumatology and/or Neurology consult. – Consider discussing with the study PI, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (*e.g.*, infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **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>
<tr><td rowspan="5">Other immune-mediated reactions</td><td colspan="3">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 PI 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).
− Consultation with relevant specialist.
− Treat accordingly, as per institutional standard.</td></tr>
<tr><td>Grade 1</td><td>No dose modifications.</td><td>- Monitor as clinically indicated.</td></tr>
<tr><td>Grade 2</td><td>- 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.</td><td>- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines.</td></tr>
<tr><td>Grade 3</td><td>- Hold study drug/study regimen.</td><td>- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines.</td></tr>
<tr><td>Grade 4</td><td>- Permanently discontinue study drug/study regimen.</td><td>- Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines.</td></tr>
<tr><td colspan="4">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 PI.”

[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.</td></tr>
</table>

Table 5c: Durvalumab or Tremelimumab 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/study regimen 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 or study protocol 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, appropriate clinical practice guidelines, and society guidelines.

Table 5d: Durvalumab or Tremelimumab 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.	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.

8. PHARMACEUTICAL INFORMATION

A list of the AEs and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agents

8.1.1 Copanlisib (NSC 784727)

Chemical Name or Amino Acid Sequence: 2-amino-N-[7-methoxy-8-(3-morpholin-4-ylpropoxy)-2,3-dihydroimidazo[1,2-c]quinazolin-5-yl]pyrimidine-5-carboxamide dihydrochloride

Other Names: BAY 80-6946 (free base); BAY 84-1236 (dihydrochloride salt)

Classification: Pan class I PI3K inhibitor

Molecular Formula: C23H28N8O4 2HCl **M.W.:** 553.45 g/mol

Approximate Solubility: Freely soluble in water and 0.1 M hydrochloric acid (HCl)

Mode of Action: Copanlisib is a pan class I PI3K inhibitor with potent activity against the delta and alpha isoforms. Class I PI3K is downstream of most cancer associated tyrosine kinase growth factor receptors or mesenchymal epithelial transition factor. PI3K delta has a critical role in regulating downstream events of the B-cell receptor.

Description: The powder is white to yellow solid substance.

How Supplied: Copanlisib is supplied by Bayer HealthCare AG and distributed by the Pharmaceutical Management Branch (PMB), CTEP, Division of Cancer Treatment and Diagnosis (DCTD), NCI. The agent is available as a lyophilized product containing 60 mg of copanlisib in a 6 mL injection vial. The excipients are mannitol, sodium hydroxide, citric acid, and water for injection.

Preparation: Using appropriate aseptic technique, reconstitute the 60 mg vial of copanlisib with 4.4 mL of 0.9% sodium chloride resulting in a concentration of 15 mg/ml. Gently shake for 30 seconds and allow the vial to stand for 1 minute to let bubbles rise to the surface. Repeat if undissolved substance is still present. The reconstituted solution may be slightly yellow and should be clear prior to being withdrawn from the vial. Withdraw the appropriate volume of the reconstituted solution and further dilute by adding to a 50-200 mL 0.9% sterile sodium chloride bag. Mix well by inverting.

Storage: Store intact vials between 2°C and 8°C.

If a storage temperature excursion is identified, promptly return copanlisib to between 2°C and 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.

Stability: Stability studies of the vials are ongoing. The diluted solution should be used immediately (stored up to 4 hours at room temperature including preparation and administration). If the diluted solution for infusion is not used immediately, it is stable for up to 24 hours refrigerated between 2°C and 8°C. It takes approximately 60 minutes for the diluted solution to return to room temperature after refrigeration. The infusion should be completed within 24 hours of preparation.

> CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 4 hours after initial entry.

Route of Administration: IV infusion

Method of Administration: The diluted solution for infusion is administered IV over 1 hour. After administration, flush the line to ensure complete dose is given. No IV glucose preparations should be administered on the days of infusion.

Potential Drug Interactions: *In vitro*, copanlisib is metabolized primarily via CYP3A4 and to a minor extent by CYP1A1. It is also a substrate of P-gp and BCRP, but not a substrate of MATEs, OCTs, OATs, or organic anion transporting polypeptides (OATPs). Concomitant administration with strong inhibitors or inducers of CYP3A4 should be avoided. Use caution when administered with strong inhibitors and inducers of CYP1A1, P-gp, and BCRP.

In vitro, copanlisib is a strong inhibitor of MATE2K. Copanlisib and its metabolite M-1 have a low risk for inhibition or induction of CYP isoforms, inhibition of UGT isoforms, and inhibition of dihydropyrimidine dehydrogenase. Copanlisib does not inhibit P-gp, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, bile salt export pump (BSEP), multidrug resistant protein 2 (MRP-2), or MATE1 at therapeutic 60 mg dose plasma concentrations. Use caution when administered with sensitive drug substrates of MATE2K.

Copanlisib is not an inducer of CYP1A2, 2B6, and 3A.

Special Handling: Copanlisib is not genotoxic *in vitro* or *in vivo*. Copanlisib is expected to adversely affect male and female reproduction.

Patient Care Implications: Females of child-bearing potential and male patients must use adequate contraception while receiving copanlisib and for 6 months after last dose of copanlisib. Do not breastfeed during treatment with copanlisib and for at least 1 month after the last dose of copanlisib.

Hypertension is frequently observed within the first 3 hours after start of infusion and hyperglycemia is frequently observed persisting for approximately 1-3 days after study drug administration. Refer to protocol document for treatment and monitoring guidelines.

Availability

Copanlisib is an investigational agent supplied to investigators by the DCTD, NCI. Copanlisib is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.2 Olaparib [AZD2281] (NSC 747856)

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

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

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

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

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

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

Description: crystalline solid

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

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

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

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

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

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

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

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

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-gp, but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), OCT1, MRP-2 efflux transporter or BCRP. Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

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

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

Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, women of child-bearing potential and their partners should agree to use two (2) highly effective forms of contraception throughout study participation and for at least six (6) months after the last dose of olaparib. It is not known whether olaparib is found in seminal fluid, so as a precaution, male study participants must use a condom during treatment and for three (3) months after the last dose and should avoid fathering a child or donating sperm during this same time period. The study investigator should discuss the most appropriate forms of highly effective contraceptive methods for each patient.

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

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

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

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

Availability

Olaparib (AZD2281) is an investigational agent supplied to investigators by the DCTD, NCI. Olaparib (AZD2281) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.3 Durvalumab [MEDI4736] (NSC 778709)

Other Names: IMFINZI™

Classification: Anti-PD-L1 MAb

Molecular Weight: ~ 149 kDa

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

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

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.

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.

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.

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). If the final product is stored at both refrigerated and ambient temperatures, the total time must not exceed 24 hours (that is, the individual storage time limits are not additive. 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.

Route of Administration: IV infusion

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.

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

8.1.4 Agent Ordering and Agent Accountability

8.1.4.1 NCI - supplied agents

8.1.4.2 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 are allowed. Agents may be ordered at the time of patient registration. Orders can be processed for delivery overnight Monday-Thursday when the site provides expedited courier information.

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

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

8.1.5 Investigator Brochure Availability

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

8.1.6 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. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 Study Design

In Step 1, the doublet combination of copanlisib and olaparib will be investigated. Dose escalation will be undertaken in patients with advanced solid tumors, with the population enriched for those with both PI3K-AKT pathway and DDR aberrations.

Step 2 will not proceed until the safety and toxicity data from Step 1 have been formally reviewed by and discussed with the study team and CTEP.

In Step 2, the RP2D of the copanlisib/olaparib combination is copanlisib 60 mg Days 1 and 15 and olaparib 300 mg BID of each 28-day cycle. Durvalumab (MEDI4736) at 1500 mg Day 1 of each 28-day cycle will be added to form a novel triplet combination. The dose escalation phase will involve patients with advanced solid tumors, with the population enriched for those with both PI3K-AKT pathway and DDR aberrations.

In Step 3, dose expansion for the copanlisib/olaparib doublet combination can proceed upon completion of Step 1 and can proceed simultaneously with Step 2. The dose expansion for the copanlisib/olaparib/durvalumab (MEDI4736) triplet combination can proceed upon completion of Step 2 and can proceed simultaneously with dose expansion for copanlisib/olaparib doublet combination. Patient assignment to the doublet or triplet combinations will be based on slot availability. During cohort expansion, patients to be assessed include: those with germline DDR aberrations, those with cancers with somatic DDR aberrations, patients with PIK3CA mutant cancers, and those with PTEN mutations. 15 patients will be recruited to each of 4 dose expansion cohorts, for a total of 60 patients in dose expansion.

We will employ the Bayesian optimal interval (BOIN) design (Liu and Yuan, 2015; Yuan *et al.*, 2016) to determine the MTD. The BOIN design is implemented in a simple way similar to the traditional 3+3 design, but is more flexible and possesses superior operating characteristics that are comparable to those of the more complex model-based designs, such as the continual reassessment method (CRM) (Zhou, *et al*., 2018).

Doublet BOIN Design

The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size is 18. We will enroll and treat patients in cohorts of size 3. The trial design is illustrated in Figure 8 and described as follows:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 3, which minimizes the probability of incorrect dose assignment. When using Table 3, please note the following:

a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
c. If none of the actions (*i.e.*, escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.
d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.

- Repeat step 2 until the maximum sample size of 18 is reached or stop the trial early when one of the following two conditions is satisfied:
  - The number of patients who experienced DLTs at the lowest dose level reaches the stopping boundaries listed in Table 4 below. In this case, no dose should be selected as the MTD.
  - The number of patients treated at the current dose >= 12.

Table 3. Dose escalation/de-escalation rule for the BOIN design.

