Summary of Changes
Amendment #1
NCI Protocol #: NRG-GY029
Local Protocol #: NRG-GY029
NCI Version Date: December 28, 2022

CTEP reviewed and disapproved Amendment 1. Please see our responses below to the review comments we received on 12/27/2022:

#	Section	Comments
1.	Informed Consent	The SOC for the Protocol Document states that the Risk Lists for docetaxel and paclitaxel protein bound have been added to the informed consent. Neither the informed consent SOC nor the ICD document risk lists include the stated updated. Please update the SOC and ICD. **PI Response: The SOC response (Comment 3 in the below table) has been updated appropriately. Changes to the ICD are not required.**
2.	Cover Page For Regulatory Requirements	*Please revise the following language:* Regulatory documentation must be submitted to the Cancer Trials Support Unit CTSU via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance. **PI Response: The suggested changes have been made.**
3.	Cover Page Protocol Document Access	*Please revise the following language:* The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires log in with a CTEP-IAM username and password~~.~~ or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the ~~CTSU Regulatory Support System (RSS).~~ Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the

<table>
<tr><th>#</th><th>Section</th><th>Comments</th></tr>
<tr><td></td><td></td><td>CTSU members' website.

<u>PI Response: The suggested changes have been made.</u></td></tr>
<tr><td>4.</td><td>8.0 Registration and study entry procedures</td><td>Please replace this section with the language from the new version of the CTSU logistics template:

1. REGISTRATION AND STUDY ENTRY PROCEDURES

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

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

RCR requires the following registration documents:

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

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and by July 1, 2023 for all users) is required to participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU)</td></tr>
</table>

#	Section	Comments
		and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following: • Addition to a site roster; • Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN; • Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and • Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL). In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov. **PI Response: The suggested changes have been made.**
5.	8.1 IRB Approval	*Please revise the following:* **IRB Approval:** ~~For CTEP~~ As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP)- and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases ~~after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB)~~. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations. Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878). Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory

#	Section	Comments
		Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes: • Local IRB documentation • IRB-signed CTSU IRB Certification Form; and/or • Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form In addition, the site-protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed: • ~~Holds~~ Have an Active CTEP status; • ~~Active~~ Have an active status at the site(s) on the IRB/REB approval (applies to US sites only) and on at least one participating organization's roster; • If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution's record; • 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 • ~~Holds~~ Have the appropriate CTEP registration type for the protocol. **Additional Requirements** Additional site requirements to obtain an approved site registration status include: • An active Federal Wide Assurance (FWA) number • An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and • An active roster affiliation with the NCI-CIRB Signatory Institution (US sites only); and. Compliance with all applicable protocol-specific requirements (PSRs). **PI Response: The suggested changes have been made.**
6.	8.1 Downloading Site Registration Documents	*Please revise the following:* **Downloading Site Registration Documents** Download the site registration forms from the NRG-GY026 page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and ~~its~~ their associated investigators and staff participating roster to view/download site registration forms: • Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password~~;~~ or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users); • Click on Protocols in the upper left of the screen

#	Section	Comments
		○ Enter the protocol number in the search field at the top of the protocol tree; or ○ Click on the By Lead Organization folder to expand, then select NRG, and protocol # NRG-GY026. 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 initiative, IRB data will load automatically to the CTSU.) **PI Response: The suggested changes have been made.**
7.	8.1 Delegation of Tasks Log	*Please revise the following:* Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section of the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and ~~include a Master Task List, which describes~~ describe DTL task assignments, CI signature, and CTEP registration requirements~~.~~, as well as include a Master Task List. **PI Response: The suggested changes have been made.**
8.	8.2.1 Oncology Patient Enrollment Network (OPEN)	*Please revise the following language:* The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave. Requirements for OPEN access: • A valid CTEP-IAM account~~;~~ and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users); • To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type; • If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and

#	Section	Comments
		Have an approved site registration for a protocol prior to patient enrollment. **PI Response: The suggested changes have been made.**
9.	14.1 Data Submission	**1.1 Data Management/Collection** Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. Requirements to access Rave via iMedidata: • A valid CTEP-IAM account~~;~~ and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);~~-~~ and • Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Rave role requirements: • Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type; • Rave Investigator role must be registered as a Non-Physician Investigator (NPIVR) or Investigator (IVR) • Rave Read Only role must have at a minimum an Associates (A) registration type. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL. Upon initial site registration approval for the study in ~~Regulatory Support System (RSS),~~ the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff museither 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 and has not yet been taken, the link to the eLearning will appear in the Studies pane located in the center of the e in 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

#	Section	Comments
		the eLearning link study name. Site staff ~~that~~ who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in ~~RSS~~ the Regulatory application will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section ~~at www.ctsu.org/RAVE/~~ or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com. **PI Response: The suggested changes have been made.**
10.	14.4 Central Monitoring	*Please revise the following:* **Central Monitoring (CM)** Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification). Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal ~~Source Document Portal~~ (SDP) ~~-~~application. This application is also available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with any of the ~~CRA or Investigator~~ Rave roles ~~in Rave~~ on a relevant site roster can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted. Additional information on the SDP is available on the CTSU ~~members' website~~ SDP application under ~~Auditing & Monitoring > Source~~ Browser > Document ~~Portal~~ Repository in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com). **PI Response: The suggested changes have been made.**
11.	14.5 Rave-CTEP-AERS	*Please revise the following:* **1.2 Rave-CTEP-AERS integration** The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of Adverse Events (AE) entered in Rave