Actions	The number of patients treated **at the current dose**											
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Escalate if # of DLT <=	0	0	**0**	0	0	**1**	1	1	**1**	1	2	**2**
De-escalate if # of DLT >=	1	1	**1**	2	2	**2**	3	3	**3**	3	4	**4**
Eliminate if # of DLT >=	NA	NA	**3**	3	3	**4**	4	4	**5**	5	6	**6**

Table 4. Stopping boundaries

Actions	The number of patients treated **at the lowest dose**											
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Stop trial if # of DLT >=	NA	NA	**2**	2	3	**3**	3	4	**4**	4	5	**5**

Triplet BOIN Design

The target toxicity rate for the MTD is $\phi = 0.25$ and the maximum sample size is 18. We will enroll and treat patients in cohorts of size 3. The trial design is illustrated in Figure 8 and described as follows:

1. Patients in the first cohort are treated at dose level 1.
2. To assign a dose to the next cohort of patients, conduct dose escalation/de-escalation according to the rule displayed in Table 5, which minimizes the probability of incorrect dose assignment. When using Table 5, please note the following:
    a. "Eliminate" means eliminate the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic.
    b. When we eliminate a dose, automatically de-escalate the dose to the next lower level. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
    c. If none of the actions (*i.e.*, escalation, de-escalation or elimination) is triggered, treat the new patients at the current dose.
    d. If the current dose is the lowest dose and the rule indicates dose de-escalation, treat the new patients at the lowest dose unless the number of DLTs reaches the elimination boundary, at which point terminate the trial for safety.
    e. If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
3. Repeat step 2 until the maximum sample size of 18 is reached or stop the trial early when one of the following two conditions is satisfied:
    a. The number of patients who experienced DLTs at the lowest dose level reaches the stopping boundaries listed in Table 6 below. In this case, no dose should be selected as the MTD.
    b. The number of patients treated at the current dose >= 12.

Table 5. Dose escalation/de-escalation rule for the BOIN design.

Actions	The number of patients treated **at the current dose**											
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Escalate if # of DLT <=	0	0	**0**	0	0	**1**	1	1	**1**	1	2	**2**
De-escalate if # of DLT >=	1	1	**1**	2	2	**2**	3	3	**3**	3	4	**4**
Eliminate if #	N	NA	**3**	3	3	**4**	4	4	**5**	5	6	**6**

of DLT >=	A											

Table 6. Stopping boundaries

Actions	The number of patients treated **at the lowest dose**											
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Stop trial if # of DLT >=	NA	NA	**2**	2	3	**3**	3	4	**4**	4	5	**5**

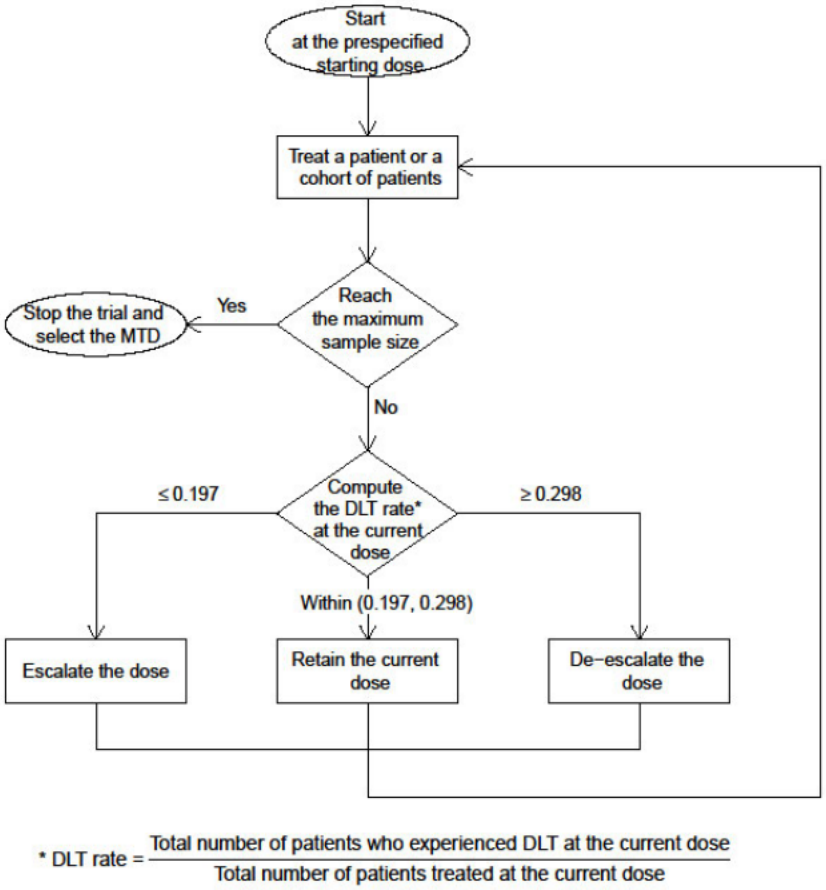


Figure 8. Flowchart for trial conduct using the BOIN design

After the trial is completed, select the MTD based on isotonic regression as specified in Liu and Yuan (2015). This computation is implemented by the shiny app "BOIN" available at http://www.trialdesign.org. Specifically, select as the MTD the dose for which the isotonic

estimate of the toxicity rate is closest to the target toxicity rate. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

Expansion Phase: Once we determine the MTD, an additional 15 patients will be enrolled for additional experience with safety and efficacy in each of 4 cohorts. We will use the elimination boundaries in the dose escalation/de-escalation rule for the BOIN Design Table for toxicity monitoring during this phase.

Operation Characteristics: The operating characteristics of the BOIN Design for the doublet and triplet combinations tables below shows the operating characteristics of the trial design based on 1000 simulations of the trial using shiny app "BOIN" available at http://www.trialdesign.org. The operating characteristics show that the design selects the true MTD, if any, with high probability and allocates more patients to the dose levels with the DLT rate closest to the target of 0.25.

Operating characteristics of the BOIN Design for the doublet combination

	Dose Level				Number of	% Early
	1	**2**	**3**	**4**	**Patients**	**Stopping**
Scenario 1						
True DLT Rate	0.25	0.42	0.5	0.59	13.53	49.6
Selection %	39.9	8.9	1.4	0.2		
# Pts Treated	7.2	5.1	1.1	0.1		
Scenario 2						
True DLT Rate	0.1	0.25	0.4	0.62	16.58	8.3
Selection %	44.4	36.5	10.4	0.4		
# Pts Treated	5.8	7.2	3	0.6		
Scenario 3						
True DLT Rate	0.02	0.1	0.25	0.42	17.5	0.5
Selection %	11	44.2	34.2	10.1		
# Pts Treated	1.8	7.4	5.9	2.4		
Scenario 4						
True DLT Rate	0.05	0.08	0.12	0.25	17.81	0.4
Selection %	8.3	14	38.5	38.8		
# Pts Treated	1.5	5.2	6	5.1		
Scenario 5						
True DLT Rate	0.45	0.55	0.65	0.75	9.36	91.2
Selection %	7.1	1.7	0	0		
# Pts Treated	5.3	3.7	0.4	0		

Operating characteristics of the BOIN Design for the triplet combination

	Dose Level	Number of	% Early

	1	2	Patients	Stopping
Scenario 1				
True DLT Rate	0.05	0.1	13.14	0.9
Selection %	11.1	88		
# Pts Treated	1.9	11.2		
Scenario 2				
True DLT Rate	0.1	0.25	14.7	9.1
Selection %	47.6	43.3		
# Pts Treated	6.3	8.4		
Scenario 3				
True DLT Rate	0.25	0.4	12.73	51.3
Selection %	37.9	10.8		
# Pts Treated	7.2	5.5		
Scenario 4				
True DLT Rate	0.45	0.6	8.89	93.6
Selection %	6	0.4		
# Pts Treated	5.4	3.5		

9.2 Sample Size/Accrual Rate

Planned accrual rate is 3 to 4 patients per month for the dose escalation phase of the study and 5 to 10 patients per month for the dose expansion phase of the study. We plan to enroll up to 108 evaluable patients.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	1	0	1	1	**3**
Asian	3	2	0	0	**5**
Native Hawaiian or Other Pacific Islander	1	1	0	0	**2**
Black or African American	11	10	0	0	**21**
White	37	24	1	1	**63**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
More Than One Race	5	5	2	2	**14**
Total	**58**	**42**	**4**	**4**	**108**

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INTERNATIONAL ESTIMATED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	0	0	0	0	**0**
White	0	0	0	0	**0**
More Than One Race	0	0	0	0	**0**
Total	**0**	**0**	**0**	**0**	**0**

9.3 Stratification Factors

N/A

9.4 Analysis of Secondary Endpoints

The first secondary objective is to assess ORR (CR + PR). We will estimate ORR with 95% confidence intervals (CI). Inferences and estimation are based on the exact binomial test. With 15 patients, the 95% CI for an observed ORR of 25% would extend from 7% to 53%. A treatment will be declared worthy of further study if we see at least 2 patients (13%) out of 15 with ORR; the probability of doing so would be 17% if the true OR rate was 5% and would be 83% if the true ORR was 20%.

The second secondary objective is to assess DOR, PFS, and OS. We will use the Kaplan-Meier method to estimate these distributions.

For correlative studies, we will assess immuno-modulatory changes using paired t-tests or Wilcoxon signed rank tests. With 15 patients, we would have 85% power to detect an effect size (mean difference divided by standard deviation of differences) = 0.83 assuming Normal data with two-sided 5% alpha. We will assess associations between marker levels and response using receiver operating characteristic (ROC) curve analysis, graphical analysis and logistic regression analysis as appropriate. If success rate is 50%, then we would have 80% power to detect an area under the ROC curve of 0.83 as statistically different from the null value of 0.50 assuming a 20% alpha and 15 patients with data.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential AEs 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.

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.

10.1.1 CAEPRs for CTEP IND Agents

10.1.1.1 CAEPR for Copanlisib

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride, NSC 784727)

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 684 patients.* Below is the CAEPR for Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride).