#	Section	Comments
	Integration	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~~ administration of the ~~Investigational Agent/Intervention~~ investigational study agent/intervention are collected using the Late Adverse Event form. Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave: • The reporting period (course/cycle) is correct; and • AEs are recorded and complete (no missing fields) and the form is query free. The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation. Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form~~.~~ (i.e., checking the box *Send All AEs for Evaluation* and save the form). Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. . Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS. In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave. Additional information about the CTEP-AERS integration is available on the CTSU members' website: • Study specific documents: *Protocols > Documents* and • *Protocol related Documents> Adverse Events* 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

#	Section	Comments
		Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf. **PI Response: The suggested changes have been made.**
12.	14.6 Data Quality Portal	*Please revise the following:* **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. ~~Review~~ Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff ~~that~~ who are rostered to a site and have access to the CTSU website. Staff ~~that~~ who have Rave study access can access the Rave study data ~~using a~~ via direct ~~link on~~ links available in the DQP modules. CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website. To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms DQP Form Status, and DQP reports modules. **PI Response: The suggested changes have been made.**

#	Section	Comments
13.	5.2.2.2	Per olaparib PI, both strong and moderate CYP3A4 inhibitor or inducers should be avoided for concomitant use. • If concomitant use of CYP3A inhibitor cannot be avoided, reduce olaparib dose as following, which can be used to update the current CSP If concomitant use cannot be avoided, reduce Lynparza dosage to: • 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor. • 150 mg twice daily when used concomitantly with a moderate CYP3A inhibi After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the l prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Phar* • As CYP3A inducers would reduce olaparib efficacy, it is strongly recommend to avoid concomitant use. the efficacy should be closely monitored if CYP3A inducers must be used. The current language for inducer part is acceptable. **PI Response: Thank you for the recommendation, however no changes will made at this time.**

Summary of Changes
Amendment #1
NCI Protocol #: NRG-GY029
Local Protocol #: NRG-GY029
NCI Version Date: December 28, 2022

CTEP reviewed and disapproved Amendment 1 on 11/10/2022. Please see our responses below the review comments:

#	Section	Comments
1.	*6.1*	Please revise this sentence added during amendment 1 to read: "Note: Substitution for paclitaxel using docetaxel or paclitaxel protein-bound particles for injectable suspension (Abraxane) is only allowed for hypersensitivity reaction. Should other issues arise, specifically a paclitaxel shortage, please contact the study team for review and approval prior to making the substitution. This will be allowed on a case by case basis and will require documentation." Neither docetaxel nor Abraxane are agents listed in this trial and paclitaxel is one agent possible in the SoC arm. **PI Response: No change has been made. It was not required as this was the language upon which CTEP and NRG came to agreement on after initial submission of this amendment and all that is required. It was discussed and agreed upon by Dr. Kohn, Dr. Aghajanian, and Dr. Johnson.**
2.	*9*	Please add new drug information sections (9.8 and 9.9) for docetaxel and paclitaxel protein-bound particles for injectable suspension (Abraxane). • Product description: • Solution preparation: • Route of administration • Agent Ordering **PI Response: The suggested language is no longer required. Please see response above.**
3.	*ICD*	Please add the risk lists for docetaxel and paclitaxel protein-bound particles for injectable suspension (Abraxane) available at: https://ctep.cancer.gov/protocolDevelopment/sideeffects/drugs.htm **PI Response: The suggested language is no longer required. Please see response to Comment #1.**

Summary of Changes
Amendment #1
NCI Protocol #: NRG-GY029
Local Protocol #: NRG-GY029
NCI Version Date: December 28, 2022

Section	Comments
Title Pages	• NCI Version Date is now December 28, 2022 • Dana Farber Cancer Institute has been added to the NRG Oncology Participating Institutions for Safety Lead-ins • Amendment 1 and version date added to document history box
TOC	• Page numbers updated
Schema	• "weekly" removed from Arm 1 text box to agree with updated dosing in Section 5.1
2.8	• "Day 8" removed to correspond with DL-1 of the safety lead-in
4.1	• Statement added immediately following timing of registration assessments and starting of C1D1 • Footnote lettering
4.2	• Updates made for clarity in Arm 1 table • Updates made for clarity in Arm 2 table • Footnote 2, in the Arm 1 table, updated to be consistent with imaging schedule in Arm 2 table
5.1	• Day 22 deleted to agree with current community standard dosing in Regimen 1 • Daily Topotecan dosing added to Regimen 3
5.2.2.2	• Additional language added for clarification and consistency regarding CYP3A Inhibitors and Inducers paragraphs
6.1	• "If substitution of paclitaxel for Docetaxel or paclitaxel protein-bound particles for injectable suspension (Abraxane) is required for reasons other than hypersensitivity reaction (e.g., drug shortage), contact the study team for review and approval prior to making the substitution" was added.
7.5.2.1	• Reporting table replaced to reflect AE reporting for commercial agents.