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

Version 2.3, April 2, 2023[1]

Adverse Events with Possible Relationship to Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CTCAE 5.0 Term) [n= 684]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
		Febrile neutropenia	
GASTROINTESTINAL DISORDERS			
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
		Electrocardiogram QT corrected interval prolonged	
	Lymphocyte count decreased		
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CTCAE 5.0 Term) [n= 684]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Anorexia		***Anorexia (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle cramp		***Muscle cramp (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis[3]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythroderma	
		Pruritus	
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
VASCULAR DISORDERS			
Hypertension			***Hypertension (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]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[3]Pneumonitis is a group term that includes interstitial lung disease, dyspnea, dyspnea at rest, and dyspnea exertional.

Adverse events reported on Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Eosinophilia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Constipation; Dry mouth; Dyspepsia; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Oral dysesthesia; Oral pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; General disorders and administration site conditions - Other (failure to thrive); Multi-organ failure; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
IMMUNE SYSTEM DISORDERS - Allergic reaction; Autoimmune disorder
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Infusion related reaction; Injury, poisoning and procedural complications - Other (drug eruption)
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Creatinine increased; Ejection fraction decreased; Electrocardiogram T wave abnormal; INR increased; Investigations - Other (electrocardiogram U wave abnormal); Investigations - Other (Hepatitis B DNA increased); Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (diabetes mellitus)

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (psoriatic arthropathy); Myalgia; Pain in extremity; Soft tissue necrosis upper limb
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor hemorrhage
NERVOUS SYSTEM DISORDERS - Amnesia; Dizziness; Dysesthesia; Dysgeusia; Headache; Paresthesia; Peripheral sensory neuropathy; Presyncope; Reversible posterior leukoencephalopathy syndrome; Syncope
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Cough; Dyspnea[3]; Hypoxia; Pleural effusion; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pulmonary congestion); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Eczema; Purpura; Rash acneiform; Stevens-Johnson syndrome
VASCULAR DISORDERS - Hypotension; Thromboembolic event; Vascular disorders - Other (circulatory collapse)

Note: Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) 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.

10.1.1.2 CAEPR for Olaparib (AZD2281) (NSC 747856)

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

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

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

Version 2.6 June 5, 2023[1]

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

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

10.1.1.3 CAEPR for durvalumab (MEDI4736, NSC 778709)

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

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

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%)**	
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]	
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)	

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%)**	
		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.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.7.

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

10.3 Expedited Adverse Event Reporting

10.3.1 Rave CTEP-AERS Integration

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

Treatment-emergent AEs: All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period 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 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.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the

system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

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

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs 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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

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

Effective Date: August 30, 2024

10.3.4 Copanlisib Adverse Events of Special Safety Interest

AESI are events of scientific and medical interest specific to the further understanding of copanlisib's safety profile and require close monitoring and rapid communication by the investigators to CTEP. An AESI may be serious or non-serious. The AESI for copanlisib are the following:

Non-infectious pneumonitis

Non-infectious pneumonitis has been observed in studies with copanlisib. As soon as there is a reasonable suspicion of a patient experiencing non-infectious pneumonitis, the investigator should report it within 24 hours via CTEP-AERS regardless of whether the event is assessed as causally related/not related to the study therapy, or as serious/non-serious by an investigator.

10.3.5 Olaparib Adverse Events of Special Interest

An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 10.3.3.

AESIs for olaparib are the Important Identified Risk of MDS/AML and the Important Potential Risks of new primary malignancy (other than MDS/AML) and pneumonitis.

Additional detailed information regarding the AESI will be requested from any investigator reporting an AESI. During the study, there may be other events identified as AESIs that require the investigators to provide additional detailed information to help characterize the event and gain a better understanding regarding the relationship between the event and the study intervention.

10.3.6 Durvalumab (MEDI4736) Adverse Events of Special Interest

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

AESIs observed with durvalumab (MEDI4736) include, but are not limited to:

- Diarrhea/Colitis and intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases
- Endocrinopathies (i.e., events of hypophysitis/hypopituitarism, thyroiditis, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash/Dermatitis
- Nephritis/Blood creatinine increases
- Pancreatitis/serum lipase and amylase increases

- Myocarditis
- Myositis/Polymyositis
- Intestinal perforations
- Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, neuromuscular toxicities (such as Guillain-Barré syndrome and myasthenia gravis), sarcoidosis, uveitis, other events involving the eye and skin, hematological events, rheumatological events, vasculitis, non-infectious meningitis, and non-infectious encephalitis

AESIs observed with durvalumab (MEDI4736) requiring reporting through CTEP ARES include:

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

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

10.3.7 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS regardless of whether they are associated with ≥24-hour hospitalization or not. However, they still must be reported through the routine reporting mechanism (Section 10.4). These are: any grade alopecia, Grade 2 hypernatremia/hyponatremia, Grade 2 hyperkalemia/hypokalemia, Grade 2 hyperphosphatemia/hypophosphatemia, Grade 2 hypermagnesia/hypomagnesia, Grade 2 anemia, Grade 2 hypoalbuminemia, Grade 2 INR, Grade 2 PTT, and Grade 2 hyperuricemia.

10.4 Routine Adverse Event Reporting

All AEs **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.4.1 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab (MEDI4736) safety follow-up period must be reported as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as a SAE within **24 hours** (For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes.") The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as a SAE.

10.4.2 Reporting of overdoses

There is currently no specific treatment in the event of overdose with olaparib and possible symptoms of overdose are not established. Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose. The MTD is 300 mg twice daily (tablet). Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

Use of durvalumab (MEDI4736) in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab (MEDI4736) and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.

- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

For overdoses associated with an SAE, the standard reporting timelines apply. For other overdoses, reporting must occur within 30 days.

10.4.3 Reporting of hepatic function abnormality

Cases where a patient shows elevations in liver biochemistry may require further evaluation. Cases of potential drug-induced liver injury (DILI) that include an elevated ALT or AST in combination

with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations may need to be reported as SAEs:

- Treatment-emergent ALT or AST >3×ULN (or >3× baseline value in disease states where LFTs may be elevated at baseline) in combination with total bilirubin >2×ULN (of which ≥35% is direct bilirubin).
- Treatment-emergent ALT or AST >3×ULN (or >3× baseline value in disease states where LFTs may be elevated at baseline) in combination with clinical jaundice

Cases of Hy's Law should be evaluated as described in Appendix H.

Please refer to Section 7.3, Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune Mediated Reactions durvalumab (MEDI4736) Monotherapy Table for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.5 Pregnancy

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

Additionally, all pregnancies and outcomes of pregnancy should be reported to CTEP via CTEP-AERS except for:

- Pregnancy discovered before the study patient has received any study drugs.
- Pregnancy of a female partner of male patient, providing there is no restriction of male patient fathering a child.

10.5.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the investigational products should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented using the Pregnancy Reporting Form as described in the NCI Guidelines for Investigators (at

http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform CTEP within 1 day, *i.e.*, immediately, but no later than 24 hours of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

10.5.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of copanlisib + olaparib + MEDI 4736 (durvalumab) combination therapy.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of copanlisib + olaparib + durvalumab combination therapy should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic informed consent form (ICF) template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/ IRBs prior to use.

10.6 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 following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, AML)
- 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.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a

metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Copanlisib + Olaparib Doublet Combination

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		
Copanlisib			A	A[p]	A		A	A[p]	A		A	A[p]	A			
Olaparib			B----------											-B		
Informed consent	X															
Demographics	X															
Medical history	X															
Physical exam[b,t]	X[t]		X[t]	X	X	X	X	X[q]	X		X		X		X	X
Thyroid function tests (TSH and fT3 and fT4)[o,t]	X[t]		X[o,t]								X[o] (see footnote for collection timepoints)					
Vital signs[t]	X[t]		X[t]	X	X	X	X	X[q]	X		X		X		X	X
Height[t]	X[t]															
Weight[t]	X[t]		X[t]	X	X	X	X	X[q]	X		X		X			X
Performance status[t]	X[t]		X[t]	X	X	X	X	X[q]	X		X		X		X	X
CBC w/diff, plts[t]	X[t]		X[t]	X	X	X	X	X[q]	X		X		X		X	X
Serum chemistry[c,t,x]	X[c,t]		X[c,t]	X[c]	X[c]	X[c]	X[c]	X[c,q]	X[c]		X[c]		X[x]		X[c]	X[c]
Coagulation factors[d,t]	X[t]		X[e,t]	X[e]	X[e]	X[e]	X[e]	X[e, q]			X[e]					X[e]
Urinalysis[n,t]		X[t]														
Adverse event evaluation			X----------											-X		
Tumor measurements[f,w]	X[w]		Tumor measurements are to be repeated every 8 weeks (after 2 cycles)[f]													
Radiologic evaluation[f,w]	X[w]		Radiologic evaluations are to be repeated every 8 weeks (after 2 cycles)[f]													
Tumor markers[t,y]	X[t]		X[t]				X				X				X	
Pregnancy Test[g,t]	X[t]		X[t]				X				X				X	X
HbA1c[t]	X[t]		X[t]								X[l]				X	X

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		
ECG (as indicated)[h]	X		X													
ECHO/MUGA	X															
Archived tumor collection	X															
Blood collection, PK[i s]				X[r]	X[r]											
Blood collection, ctDNA		X			X				X		X (each restaging)				X	
Tumor biopsy collection		X[j]			X[j, k]				X[k]						X[m]	
Frozen tumor biopsy collection		X[j]			X[j, k]				X[k]						X[m]	

A: Copanlisib: Dose as assigned. Each cycle is 28 days. Copanlisib infusions must be given at least 6 days apart

B: Olaparib: Dose as assigned, twice daily. Each cycle is 28 days

a: Off-study evaluation will occur 30 days (±7 days) after last dose of study treatment. See Section 6.8 for extended follow-up procedures.

b: Physical examinations will occur at baseline (within 3 days prior to C1D1), weekly (D1, D8, D15, D22) during cycle 1, three times during cycle 2 (D1, D8, and D15), then twice thereafter for every cycle (D1 and D15), or more frequently if clinically indicated (a window of ±2 days prior to treatment may be applied to all timepoints with the exception of the baseline assessment). Note: a window of ± 10 minutes is allowed for all BP measurements, except for pre-dose (0 hour) measurement. NOTE: patients treated at dose level 3a will not undergo the C2D8 assessment (unless clinically indicated). BP measurement will also be performed at multiple timepoints on treatment days as defined in section 7.1.2 and a window of ± 10 minutes is allowed for all BP measurements, except for pre-dose (0 hour) measurement, which may apply a window of ±5 minutes.

c: Albumin, alkaline phosphatase, amylase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, LDH, lipase, phosphorus, potassium, magnesium, total protein, SGOT [AST], SGPT [ALT], and sodium. If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, C1D1, Day 1 of every cycle thereafter, and as clinically indicated. Depending on the profile of the combination agent, the frequency of the hematology, serum chemistry and liver function test (LFT) testing may need to be increased to every two weeks.

d: aPTT, INR; required at baseline/pre-study and as clinically indicated. Patients receiving warfarin require additional assessments (see footnote e). Each coagulation test result will be recorded in the CRF.

e: Patients receiving warfarin must also be assessed weekly for aPTT and INR during the first month of the study; if the INR is stable, coagulation factor assessments may be performed on a monthly basis.

f: Restaging scans at the end of cycle 2 (before cycle 3), and at the end of every 2 cycles thereafter (every 3 cycles for patients on study for more than 1 year). Scan window of – 7 days can be utilized. Radiologic documentation must be provided for patients removed from study for disease progression.

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		

g: Pregnancy test (women of childbearing potential). Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment and at the beginning of each cycle during study treatment and at the EOT visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

h: Screening EKGs will be in triplicate (1 minute apart), if there is no cardiac concern (at the discretion of the investigator) all subsequent EKGs can be single. A single EKG will be taken within an hour prior to the C1D1 dose copanlisib and 3 hours (+/- 1 hour) after copanlisib. Subsequent EKGs will be done as clinically indicated.

i: Only to be collected for patients enrolled in Step 1. Samples will be collected at:

- C1D8: baseline (pre-dose), 30 minutes, 55 min post start copanlisib infusion (5 min pre-end infusion (± 5 minutes)), and 1h (± 10 minutes), 3h (± 30 minutes), 5hr (± 1 hour), 7hr (± 1 hour), and 23h (± 1 hour) after end of copanlisib infusion.
- C1D15: baseline (pre-dose), 30 minutes, 55 min post start copanlisib infusion (5 min pre-end infusion (± 5 minutes)).

j: A tumor biopsy at baseline and C1D15 (performed within 24 hours after Cycle 1 Day 15 copanlisib administration) is mandatory.

k: Only if the C1D15 Copanlisib dose is not given, should the C1D15 biopsy be performed at C2D15 (within 24 hours after Cycle 2 Day 15 copanlisib administration); otherwise a biopsy at C2D15 will not be collected. An alternate biopsy collection date may be considered with approval from the study investigator.

l: HbA1c testing is required on Day 1 of every three cycles starting from Cycle 4 (4, 7, 10, *etc.*). It is also required at the end of treatment (EOT) visit [this testing is not required if the previous test was performed within 4 weeks preceding the EOT visit]. HbA1c testing is also required approximately 3 months after EOT visit.

m: This tumor biopsy is optional.

n: The urinalysis will include hemoglobin/erythrocytes/blood; protein/albumin; and glucose.

o: Free T3 and T4 will only be measured if TSH is abnormal. Thyroid testing (TSH) will be tested at screening, C1D1, and D1 of every third cycle starting from cycle 4 (C4D1, C7D1, C10D1, etc).

p: Patients treated at dose level 3a of step 1 or step 3 expansion cohorts will not receive copanlisib infusions on Day 8 of each cycle.

q: Patients treated at dose level 3a of step 1 or step 3 expansion cohorts will not require the following C2D8 assessments (unless clinically indicated): physical examination, vitals, weight, performance status, CBC, serum chemistry, and coagulation factors.

r: Only to be collected for patients enrolled in Step 1. PK sample collection for patients treated at dose level 3a will be as follows:

- C1D8: No samples will be collected on this day.
- C1D15: baseline (pre-dose), 30 min post start copanlisib infusion, 55 min post start copanlisib infusion (5 min pre-end infusion [± 5 minutes]), and 1 h (± 10 min), 3 h (± 30 min), 5 h (± 1 h), 7 h (± 1 h), and 23 h (± 1 h) post end of copanlisib infusion.

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		

s: No PK sample collection will be performed on patients enrolled in step 3 expansion cohorts.

t: The pre-study/baseline and C1D1 assessment may be combined if completed within 3 days prior to C1D1.

w: Scans and x-rays must be done ≤4 weeks prior to the start of therapy at C1D1. Scans performed as part of standard of care may be used if performed within the specified timeframe.

x: Mandatory serum chemistry labs Day 15 of each cycle, beginning at C3D15: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], and sodium. Depending on the profile of the combination agent, the frequency of serum chemistry and liver function test (LFT) testing may need to be increased to every two weeks.

y. Relevant tumor markers will be collected (only if applicable to cancer-type) to assess treatment response.

Copanlisib + Olaparib + MED4736 Triplet Combination

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		
Copanlisb			A		A		A		A		A		A			
Olaparib			B----------											-B		
Durvalumab (MEDI4736)[a]							C				C					
Informed consent	X															
Demographics	X															
Medical history	X															
Physical exam[b, r]	X[r]		X[r]	X	X	X	X	X	X		X		X		X	X
Vital signs[r]	X[r]		X[r]	X	X	X	X	X	X		X		X		X	X
Height[r]	X[r]															
Weight[r]	X[r]		X[r]	X	X	X	X	X	X		X		X			X
Performance status[r]	X[r]		X[r]	X	X	X	X	X	X		X		X		X	X
CBC w/diff, plts[r]	X[r]		X[r]	X	X	X	X	X	X		X		X		X	X
Serum chemistry[c, r, t]	X[c,r]		X[c,r]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]		X[c]		X[t]		X[c]	X[c]
Coagulation factors[d, r]	X[r]		X[e,r]	X[e]	X[e]	X[e]	X[e]				X[e]					X[e]
Urinalysis[p, r]		X[r]														
Adverse event evaluation			X----------											-X		
Tumor measurements[f,s]	X[s]		Tumor measurements are to be repeated every 8 weeks (after every 2 cycles)[f]													
Radiologic evaluation[f,s]	X[s]		Radiologic evaluations are to be repeated every 8 weeks (after every 2 cycles)[f]													
Tumor markers[r,u]	X[r]		X[r]				X				X				X	
Pregnancy Test[g,r]	X[r]		X[r]				X				X				X	X
HbA1c[r]	X[r]		X[r]								X[m]				X	X
ECG (as indicated)[h]	X		X													
ECHO/MUGA	X															

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		
Thyroid function tests (TSH and fT3 and fT4)[j,r]	X[r]		X[i,r]								X[i] (see footnote for collection timepoints)					
Archived tumor collection	X															
Blood collection, PK[j,q]		X			X		X				X					
Blood collection, ctDNA		X			X				X		X (each restaging)				X	
Tumor biopsy collection[k,l,o]		X[k]			X[k,l]				X[l,o]				X[l,o]		X[o]	
Frozen tumor biopsy collection[k,l,o]		X[k]			X[k,l]				X[l,o]				X[l,o]		X[o]	

A: Copanlisib: Dose as assigned. Each cycle is 28 days. Copanlisib infusions must be given at least 6 days apart. Olaparib and Copanlisib can be given together.

B: Olaparib: Dose as assigned, twice daily. Each cycle is 28 days

C: Durvalumab: The first dose will be administered on Cycle 2 Day 1 at 1,500 mg. Subsequent doses will be administered at 1,500 mg Day 1 every 28 days. Each cycle is 28 days. Durvalumab (MEDI4736) will be added first in Steps 2 and 3 for the triplet combination.

a: Off-study evaluation will occur 30 days (±7 days) after last dose of study treatment. See Section 6.8 for extended follow-up procedures.

b: Physical examination at baseline(within 3 days prior to C1D1), weekly (D1, D8, D15, D22) during cycle 1, then twice thereafter for every cycle at cycle 2 and beyond (D1 and D15), or more frequently if clinically indicated (a window of ±2 days prior to treatment may be applied to all timepoints with the exception of the baseline assessment). On durvalumab infusion days, blood pressure should be measured, predose. On days where copanlisib is given, blood pressure should be measured pre-dose, mid-infusion, end of infusion, and 1 and 2 hours after the end of infusion. BP measurement will also be performed at multiple timepoints on treatment days as defined in section 7.1.2 and a window of ± 10 minutes is allowed for all BP measurements, except for pre-dose (0 hour) measurement, which may apply a window of ±5 minutes.

c: Albumin, alkaline phosphatase, amylase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, LDH, lipase, phosphorus, potassium, magnesium, total protein, SGOT [AST], SGPT [ALT], and sodium. If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, C1D1, Day 1 of every cycle thereafter, and as clinically indicated. Depending on the profile of the combination agent, the frequency of the hematology, serum chemistry and liver function test (LFT) testing may need to be increased to every two weeks.

d: aPTT, INR; required at baseline/pre-study and as clinically indicated. Patients receiving warfarin require additional assessments (see footnote e). Each coagulation test result will be recorded in the CRF.

e: Patients receiving warfarin must also be assessed weekly for aPTT and INR during the first month of the study; if the INR is stable, coagulation factor assessments may be performed on a monthly basis.