NRG Oncology
Four Penn Center
1600 JFK BLVD Suite 1020
Philadelphia, PA 19103
Nrgoncology.org

NRG-GY029: A Randomized Phase II trial comparing the combination of PI3K inhibitor Copanlisib (BAY 80-6946) and PARP inhibitor Olaparib (AZD2281) to standard chemotherapy in patients with recurrent platinum resistant ovarian, fallopian tube, or primary peritoneal cancer who have progressed through prior PARP inhibitor therapy

ClinicalTrials.gov Identifier NCT TBD
NCI Version Date: December 28, 2022

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

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

Protocol Agents:

Agent	Supply	NSC#	IND#	IND Sponsor
Copanlisib	CTEP	784727	IND#	DCTD, NCI
Olaparib	CTEP	747856		
Paclitaxel	Commercial	673089		
Liposomal doxorubicin	Commercial	712227		
Topotecan	Commercial	609699		

NRG Oncology Participating Institutions for Safety Lead-ins	
AZ017	Banner University Medical Center -Tucson
CA249	UC San Diego Moores Cancer Center
CA070	University of Colorado Hospital
CT009	Hartford Hospital
FL015	University of Florida Health Science Center - Gainesville
GA020	Augusta University Medical Center
IA018	University of Iowa/Holden Comprehensive Cancer Center
IL057	University of Chicago Comprehensive Cancer Center
MA036	Dana Farber Cancer Institute **(28-DEC-2022)**
MD017	Johns Hopkins Sidney Kimmel Comprehensive Cancer Center
MI020	Wayne State University – Karmanos Cancer Institute
MN022	University of Minnesota/Masonic Cancer Center
MO011	Washington University School of Medicine
NM004	University of New Mexico Cancer Center
NY016	Memorial Sloan Kettering Cancer Center
NY158	Roswell Park Cancer Institute
OH007	Ohio State University Comprehensive Cancer Center
OH027	Cleveland Clinic Foundation
OH029	Case Western Reserve/University Hospital Cleveland Medical Center
OH070	University of Cincinnati Cancer Center-UC Medical Center
OK003	University of Oklahoma Health Science Center
PA015	UPMC Hillman Cancer Center
PA075	University of Pennsylvania/Abramson Cancer Center
PA086	Fox Chase Cancer Center
PA121	Thomas Jefferson University Hospital
RI012	Women and Infants Hospital
TX035	M D Anderson Cancer Center
VA009	University of Virginia Cancer Center
VA010	Virginia Commonwealth University Massey Cancer Center
WA008	Fred Hutchinson Cancer Research Center
WI013	Medical College of Wisconsin

Document History	
Initial	**June 02, 2022**
Amendment 1	**December 28, 2022**

STUDY TEAM

PRINCIPAL INVESTIGATOR	STATISTICIAN
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Research Nurse Sarah Hindenach, BSN, RN, OCN Dana-Farber Cancer Institute 450 Brookline Avenue Boston, MA 02215 617-632-3472 Sarah_Hindenach@dfci.harvard.edu	

STUDY-SPECIFIC CONTACTS AND RESOURCES	
For questions/comments related to:	**Contact:**
Protocol Document, IRB review, informed consent documents and amendments	Leah Madden, CCRP Protocol Coordinator NRG Oncology 1600 JKF Blvd., Suite 1020 Philadelphia, PA 19103 215-854-0770 maddenl@nrgoncology.org
Data Management Including submission, eligibility	Dolores Kirschner, MPH NRG Statistics and Data Management Center - Pittsburgh 412-383-4912 kirschnerd@nrgoncology.org
Regulatory	NRG-GY-Regulatory@nrgoncology.org
NRG Oncology Gynecologic Oncology Chair	Carol Aghajanian, MD Memorial Sloan Kettering Cancer Center New York, NY 646-888-4217 Aghajanc@mskcc.org

<table>
<tr><th colspan="3">CONTACT INFORMATION (28-DEC-2022)</th></tr>
<tr><th>For regulatory requirements:</th><th>For patient enrollments:</th><th>For data submission:</th></tr>
<tr><td>Regulatory documentation must be submitted to the Clinical Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@cocc.org for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN-related questions by phone or email: 1-888-823-5923, or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires logging in with a CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users).

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) or the CTSU members' website.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e., patient eligibility or treatment-related)</u> contact the Study PI of the Lead Protocol Organization.</td></tr>
<tr><td colspan="3"><u>For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission)</u> Contact the CTSU Help Desk by phone or e-mail:
CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.</td></tr>
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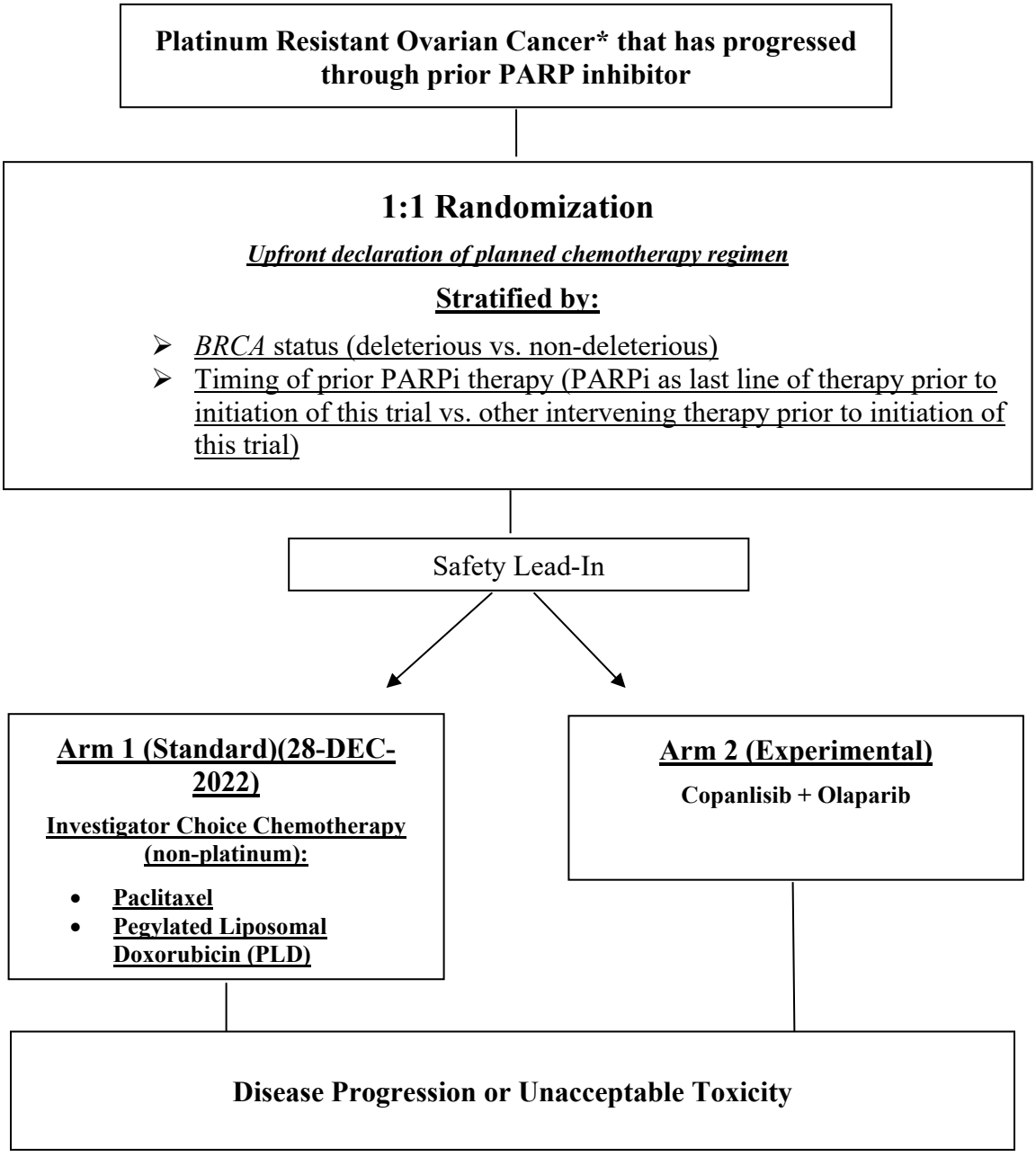
SCHEMA



***Ovarian cancer = ovarian, fallopian tube, and primary peritoneal cancer**
Eligible histology: 1) high grade serous, 2) endometrioid, grade 3, 3) Any histology with BRCA1 and/or BRCA2 deleterious mutation (germline or somatic)

1. OBJECTIVES

We hypothesize that the combination of copanlisib/olaparib will be associated with improved clinical efficacy compared to standard chemotherapy, as measured by investigator-assessed progression free survival (PFS), in recurrent platinum resistant ovarian cancer that has progressed through prior PARP inhibitor therapy.

1.1 Primary Objective

1.1.1 To assess the clinical efficacy of the combination of copanlisib/olaparib, as measured by investigator-assessed progression free survival (PFS), compared to standard chemotherapy in the setting of recurrent platinum resistant ovarian cancer that has progressed through prior PARP inhibitor therapy.

1.2 Secondary Objectives

1.2.1 To assess the clinical efficacy of the combination of copanlisib/olaparib, as measured by objective response rate (ORR), per RECIST 1.1.

1.2.2 To assess the clinical efficacy of the combination of copanlisib/olaparib, as measured by overall survival (OS), compared to standard chemotherapy in the setting of recurrent platinum resistant ovarian cancer that has progressed through prior PARP inhibitor therapy.

1.2.1 To determine the nature, frequency and degree of toxicity as assessed by CTCAE v.5.0 for each treatment arm.

2. BACKGROUND

Combination of PARP inhibitors (PARPi) with agents that inhibit homologous recombination (HR) represents an effective strategy to sensitize HR proficient cancers to PARPi (Konstantinopoulos, 2015). In our preclinical work discussed below, we have demonstrated that PI3K inhibitors (PI3Ki) inhibit HR and sensitize platinum and PARPi resistant models to PARPi olaparib.

Based on these preclinical data as well as clinical data (which are discussed below), we hypothesize that the addition of the PI3K inhibitor copanlisib to olaparib will sensitize platinum resistant ovarian cancers that have progressed through prior PARPi to olaparib and that the combination of olaparib and copanlisib will fare better than standard chemotherapy in this setting.

2.1 Initial Evidence of PI3Ki/PARPi synergism in Breast Cancer Models

In vivo synergy of the oral pan-class I PI3K inhibitor BKM120 with the PARPi olaparib was initially reported in BRCA-proficient triple negative breast cancer (TNBC) (Ibrahim, 2012) and in a mouse model of BRCA1-related breast cancer (Juvekar, 2012). In BRCA-proficient TNBC cells, PI3K inhibition led to DNA damage, downregulation of BRCA1/2, gain in poly-ADP-ribosylation, and subsequent sensitization to PARP inhibition. Specifically, siRNA-induced silencing of *PIK3CA* in a *BRCA* wild type, *PTEN* mutant triple-negative cell line induced accumulation of phosphorylated histone H2AX (γ-H2AX), a marker of DNA damage, inferring that the loss of *PIK3CA* results in genomic instability, which was enhanced by the addition of the PARPi olaparib. Furthermore, pharmacologic