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		

f: Restaging scans at the end of cycle 2 (before cycle 3), and at the end of every 2 cycles thereafter (every 3 cycles for patients on study for more than 1 year). Scan window of – 7 days can be utilized. Radiologic documentation must be provided for patients removed from study for disease progression.

g: Pregnancy test (women of childbearing potential). Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to the start of study treatment, on Day 1 of the study prior to commencing treatment and at each subsequent visit during study treatment and at the EOT visit. Tests will be performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from study treatment immediately. Details of the pregnancy tests must be recorded in the patient's medical records.

h: Screening EKGs will be in triplicate (1 minute apart), if there is no cardiac concern (at the discretion of the investigator) all subsequent EKGs can be single. A single EKG will be taken within an hour prior to the C1D1 dose copanlisib and 3 hours (+/- 1 hour) after copanlisib. Subsequent EKGs will be done as clinically indicated.

i: Free T3 and T4 will only be measured if TSH is abnormal. Thyroid testing (TSH) will be tested at screening, C1D1, and D1 of every third cycle starting from cycle 4 (C4D1, C7D1, C10D1, etc

j: Only to be collected for patients enrolled in Step 2. Samples will be collected at:

1. Baseline (within 7 days of or prior to treatment on C1D1)
2. C1D15: baseline (pre-dose), 30 min post start copanlisib infusion, 55 min post start copanlisib infusion (5 min pre-end infusion [± 5 minutes]), and 1 h (± 10 min), 3 h (± 30 min), 5 h (± 1 h), 7 h (± 1 h), and 23 h (± 1 h) post end of copanlisib infusion.
3. C2D1: baseline (pre-dose), 50 min post start durvalumab infusion (10 min pre-end infusion (± 5 minutes)).
4. C3D1: baseline (pre-dose), 50 min post start durvalumab infusion (10 min pre-end infusion (± 5 minutes)).
5. C4D1: baseline (pre-dose), 50 min post start durvalumab infusion (10 min pre-end infusion (± 5 minutes)).
6. C5D1: baseline (pre-dose), 50 min post start durvalumab infusion (10 min pre-end infusion (± 5 minutes)).

k: A tumor biopsy at baseline and C1D15 (within 24 hours after Cycle 1 Day 15 copanlisib administration) is mandatory.

l: Only if C1D15 Copanlisib dose is not given, should the C1D15 biopsy be performed at C2D15 (within 24 hours after Cycle 2 Day 15 copanlisib administration). When the C1D15 biopsy is moved to C2D15 due to missed copanlisib dose, then the optional C2D15 biopsy will be performed at C3D15 (within 24 hours after Cycle 3 Day 15 copanlisib administration); otherwise, no biopsy is planned to occur on C3D15. Refer to subscript 'o' to ensure the mandatory C1D15 and optional C2D15 biopsies do not fall on the same collection date. An alternate biopsy collection date may be considered with approval from the study investigator.

m: HbA1c testing is required on Day 1 of every three cycles beginning Cycle 4 (C4D1, C7D1, C10D1, *etc.*). It is also required at the end of treatment (EOT) visit [this testing is not required if the previous test was performed within 4 weeks preceding the EOT visit]. HbA1c testing is also required approximately 3 months after EOT visit.

n: Durvalumab (MEDI4736) will be started on cycle 2 day 1 (C2D1). Durvalumab treatment should be given for a maximum of 24 months or until disease progression, whichever is earlier.

o: The C2D15 on treatment tumor biopsy and disease progression biopsy are optional.

p: The urinalysis will include hemoglobin/erythrocytes/blood; protein/albumin; and glucose.

q: No PK sample collection will be performed in patients treated in Step 3 expansion cohorts.

r: The pre-study/baseline and C1D1 assessments may be combined if completed within 3 days prior to C1D1.

	Pre-Study (within 28 days of C1D1)	Baseline (within 7 days of C1D1)	Cycle 1				Cycle 2				Cycle 3+				EOT/ Disease progression	Off Study[a]
			Day 1 ± 3	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2	Day 1 ± 2	Day 8 ± 2	Day 15 ± 2	Day 22 ± 2		

s: Scans and x-rays must be done ≤4 weeks prior to the start of therapy at C1D1. Scans performed as part of standard of care may be used if performed within the specified timeframe.

t: Mandatory serum chemistry labs Day 15 of each cycle, beginning at C3D15: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, potassium, total protein, SGOT [AST], SGPT [ALT], and sodium. Depending on the profile of the combination agent, the frequency of serum chemistry and liver function test (LFT) testing may need to be increased to every two weeks.

u. Relevant tumor markers will be collected (only if applicable to cancer-type) to assess treatment response.

11.1 Laboratory Assessments

Full hematology assessments for safety (hemoglobin, red blood cells [RBC], platelets, mean cell volume [MCV], mean cell hemoglobin concentration [MCHC], mean cell hemoglobin [MCH], white blood cells [WBC], absolute differential white cell count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and absolute neutrophil count or segmented neutrophil count and band forms should be performed at each visit and when clinically indicated. If absolute differentials are not available, please provide % differentials.

Serum biochemistry assessments for safety include sodium, potassium, calcium, magnesium, fasting glucose, creatinine, total bilirubin, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), urea or blood urea nitrogen (BUN), total protein, albumin, bicarbonate, chloride, phosphorus, amylase, lipase, and lactic dehydrogenase (LDH). These assessments should be performed at every clinic visit and when clinically indicated.

Coagulation (activated partial thromboplastin time [aPTT] and INR) will be performed at baseline and if clinically indicated unless the patient is receiving warfarin. Patients taking warfarin may participate in this study; however, it is recommended that prothrombin time (INR and aPTT) be monitored carefully at least once per week for the first month, then monthly if the INR is stable.

Gamma glutamyltransferase (GGT), will be conducted pre-study, C1D1 and D1 of every cycle thereafter. Free T3 and free T4 only need to be tested if TSH is abnormal. Testing can be added more frequently, if clinically indicated.

HbA1C will be conducted pre-study, C1D1, D1 of every third cycle beginning at cycle 4 (C4D1, C7D1, C10D1, etc.). It is also required at end of treatment (EOT) [this testing is not required if the previous test was performed within 4 weeks preceding the EOT visit] and 3 months after the EOT visit.

Thyroid testing (TSH) will be conducted pre-study, C1D1 and then every other cycle. Free T3 and free T4 only need to be tested if TSH is abnormal. Testing can be added if clinically indicated.

Urinalysis by dipstick should be performed at baseline and only if clinically indicated thereafter. Microscopic analysis should be performed by the hospital's local laboratory if required.

Bone marrow or blood cytogenetic samples may be collected for patients with prolonged hematological toxicities as defined in Section 7.2.3.3.

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. Full reports must be provided by the investigator for documentation on the Patient Safety database. These data are not required to be entered into CRF.

These tests will be performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF.

In case a patient shows an AST **or** ALT ≥3×ULN **or** total bilirubin ≥2×ULN, patients should be evaluated for potential DILI (please refer to Appendix H, "Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law", for further instructions).

11.2 ECG

ECGs are required within 7 days prior to starting study treatment and when clinically indicated.

Twelve-lead ECGs will be obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The investigator or designated physician will review the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. ECGs will be recorded at 25 mm/sec. All ECGs should be assessed by the investigator as to whether they are clinically significantly abnormal/not clinically significantly abnormal. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF. The original ECG traces must be stored in the patient medical record as source data.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 8 weeks. In addition to a baseline scan, confirmatory scans will also be obtained at least 4 weeks following initial documentation of an objective response.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 (not less than 4) weeks following initial documentation of objective response.

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.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with copanlisib, olaparib, and durvalumab (MEDI4736).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy in accordance with evaluability criteria listed in section 6.2.1, 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 in accordance with evaluability criteria listed in section 6.2.1, 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.

12.1.2 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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) 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 might or might not be considered measurable. Tumor lesions that are situated in a previously irradiated area may be considered measurable if they have progressed by RECIST since being irradiated.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] 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.

12.1.3 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 (≥1 cm) 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 (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens

during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and PD.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.
d. Since Copanlisib is a potent inhibitor of Glucose Transporter 1 (Glut1), it may inhibit cancer cell uptake of glucose or FDG. This may cause decreased FDG uptake to be noted on scans and suggest an antitumor effect rather than just a pharmacodynamic effect. FDG-PET testing should be done at least one week after the last dose of copanlisib.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 Evaluation of Target Lesions

CR: Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

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

PD: At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered

progressions).

SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12.1.4.2 Evaluation of Non-Target Lesions

CR: Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR

Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

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

12.1.5 Duration of Response

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

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

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

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.2 Other Response Parameters

The response to immunotherapy may differ from the typical responses observed with cytotoxic

chemotherapy including the following (Wolchok *et al*., 2009):

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, *e.g*., European Medicines Agency's "Guideline on the evaluation of anticancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with copanlisib + olaparib, or copanlib + olaparib + durvalumab (MEDI4736) would continue between the initial assessment of progression and confirmation for progression.

Modification of RECIST as described may discourage the early discontinuation of copanlisib + olaparib + durvalumab (MEDI4736) and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. **Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.**

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anticancer therapy other than copanlisib + olaparib + durvalumab (MEDI4736) or with symptomatic progression that requires urgent medical intervention (*e.g*., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression).

12.2.1 Efficacy Variable

Patients who have disease control following completion of 24 months of treatment or patients who are withdrawn from copanlisib + olaparib (+ durvalumab [MEDI4736]) treatment for reasons other than confirmed PD will continue to have objective tumor assessments.

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions;
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of PD in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression; and

Confirmed objective disease progression refers to either of the following scenarios: 1) clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2) in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of

progression criteria listed below. (RECIST 1.1 modified for confirmation of progression refers to the second scenario above). The confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),
- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above).

- In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.
- If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan.