inhibition with a pan-PI3K inhibitor (BKM120) was accompanied by a concomitant reduction in the expression of BRCA1 and BRCA2 and a reduction in the cellular capacity to conduct HR (Ibrahim, 2012, Juvekar, 2012). Consistent with the reduction in BRCA1/2 expression, PI3K pathway blockade induced sensitivity to PARPi olaparib and ABT888 *in vitro*. These findings were validated *in vivo* in 3 patient-derived xenografts (PDX) of triple-negative breast cancer, which confirmed elevated γ-H2AX and decreased BRCA1 expression following treatment with a PI3K inhibitor in two of the three models. Furthermore, the decrease in BRCA1 expression correlated with an enhanced response to the combination of PARP inhibitor and PI3K inhibitor when compared with either drug alone. Mechanistically, downregulation of BRCA1/2 was mediated by ERK-dependent activation of the ETS transcription factor, which suppresses BRCA gene transcription, thereby causing a deficiency in HR and concomitant PARP inhibitor sensitivity (Ibrahim, 2012, Rehman, 2012).

Synergism between PI3Ki and PARPi was similarly demonstrated in the context of *BRCA1* deficiency (Juvekar, 2012) in the *MMTV-CreBrca1$^{f/f}$p53$^{+/-}$* mouse (a genetically engineered model of spontaneous breast cancer in which tumors carry a hypomorphic *BRCA1* allele) whereby both AKT and ERK phosphorylation are increased while PTEN and INPP4B expression are absent. FDG–positron emission tomographic (PET) imaging was used to determine the effects of PI3K inhibition, illustrating that the initially avid FDG uptake in tumors was reduced by a median of 46.7% within 48 hours of treatment with the pan-PI3K inhibitor BKM120, a biomarker effect sustained over a period of 2 weeks with continued treatment. This response was accompanied by a decrease in the levels of phosphorylated AKT and a reduction in the vascularity of tumors. As in the BRCA-proficient TNBC models, PI3K inhibition led to an increase in γ-H2AX accumulation and a reduction in AKT phosphorylation, which was exacerbated by the addition of a PARPi. Of note, RAD51 foci formation and residual baseline HR function in the *BRCA1* hypomorphic model was completely blocked by treatment with a PI3K inhibitor; a similar result was obtained by use of PI3K siRNA. Significant suppression of tumor growth was also observed in two patient-derived xenografts, with sustained responses to the combination of a PI3Ki and a PARPi. A subsequent report showed that the enhanced DNA damage induced by PI3Ki may be a consequence of impaired production of nucleotides needed for DNA synthesis and DNA repair (Juvekar, 2016). Specifically, PI3K inhibition disproportionately affects the nonoxidative pentose phosphate pathway that delivers Ribose-5-phosphate required for base ribosylation and induces reduction in all four nucleotide triphosphates.

2.2 In Vivo PI3Ki/PARPi Synergism in Platinum Resistant and PARPi Resistant PDX Models of High Grade Serous Ovarian Cancer (HGSOC)

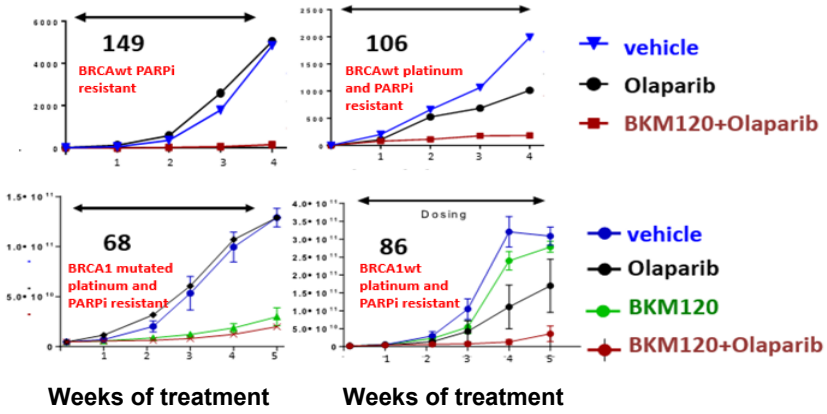
We have explored whether two PI3Ki (BKM120/buparlisib and BYL719/alpelisib) could enhance the efficacy of the PARPi olaparib in a group of ovarian cancer (OC) PDX models that have been established and molecularly characterized at Dana-Farber Cancer Institute; these HGSOC PDX models have been previously shown to faithfully model the clinical spectrum and responsiveness to standard-of-care chemotherapy (Liu, 2016). All models presented below (except for DF149) are from patients who have developed platinum resistant disease. Furthermore, all PDX models presented below are resistant to olaparib monotherapy. Of note, one of the PDX models (DF68) is from a patient who had progressed

through prior PARPi therapy.

2.2.1 Olaparib/BKM120 in platinum resistant and PARPi therapy

The evaluation of pan-PI3K inhibitor BKM120 (IC50 for p110α/β/δ/γ is 52 nM/166 nM/116 nM/262 nM respectively) in combination with olaparib in HGSOC PDX models is shown in Figure 1. All models presented in Figure 1. (except for DF149) are from patients who have developed platinum resistant disease and all PDX models in Figure 1. are resistant to olaparib monotherapy. Of note, DF68 was derived from a patient who progressed through prior PARPi therapy. As shown in Figure 1, in all these models there was evidence of growth inhibition to the combination of BKM120 with olaparib, while there was no response to olaparib alone.

Figure 1. Olaparib/BKM120 in HGSOC PDX models.



2.2.2 Olaparib/BYL719

We also assessed the alpha specific PI3-Kinase inhibitor BYL719 (IC50 for p110α/β/δ/γ is 5nM/1250nM/290nM/250 nM respectively) in combination with olaparib in platinum resistant and PARPi resistant HGSOC PDX models (Figure 2). All models presented in Figure 2 are from patients who have developed platinum resistant disease and all PDX models are resistant to olaparib monotherapy.

As shown in Figure 2, in all these models there was evidence of growth inhibition to the combination of BYL719 with olaparib, while there was no response to olaparib alone.

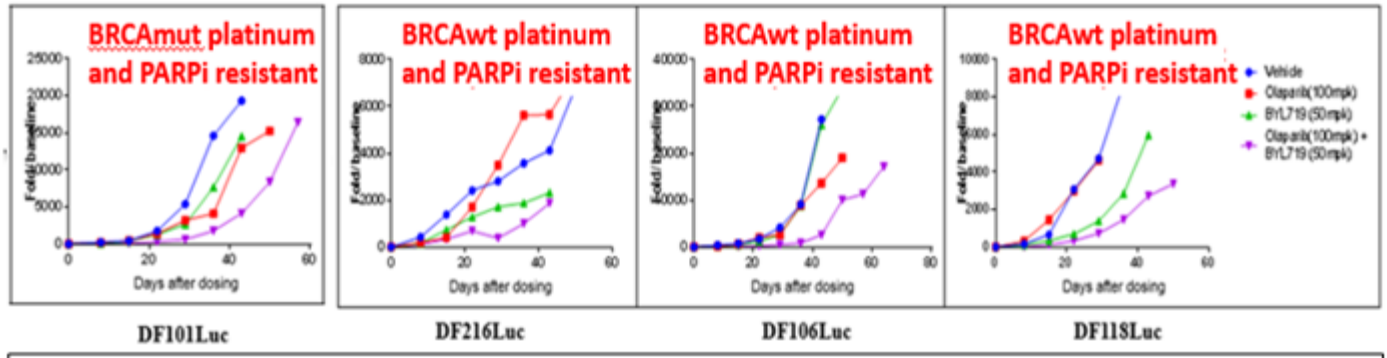
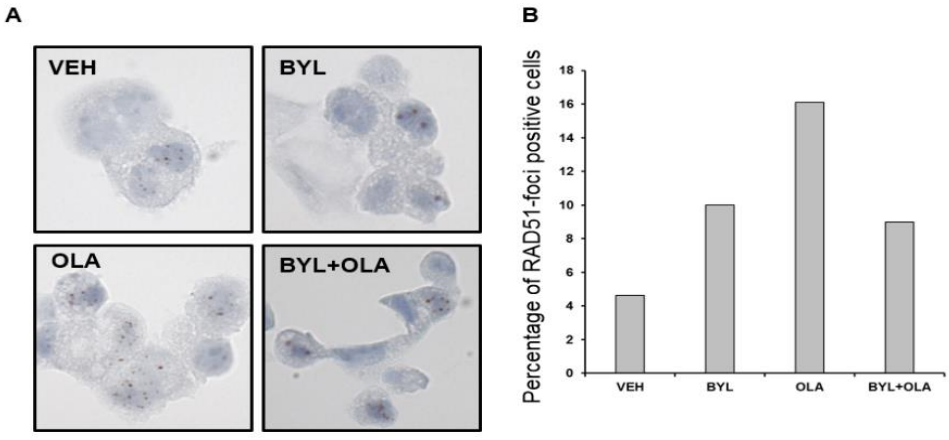


Figure 2. Olaparib/BYL719 in platinum resistant and PARPi resistant HGSOC PDX models.

2.3 In Vivo Proof of Mechanism Studies: PI3Ki inhibits HR in Platinum and PARPi Resistant

In addition to the efficacy studies, we have performed proof of mechanism studies in the ovarian PDX models. As shown in Figure 3, BYL719 (alpelisib) inhibits HR in the platinum and PARPi resistant HGSOC DF216 model as evidenced by the decrease in the RAD51 foci positive cells after treatment with olaparib/alpelisib compared to treatment with olaparib alone. Specifically, ascites from mice harboring PDX model DF216 was collected and treated ex vivo with vehicle (VEH), BYL719 (BYL) or olaparib (OLA) individually or a combination of BYL719 and OLA for 48 hours. Paraffin sections of these cells were stained using an antibody specific to RAD51 (Figure 3A). The number of RAD51 foci/cell was highly reduced in the presence of olaparib/alpelisib when compared to olaparib treated cells (Figure 3B).

Figure 3. BYL719 inhibits HR in the platinum and PARPi resistant DF216 HGSOC PDX



2.3.1 Similar data have been obtained with BKM120 in breast models. Specifically, BKM120 inhibits HR as evident by the absence of RAD51 foci formation after ionizing radiation (IR) in breast cancer cells isolated from primary tumors from MMTV-CreBrca1$^{f/f}$Trp53$^{+/-}$mice treated with BKM120 (Figure 4E) compared to cells treated with vehicle control (Figure 4C). As evident in Figure 4C, vehicle treated cells form RAD51 after IR while BKM-120 treated cells do not (Figure 4E).