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol PI is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and SAEs; reporting of expedited AEs; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol PI and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

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

Requirements to access Rave via iMedidata:

- •Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems, 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:

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

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

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. No action will be required; each study invitation will be automatically accepted and study access to the study 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 invitation (previously sent but not accepted or declined by 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 Data Manaement 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 or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

13.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-

based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.2.3 Data Quality Portal

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

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

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

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to

these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

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

13.3 CTEP Multicenter Guidelines

N/A

13.4 Collaborative Agreements Language

The agents 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 Companies (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. Agents may not be used for any purpose outside the scope of this protocol, nor can Agents be transferred or licensed to any party not participating in the clinical study. Collaborators data for agents are confidential and proprietary to collaborators 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 other agents, 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 Collaborators. No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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APPENDIX A PERFORMANCE STATUS CRITERIA

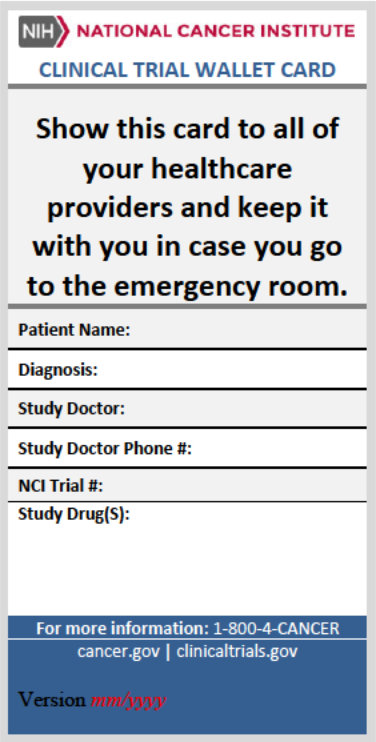
ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B LIST OF PROHIBITED MEDICATIONS WHILE ON COPANLISIB TREATMENT

This list is not comprehensive. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference for a list of drugs to avoid or minimize use of.

Category	Drug name
Strong Cytochrome P450 3A (CYP3A) Inhibitors	Voriconazole, Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin,
Strong CYP3A Inducers	Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum)
Herbal Preparations/ Medications	Herbal preparations/medications are prohibited throughout the study. These herbal medications include, but are not limited to: St. John's Wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 7 days prior to first dose of study drug

APPENDIX C PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD FOR COPANLISIB AND OLAPARIB COMBINATION OR COPANLISIB, OLAPARIB, AND DURVALUMAB (MEDI4736) COMBINATION



NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

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

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

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

Version *mm/yyyy*

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APPENDIX D THE AVERAGE GLYCEMIC INDEX OF COMMON FOODS DERIVED FROM MULTIPLE STUDIES BY DIFFERENT LABORAORIES

Foods are categorized as having a low-glycemic index if the glucose reference index is ≤55. High-Glycemic Index foods have a glucose reference index >55. The summary table below contains glucose reference for common foods.

High-carbohydrate foods		Breakfast cereals		Fruit and fruit products		Vegetables	
White wheat bread*	75 ± 2	Cornflakes	81 ± 6	Apple, raw†	36 ± 2	Potato, boiled	78 ± 4
Whole wheat/whole meal bread	74 ± 2	Wheat flake biscuits	69 ± 2	Orange, raw†	43 ± 3	Potato, instant mash	87 ± 3
Specialty grain bread	53 ± 2	Porridge, rolled oats	55 ± 2	Banana, raw†	51 ± 3	Potato, french fries	63 ± 5
Unleavened wheat bread	70 ± 5	Instant oat porridge	79 ± 3	Pineapple, raw	59 ± 8	Carrots, boiled	39 ± 4
Wheat roti	62 ± 3	Rice porridge/congee	78 ± 9	Mango, raw†	51 ± 5	Sweet potato, boiled	63 ± 6
Chapatti	52 ± 4	Millet porridge	67 ± 5	Watermelon, raw	76 ± 4	Pumpkin, boiled	64 ± 7
Corn tortilla	46 ± 4	Muesli	57 ± 2	Dates, raw	42 ± 4	Plantain/green banana	55 ± 6
White rice, boiled*	73 ± 4			Peaches, canned†	43 ± 5	Taro, boiled	53 ± 2
Brown rice, boiled	68 ± 4			Strawberry jam/jelly	49 ± 3	Vegetable soup	48 ± 5
Barley	28 ± 2			Apple juice	41 ± 2		
Sweet corn	52 ± 5			Orange juice	50 ± 2		
Spaghetti, white	49 ± 2						
Spaghetti, whole meal	48 ± 5						
Rice noodles†	53 ± 7						
Udon noodles	55 ± 7						
Couscous†	65 ± 4						
Dairy products and alternatives		**Legumes**		**Snack products**		**Sugars**	
Milk, full fat	39 ± 3	Chickpeas	28 ± 9	Chocolate	40 ± 3	Fructose	15 ± 4
Milk, skim	37 ± 4	Kidney beans	24 ± 4	Popcorn	65 ± 5	Sucrose	65 ± 4
Ice cream	51 ± 3	Lentils	32 ± 5	Potato crisps	56 ± 3	Glucose	103 ± 3
Yogurt, fruit	41 ± 2	Soya beans	16 ± 1	Soft drink/soda	59 ± 3	Honey	61 ± 3
Soy milk	34 ± 4			Rice crackers/crisps	87 ± 2		
Rice milk	86 ± 7						

Data are means ± SEM. *Low-GI varieties were also identified. †Average of all available data.

APPENDIX E FROZEN BIOPSY SPECIMEN BATCH RECORD

Batch Record

A separate Batch Record should be started for each patient sample.

Facility / Clinic Collecting Specimens: _____

NCI Protocol Number: 10217
Patient ID:_____

- Biopsy Collection

	1st Pass	2nd Pass	3rd Pass	4th Pass
Specimen ID				
Biopsy size prepared for PD or histological analysis:	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved	☐ Full ☐ Halved
Required: Time elapsed from collection to placement in tube	min sec	min sec	min sec	min sec
Time biopsy collected (opt)	:	:	:	:
Time biopsy placed in tube (opt)	:	:	:	:

- Biopsy Procedure Details

Specimen ID	
Time local anesthesia administered	:
Dose of local anesthetic	mg
Name of local anesthetic used (from Research Nurse)	
Time of skin incision	:
Needle Type (e.g., Temno)	
Needle diameter	gauge
Needle Length	cm
Time guide needle introduced	:
Time guide needle placement confirmed	:
Time biopsy needle introduced	:

- Biopsy Storage

Date/time biopsy specimen(s) placed at -80°C (or lower)	_____/ /_____	_____: _____	_____°C

- Notes, including any deviations from this protocol

_____

_____

_____

- Review of Batch Record

Laboratory Personnel: _____ (Print)

Laboratory Personnel: _____ (Sign)

Date: _____

APPENDIX F PATIENT MEDICATION DIARY

CTEP-assigned Protocol #__10217__
Local Protocol # _____

PATIENT'S MEDICATION DIARY

Today's date _____ **Agent** _____Olaparib_____

Patient Name_____ (*initials acceptable)* Patient **Study ID**

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each month.
2. You will take ___ tablets each day, ___ in the morning and ___ in the evening. You should take the tablets with 8 oz. water, with or without any moderate fat or low-fat food.
3. The olaparib tablet s should be swallowed whole and not chewed, crushed, dissolved, or divided. Do not take with grapefruit juice or Seville oranges.
4. If a dose is vomited shortly after being taken, retake the dose only if the intake tablets can be seen and counted.
5. If a dose is missed, the dose can be taken within 2 hours of the scheduled time. Otherwise, skip the dose and take the next dose at the scheduled time. Note this in the **Comments** column.
6. Record the date, the number of tablets you took, and when you took them.
7. If you have any comments or notice any side effects, please record them in the Comments column.
8. Please return the forms to your physician when you go for your next appointment.

Day	Date	Time of morning dose	# of tablets taken	Time of evening dose	# of tablets taken	Comments
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						

23						
24						
25						
26						
27						
28						

Patient's

Signature_____

_____

Physician's Office will complete this section:

1. Date patient started protocol treatment_____
2. Date patient was removed from study_____
3. Patient's planned total daily dose_____
4. Total number of tablets taken this month _____
5. Physician/Nurse/Coordinator/ or Data Manager's Signature _____

APPENDIX G ACCEPTABLE BIRTH CONTROL METHODS

Olaparib is regarded as a compound with medium/high fetal risk.

Patients of child bearing potential and their partners, who are sexually active, must agree to the use of TWO highly effective forms of contraception in combination (as listed below) throughout their participation in the study. Moreover, women study participants are expected to use highly effective contraception for 6 months after the last dose of study drug and men are expected to use highly effective contraception for 3 months.

Male patients should not donate sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib. Acceptable birth control methods are listed below.

Condom with spermicide and one of the following:

- Oral contraceptive or hormonal therapy (e.g. hormone implants)
- Placement of an intra-uterine device

Acceptable non-hormonal birth control methods include:

- Total sexual 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 6 months after the last dose of study drug for female patients, and 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 with spermicide.
- Intrauterine Device (IUD) plus male condom+spermicide. Provided coils are copper-banded.

Acceptable hormonal methods:

- Etonogestrel implants (e.g., Implanon, Norplan)+male condom with spermicide
- Normal and low dose combined oral pills+male condom with spermicide
- Norelgestromin/ethinyl estradiol (EE) transdermal system+male condom with spermicide
- Intravaginal device+male condom with spermicide (e.g., EE and etonogestrel)
- Cerazette (desogestrel)+male condom with spermicide. Cerazette is currently the only highly efficacious progesterone-based pill.
- Hormonal shot or injection (e.g., Depo-Provera) 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

APPENDIX H ACTIONS REQUIRED IN CASES OF COMBINED INCREASE OF AMINOTRANSFERASE AND TOTAL BILIRUBIN – HY'S LAW

Briefly, Hy's Law cases have the following three components:

The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo

Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)

No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury

Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe drug induced liver injury (DILI) when given to a larger population.

The following actions are required in cases of combined increase of aminotransferase and total bilirubin:

1. **Confirmation**

In general, an increase of serum AST/A:T to >3xULN should be followed by repeat testing within 48 to 72 hours of all four of the usual serum measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing. There also should be inquiry made about symptoms. Serum AT may rise and fall quite rapidly, and waiting a week or two before obtaining confirmation of elevations may lead to a false conclusion that the initially observed abnormality was spurious. Of greater concern, delay in retesting may allow progression to severe worsening if the initial abnormality was the herald of a severe reaction to follow. The need for prompt repeat testing is especially great if AST/ALT is much greater than 3xULN and/or TBL is greater than 2xULN. For outpatient trials, or trials in which subjects are far away from the trial site, it may be difficult for the subjects to return to the trial site promptly. In this case, the subjects should be retested locally, but normal laboratory ranges should be recorded, results should be made available to trial investigators immediately, and the data should be included in the case reports. If symptoms persist or repeat testing shows AST/ALT >3xULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, it is appropriate to initiate close observation to determine whether the abnormalities are improving or worsening. If close monitoring is not possible, the drug should be discontinued.