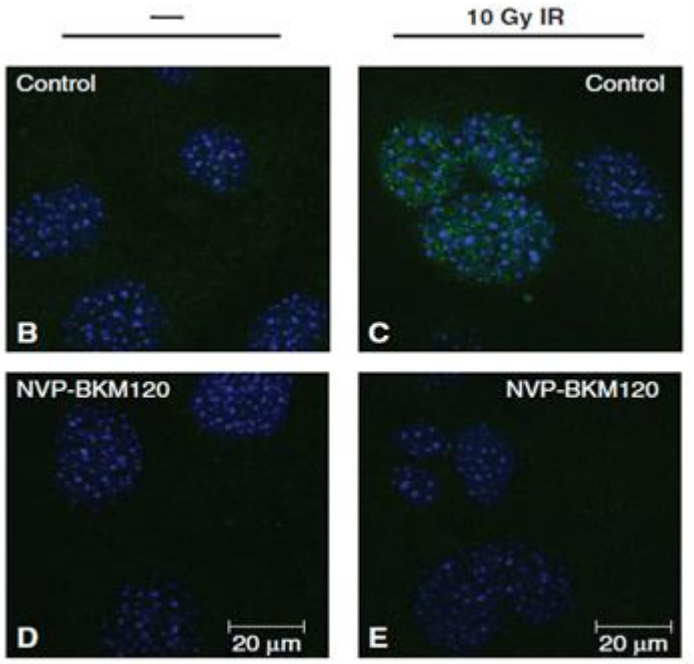


Figure 4. BKM120 inhibits HR in the MMTV-CreBrca1$^{f/f}$Trp53$^{+/-}$model

2.4 Clinical Evaluation of PI3Ki/PARPi Combinations

We have now completed Phase I evaluation of both BKM120/olaparib and BYL719/olaparib in ovarian and breast cancer patients.

2.4.1 Phase I Trial of Olaparib/BKM120

Initially, we performed a Phase I dose escalation study BKM120 and olaparib for the treatment of recurrent ovarian and breast cancer (BC) patients with dose expansion cohorts in each tumor type (Matulonis, 2016). Detailed results of this study were published previously (Matulonis, 2016). Anticancer activity was observed in BC and OC and in patients both with and without BRCA mutations. Specifically, in the ovarian cancer cohort, the objective response rate (ORR) by RECIST 1.1 was 29% (12 of 41 patients, all partial responses (PRs). The ORR was seen irrespective of platinum sensitivity status; specifically, ORR was 32% in platinum sensitive disease (6 of 19 patients) and 27% in platinum resistant disease (6 of 22 patients) (Matulonis, 2016).

2.4.2 Phase I Trial of Olaparib/BYL719

We have also evaluated the alpha specific PI3-Kinase inhibitor BYL719 in combination with olaparib in a Phase I study in recurrent ovarian cancer and breast cancer (BC) (Konstantinopoulous, 2019).

Olaparib was administered twice daily (tablet formulation) and BYL719 daily on a 28-day cycle, both orally. Eligibility included recurrent TNBC or high grade serous OC, or any histology of OC or BC with presence of a germline BRCA mutation and performance status of 0-1. Patients with platinum sensitive or resistant or refractory OC were eligible; and prior PARP inhibitor use was allowed. Dose-expansion cohorts at the MTD were enrolled for both BC and OC.

The olaparib/alpelisib combination showed evidence of clinical activity, with an ORR of 36% (10/28 evaluable patients, all partial responses), (Figure 5). The proportion of all OC patients achieving a PR was similar for those with and without germline *BRCA* mutations (30% *vs* 35% respectively), (Figure 6) and was 35% in patients with platinum resistant/refractory disease. The objective response rate in patients which were BRCAwt (germline and somatic) and had platinum resistant/refractory tumors was 33%, markedly higher than that seen with olaparib monotherapy (4%) in prior studies (Gelmon, 2011, Moore, 2019).

Figure 5. Olaparib/BYL719: Best response for target lesions by patient, based on maximal percentage of tumor reduction

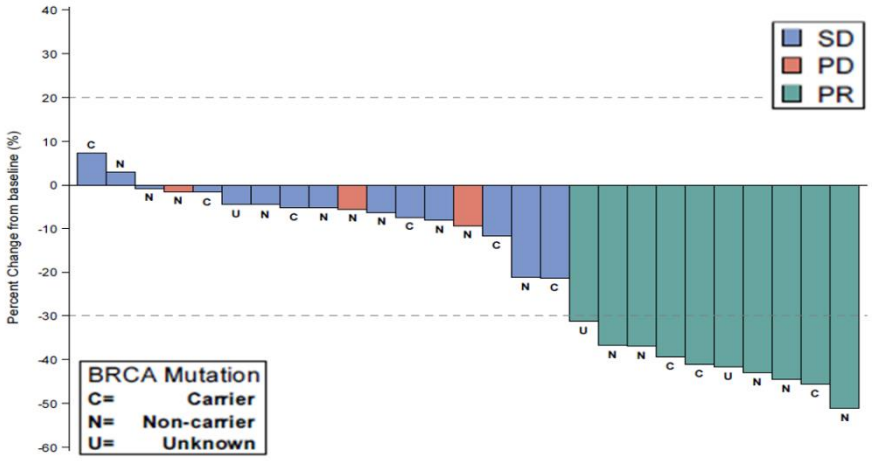


Figure 6. Ovarian Cancer Cohort: Best overall response by RECIST by BRCA mutation status (all patients)

	gBRCA mutation status						Overall	
	gBRCA mutation carrier		gBRCA mutation non-carrier		gBRCA mutation unknown			
	N	%	N	%	N	%	N	%
Best Response PR	3	30.0	6	35.3	1	100	10	35.7
SD	7	70.0	7	41.2	-	-	14	50.0
PD	-	-	3	17.6	-	-	3	10.7
Unevaluable	-	-	1	5.9	-	-	1	3.6
Total	10	100	17	100	1	100	28	100