15. **Close Observation**

It is critical to initiate close observation immediately upon detection and confirmation of early signals of possible DILI, and not to wait until the next scheduled visit or monitoring interval. A threshold of aminotransferase levels greater than 3xULN seems reasonable, as lesser elevations are common and nonspecific. If additional testing, beyond that specified in the trial protocol, is carried out, it is important that the subject's information be added to the case report forms and database.
Close observation includes:

Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
Obtaining a more detailed history of symptoms and prior or concurrent diseases.
Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; nonalcoholic steatohepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease.
Obtaining a history of exposure to environmental chemical agents.
Obtaining additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
Considering gastroenterology or hepatology consultations.

16. **Decision to Stop Drug Administration**

It has been observed that de-challenge (stopping drug administration) does not always result in immediate improvement in abnormal lab values. Abnormal test values and symptoms may progress for several days or even weeks after discontinuation of the drug that caused the abnormality. For example, rising TBL usually follows serum AT increases by a few days to weeks. The primary goal of close observation is to determine as quickly as possible whether observed abnormal findings are transient and will resolve spontaneously or will progress. For most DILI, no specific antidotes are available (except N-acetylcysteine for acute acetaminophen overdose if given promptly, and, possibly, intravenous carnitine for valproic acid hepatotoxicity).

Promptly stopping the offending drug usually is the only potentially effective therapy.

Because transient fluctuations of ALT or AST are common, and progression to severe DILI or acute liver failure is uncommon, automatic discontinuation of trial drug upon finding a greater than 3xULN elevation of ALT or AST may be unnecessary. For most people, the liver appears capable of adapting to injury by foreign chemical substances, which may render a person tolerant to the drug despite continued exposure. Stopping a drug at the first hint of mild injury does not permit learning whether adaptation will occur, as it does for drugs such as tacrine, which cause liver injury but do not cause severe DILI. On the other hand, continuing drug appears unacceptably dangerous if there is marked serum aminotransferase elevation or evidence of functional impairment, as indicated by rising bilirubin or INR, which represent substantial liver

injury. Although there is no published consensus on exactly when to stop a drug in the face of laboratory abnormalities and the decision will be affected by information on related drugs, the accumulating clinical experience, the clinical status of the patient, and many other factors, the following can be considered a basic guide. Discontinuation of treatment should be considered if:

ALT or AST >8xULN
ALT or AST >5xULN for more than 2 weeks
ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

It should be noted that although these guidelines have not been evaluated systematically in a prospective fashion, they represent an approach that is similar to current practice.

2. **Evaluating Data for Alternative Causes**

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

Acute viral hepatitis. The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.

Alcoholic and autoimmune hepatitis. Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).

Hepatobiliary disorders. Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.

Nonalcoholic steatohepatitis. Nonalcoholic steatohepatitis may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.

Cardiovascular causes. Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (ischemic hepatitis) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.

Concomitant treatments. It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

3. **Follow-Up to Resolution**

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. DILI may develop or progress even after the causative drug has been stopped. Results should be recorded on the case report form and in the database. Note that longer follow-up can sometimes reveal an off-drug repetition of what had appeared to be DILI, indicating that liver injury was related to underlying liver disease.

4. **Re-challenge**

Whether or not to re-challenge a subject who showed mild DILI is a difficult decision. Re-exposure may initiate a sometimes explosive and more severe reaction, as was observed with halothane several decades ago. Some cases of DILI show indicators of immunological reaction such as eosinophilia, rash, fever, or other symptoms or findings, and it is possible that such cases are more prone to recur with re-exposure. Re-challenge may not be considered negative unless the subject is exposed to and tolerates the same dose and treatment duration that preceded the original reaction. A negative re-challenge does not necessarily allow a conclusion that the drug did not cause the injury. Most people can adapt to xenobiotic substances, including new drugs, and develop tolerance for them. This has been observed even for drugs that can cause severe injury, such as isoniazid. The large majority of people showing hepatocellular injury while taking isoniazid recover fully or recover while continuing to take the drug, and some, but not all, can resume or continue taking the drug without further adverse consequence. If such tolerance has developed, the use of re-challenge to verify drug causation would give a false negative result.

Generally, re-challenge of subjects with significant AT elevations (>5xULN) should not be attempted. If such subjects are re-challenged, they should be followed closely. Re-challenge can

be considered if the subject has shown important benefit from the drug and other options are not available or if substantial accumulated data with the test drug do not show a potential for severe injury. The subject should be made aware of the potential risk, and consent to the re-challenge, and the PI consulted.

APPENDIX I PHARMACOKINETICS SHEET BASELINE (STEP 2 TRIPLET ONLY)

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each PK time point, **~3-4 mL** of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Olaparib (O), Copanlisib (C)

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL red-top tube; Clot upright at RT 30-60 min max; centrifuge 10 min 1,200 x g RT; store serum at -70°C until shipment.
Cycle 1 Day 1 or before Copanlisib (C) infusion (nominal 60 min) Copanlisib Dose (mg):_____ Olaparib Dose (mg):_____			
pre sample			**ONLY IN PATIENTS WITH TRIPLE COMBINATION (DURVALUMAB)**
C infusion **start** **=O dosing**			

APPENDIX I PHARMACOKINETICS SHEET C1D8

Note: C1D8 PK samples will not be collected for patients treated at dose level 3a in Step 1 or patients treated in Step 2.

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each PK time point, **~3-4 mL** of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Olaparib (O), Copanlisib (C)

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL purple top EDTA tube; Invert to mix blood and place on ice; process within 30 min; centrifuge 10 min at ~1000 x g; store plasma at -70 °C until
Cycle 1 Day 8	**Administer the olaparib at start of copanlisib infusion**		
Copanlisib (C) infusion (nominal 60 min) Copanlisib Dose (mg):_____ Olaparib Dose (mg):_____			
pre/trough sample			
C infusion **start** =O dosing			
30 min post C start			
55 min post C start (~5 min pre end C infusion)			
C infusion **end**			
1 h post **end** C			
3 h post end C			
5 h post end C			
7 h post end C			
Cycle 1 Day 9			
pre/trough sample (~24 h post start C D8)			
Olaparib dose			

APPENDIX I PHARMACOKINETICS SHEET C1D15

Note: Do not use this PK sheet for patients treated at dose level 3a in Step 1 or patients treated in Step 2. Use the corresponding C1D15 PK Sheet for patients treated at dose level 3a in Step 1 and patients treated in Step 2.

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each PK time point, **~3-4 mL** of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Olaparib (O), Copanlisib (C)

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL purple top EDTA tube; Invert to mix blood and place on ice; process within 30 min; centrifuge 10 min at ~1000 x g; store plasma at -70 °C until
Cycle 1 Day 15	**Administer the olaparib at start of copanlisib infusion**		
Copanlisib (C) infusion (nominal 60 min) Copanlisib Dose (mg):_____ Olaparib Dose (mg):_____			
pre/trough sample			
C infusion **start** **=O dosing**			
30 min post C start			
55 min post C start (~5 min pre end C infusion)			
C infusion **end**			

APPENDIX I PHARMACOKINETICS SHEET C1D15 (FOR PATIENTS TREATED AT DOSE LEVEL 3A IN STEP 1 AND PATIENTS TREATED IN STEP 2)

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection (for patients treated at dose level 3a in STEP 1 and patients treated in STEP 2 only)

At each PK time point, ~3-4 mL of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws

Olaparib (O), Copanlisib (C)

Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL purple top EDTA tube; Invert to mix blood and place on ice; process within 30 min; centrifuge 10 min at ~1000 x g; store plasma at -70 °C until shipment
Cycle 1 Day 15 (for patients treated at dose level 3a in STEP 1 and patient treated in STEP 2 only) **Administer the olaparib at start of copanlisib infusion** Copanlisib (C) infusion (nominal 60 min) Copanlisib Dose (mg):_____ Olaparib Dose (mg):_____			
pre/trough sample			
C infusion start =O dosing			
30 min post C start			
55 min post C start (~5 min pre end C infusion)			
C infusion end			
1 h post end C			
3 h post end C			
5 h post end C			
7 h post end C			
Cycle 1 Day 16 (for patients treated at dose level 3a in STEP 1 and patient treated in STEP 2 only)			
pre/trough sample †23 h post start C1D16)			
Olaparib dose (post-sample collection)			

APPENDIX I PHARMACOKINETICS SHEET C2D1 (STEP 2 TRIPLET ONLY)

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each PK time point, **~3-4 mL** of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Durvalumab (D)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL red-top tube; Clot upright at RT 30-60 min max; centrifuge 10 min 1,200 x g RT; store serum at -70°C until shipment.
Cycle 2 Day 1 **Administer the olaparib at start of copanlisib infusion** Durvalumab (D) infusion (nominal 60 min) (mg):_____ Olaparib Dose (mg):_____			
pre/trough sample			**ONLY IN PATIENTS WITH TRIPLE COMBINATION (DURVALUMAB)**
D infusion **start**			
55 min post D start (~5 min pre end D infusion)			
D infusion **end** (=C infusion start =O dosing)			

APPENDIX I PHARMACOKINETICS SHEET C3D1 (STEP 2 TRIPLET ONLY)

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each PK time point, **~3-4 mL** of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Durvalumab (D)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL red-top tube; Clot upright at RT 30-60 min max; centrifuge 10 min 1,200 x g RT; store serum at -70°C until shipment.
Cycle 3 Day 1 **Administer the olaparib at start of copanlisib infusion** Durvalumab (D) infusion (nominal 60 min) (mg):_____ Olaparib Dose (mg):_____			
pre/trough sample			**ONLY IN PATIENTS WITH TRIPLE COMBINATION (DURVALUMAB)**
D infusion **start**			
55 min post D start (~5 min pre end D infusion)			
D infusion **end** (=C infusion start =O dosing)			

APPENDIX I PHARMACOKINETICS SHEET C4D1 (STEP 2 TRIPLET ONLY)

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each PK time point, **~3-4 mL** of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Durvalumab (D)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL red-top tube; Clot upright at RT 30-60 min max; centrifuge 10 min 1,200 x g RT; store serum at -70°C until shipment.
Cycle 4 Day 1 **Administer the olaparib at start of copanlisib infusion** Durvalumab (D) infusion (nominal 60 min) (mg):_____ Olaparib Dose (mg):_____			
pre/trough sample 1			**ONLY IN PATIENTS WITH TRIPLE COMBINATION (DURVALUMAB)**
pre/trough sample 2 Anti-drug-antibody sample			
D infusion **start**			
55 min post D start (~5 min pre end D infusion)			
D infusion **end** (=C infusion start =O dosing)			

APPENDIX I PHARMACOKINETICS SHEET C5D1 (STEP 2 TRIPLET ONLY)

NCI 10217 A Phase 1b Biomarker-Driven Combination Trial of Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients with Advanced Solid Tumors

Study Sample Collection Log

Subject Initials: (First_Middle_Last)	**Subject ID:**	**Date:**	**BSA: (m^2)**	**Site Name:**

Pharmacokinetic (PK) Sample Collection

At each PK time point, **~3-4 mL** of peripheral blood will be collected. After sample processing, store plasma or serum samples at -70°C or below until shipment. *See Section 5 of the protocol for more specific processing instructions and shipping instructions. At the time of sample transfer, a copy of this completed PK form must be transferred also.*

Note the start and stop times of infusions / administering of oral dose, in this form. Whenever the timing of drawing samples is dependent on the recent start or end of an infusion, a green arrow indicates which time-point starts the clock on subsequent blood draws.

Durvalumab (D)			
Protocol Sample and Time Point	**Projected Sample Due Time (24 hr clock)**	**Actual Time (24 hr clock)**	**Comments** Collect 3-4 mL red-top tube; Clot upright at RT 30-60 min max; centrifuge 10 min 1,200 x g RT; store serum at -70°C until shipment.
Cycle 5 Day 1 **Administer the olaparib at start of copanlisib infusion** Durvalumab (D) infusion (nominal 60 min) (mg):_____ Olaparib Dose (mg):_____			
pre/trough sample			**ONLY IN PATIENTS WITH TRIPLE COMBINATION (DURVALUMAB)**
D infusion **start**			
55 min post D start (~5 min pre end D infusion)			
D infusion **end** (=C infusion start =O dosing)			

APPENDIX J TISSUE BIOPSY VERIFICATION FORM

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the

EET Biobank.

If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.

Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Primary Metastatic

Time point (circle one): Baseline C1D15 C2D15 Progression

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

Clinician Signature _____ Date _____

Clinician Printed Name _____

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.

Version: 1
Effective Date: 9/2019

APPENDIX K INTERVENTION GUIDELINES FOR COMMON TREATMENT RELATED ADVERSE EVENTS (AE)

This section is meant to provide **additional intervention guidelines** for common treatment related AEs.

Management of Copanlisib-related rash maculo-papular

Rash maculo-papular (CTCAE v5)	Management	Additional recommended intervention
Grade 1	Hold copanlisib until rash resolves	Apply emollients/creams liberally as needed until rash resolves. Face: Desonide 0.05% cream Body: Triamcinolone 0.1% cream
Grade 2	• Hold copanlisib and olaparib until rash resolves. • Can restart olaparib if rash recovers to Grade 1 or completely resolves. • Can restart copanlisib when rash completely resolves	• Apply emollients/creams liberally as needed until rash resolves. o Face: Desonide 0.05% cream o Body: Triamcinolone 0.1% cream • Short-term steroid taper o Medrol dose pack
Grade ≥3	• Hold copanlisib and olaparib until rash resolves. • Can restart olaparib if rash recovers to Grade 1 or completely resolves. • Can restart copanlisib when rash completely resolves	• Apply emollients/creams liberally as needed until rash resolves. o Face: Desonide 0.05% cream o Body: Triamcinolone 0.1% cream • Short-term steroid taper o Medrol dose pack • Hospital admission and IV steroid administration.

Management of transient glucose increase prior to copanlisib infusion

Criteria	Management	Additional recommended intervention
Asymptomatic glucose increase ≥200-250 mg/dL	Patients who develop transient post-infusion glucose ≥200-250 mg/dL after study drug administration may continue treatment; however, the subsequent infusion can only take place as long as glucose levels return to pre-infusion levels of <160 mg/dL (fasting) or <200 mg/dL (non-fasting)	Does not generally require intervention with glucose lowering medication.
Asymptomatic glucose increase to >250 mg/dL	• Patients who develop transient post-infusion glucose >250 mg/dL after study drug administration may continue treatment; however, the subsequent infusion can only take place as long as glucose levels return to pre-infusion levels of <160 mg/dL (fasting) or <200 mg/dL (non-fasting) • Should have repeated laboratory glucose determination. • If the repeated glucose value is decreasing, the glucose may be followed without glucose lowering medication treatment if hydration status is normal as clinically assessed. • Consultation with endocrinologist is recommended.	• Hydration if appropriate. • Consider prophylaxis with oral glucose lowering medication when planning next infusion.
Symptomatic or persisting glucose increases to a value >250 mg/dL	• Patients who develop transient post-infusion glucose >250 mg/dL after study drug administration	• Rapid/ short acting insulin may be given for glucose persisting at >250 mg/dL, or if the

	may continue treatment; however, the subsequent infusion can only take place as long as glucose levels return to pre-infusion levels of <160 mg/dL (fasting) or <200 mg/dL (non-fasting) • Hydration status should be clinically assessed. If clinical assessment is consistent with dehydration, fluids should be given as clinically appropriate (orally or IV). • Laboratory test confirming increase should be repeated. If the repeated glucose value is persistent and/or patient is symptomatic and/or the hydration status indicates the need for hydration, glucose lowering medication should be administered. • Prompt input from a diabetes specialist should be obtained.	patient is symptomatic during the infusion day. • Rapid/short acting insulin. • According to the institution sliding scale coverage of glucose persisting at >250 mg/dL is recommended, with oral or IV hydration as clinically appropriate. When planning next infusion, consider prophylaxis with oral glucose lowering medication.

Management of glucose increases post-copanlisib infusion

Hyperglycemia (CTCAE v5)	Management	Additional recommended intervention and/or action
Grade 1	Continue study treatment	None.
Grade 2	• Hydration as clinically indicated • When planning next infusion prophylaxis with oral glucose lowering medication per local SOC is recommended. • Consultation with endocrinologist for diabetic patients is recommended	• Continuing occurrence of post-infusion blood glucose >500 mg/dL, based on repeated laboratory analysis despite optimal glucose lowering therapy after 2 infusions of copanlisib, **and will require dose reduction by one dose level.**
Grade ≥3	• Hydration as clinically indicated (orally, IV) • Insulin therapy per local SOC	• **Requires permanent discontinuation** of the study drug if persistent occurrence of post-infusion blood glucose >500 mg/dL based on

	• When planning next infusion consider prophylaxis with oral glucose lowering medication per local SOC • Consultation with endocrinologist is recommended	laboratory analysis, which occurred at the lowest dose level despite optimal glucose lowering therapy (after at least one cycle of treatment) and with consultation of a diabetes specialist.

Management of glucose increases on subsequent days post-copanlisib infusion

Criteria	Management	Additional recommended intervention
Grade 2 Max post-infusion glucose level of >200 mg/dL	• Oral glucose lowering medication recommended on subsequent days. • Consultation with endocrinologist is recommended	• Use of sulfonylurea/metaglinides, insulin secretagogues medications to manage increased glucose levels post-infusions are not recommended. • Treatment with glucose lowering medication suggested according to the local standard practice. • Based on the mechanisms of action and decreased risk of hypoglycemia; metformin, sodium-glucose co-transporter-2 (SGLT-2) inhibitor or dipeptidyl peptidase-4 (DPP-4) inhibitor might be useful treatment options.

Management of copanlisib-related arterial hypertension

Hypertension (CTCAE v5)	Management	Additional recommended intervention and/or action
Pre-dose measurements BP ≥150/90 mmHg	No dose should be given until recovery to <150/90 mmHg	• Consider BP lowering medication. • Dosing can proceed on the scheduled day if after at least 2 consecutive measurements BP returns to <150/90 mmHg. If BP doesn't return to <150/90 mmHg, delay dosing until next visit.
During infusion Grade 3 or ≥160/100 mmHg	Infusion can be interrupted or slowed down and administration of BP lowering therapy should be initiated	• Infusion may be resumed when BP has returned to <150/90 mmHg at the investigator's discretion or skipped. • Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion
Post-dose Drug-related grade 3 or ≥160/100 mmHg"	None	• Administration of BP lowering therapy should be initiated according to local standard of care. • Additional measurements to be performed as clinically

		indicated until recovery to <150/90 mmHg. • Subsequent study drug administrations may be reduced by 1 dose level at the investigator's discretion
Grade 4	Permanent discontinuation.	

Recommended meal timing on days of copanlisib infusion

Consumption of meals in close proximity to copanlisib infusion may exacerbate a glucose level increase. Therefore, caloric restriction is recommended on infusion days. The timing and content of meal intake and additional glucose testing (if clinically indicated) is managed and monitored by the investigators based on glucose response patterns during prior treatment days.

Scenario 1:

- Study labs drawn
- Meal after labs drawn but before copanlisib infusion
- Repeat glucose measurement prior to copanlisib infusion
    - 1 hour post-meal – repeat glucose measurement (point of care measurement is acceptable)
    - 2 hours post-meal – repeat glucose measurement (point of care measurement is acceptable)

Scenario 2:

- Meal before study labs drawn
- Study labs drawn within 1-2 hours of meal
- If labs are drawn 1-2 hours after meal, repeat glucose prior to copanlisib infusion (point of care measurement is acceptable)