2.5 Copanlisib

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). Tumors with mutations in PIK3CA or loss of PTEN have been found to be sensitive to inhibitors targeting PI3Kα. PI3Kδ-specific inhibitors have shown remarkable therapeutic efficacy in some human leukemias and lymphomas (Yang *et al*., 2015). Inhibition of PI3Kδ in the B-cell malignancies was shown to attenuate the responsiveness of the tumor cells to supportive stimuli from the microenvironment (Okkenhaug and Burger, 2016). Inactivation of PI3Kδ appears to break regulatory T-cell (Treg)-mediated immune tolerance unleashing cytotoxic T-cell response that leads to tumor regression (Ali *et al*., 2014).

Copanlisib is a novel intravenous (IV) pan-class I PI3K inhibitor with predominant inhibitory potency against δ and α PI3K isoforms (Copanlisib Investigator's Brochure, 2018). 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).

Nonclinical Studies

Copanlisib free base (BAY 80-6946) is an active ingredient of copanlisib dihydrochloride salt (BAY 84-1236). A majority of nonclinical data were produced using the copanlisib free-base.

Mechanism of Action

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

Copanlisib has potent and broad *in vitro* antitumor activity (IC_{50} of 1-760 nmol/L) in cancers of the breast, ovary, ovary, prostate, colon, lung, liver, brain, kidney, melanoma, pancreas, fibrosarcoma, and in various hematological cancers (Copanlisib Investigator's Brochure, 2018). Copanlisib effectively inhibits tumor growth in diffuse large B-cell lymphoma (DLBCL) animal models where the PI3Kδ-selective inhibitor idelalisib is not active. Intermittent dosing results in improved efficacy with better tolerability.

Nonclinical Pharmacokinetics

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 to those from single-dosing studies and suggested no drug accumulation in plasma.

In tumor xenograft model studies, the efficacious exposure of copanlisib, expressed as the area under the concentration-time curve (AUC) for the unbound/free drug (AUC_u) in plasma, was estimated to be 370 mcg•h/L in rats and 170-460 mcg•h/L in mice based on weekly dosing (Copanlisib Investigator's Brochure, 2018).

Copanlisib had a higher clearance (16 L/kg/h), shorter $t_{1/2}$ (0.7 h) and smaller V_d (12.9 L/kg) in mice than rats (Liu *et al*., 2013). 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.

Nonclinical Pharmacology and Metabolism

The extent of plasma protein binding of copanlisib was low in various species with free fractions between 10% and 42% (15.8% in human plasma). Copanlisib demonstrated high distribution from blood to the organs and tissues and moderate penetration of the blood-

brain barrier (BBB) and placental barrier, and high affinity to melanin-bearing tissues (Copanlisib Investigator's Brochure, 2018).

Copanlisib is primarily metabolized by the cytochrome P450 (CYP) isoform 3A4 (CYP3A4), while CYP1A1 contributes to a minor extent (<10%) based on *in vitro* data (Copanlisib Investigator's Brochure, 2018). Copanlisib is a weak substrate of permeability 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 by copanlisib. Copanlisib also inhibits P-gp (IC_{50} 7-7.6 mcmol/L) and BCRP (IC_{50}=11.5 mcmol/L). Furthermore, copanlisib was a strong inhibitor of the drug transporter multidrug and toxin extrusion protein 2 (MATE2K).

Nonclinical Safety and Toxicity

Based on clinical pathology and morphological findings in repeat-dosing IV studies, target organs were lymphoid and hematopoietic system, liver, kidneys, teeth, bone, heart, male, and female genital systems in the rat (Copanlisib Investigator's Brochure, 2018). Dogs showed adverse effects in the lymphoid and hematopoietic system, stomach, and male genital system. Intravenous 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. 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 [Cmax,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 (Copanlisib Investigator's Brochure, 2018). 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 the rat starting at low doses. Copanlisib was not genotoxic *in vitro* or *in vivo*. Appropriate precautions should be taken to avoid pregnancy in female subjects included in the clinical trials.

There is no evidence that copanlisib has phototoxic potential (Copanlisib Investigator's Brochure, 2018).

Effects in Humans

Drug-Drug Interactions

In vitro studies in human hepatocytes indicate that CYP3A4 is a major metabolizer (>90%)

while CYP1A1 contributes <10% to metabolism of copanlisib (Investigator's Brochure, 2018). Preliminary results of copanlisib co-administered with rifampin, a strong inducer of CYP3A4, resulted in 63% decrease in the mean AUC of copanlisib with a minor effect on C_{max} (15%). Therefore, the concomitant use of copanlisib and strong inducers of CYP3A4 (rifampin, phenytoin, carbamazepine, phenobarbital, enzalutamide, mitotane, and St. John's Wort, *etc.*) should be avoided. Co-administration of itraconazole (200 mg), a strong inhibitor of CYP3A4 with copanlisib (60 mg IV) resulted in 1.53-fold increase in copanlisib AUC but had no effect on its C_{max}. Increases in AUC between 1.25-fold and 2-fold are considered weak. No dose adjustment of copanlisib is necessary when co-administered with CYP3A4 inhibitors but patients need to be closely monitored for toxicity when co-administred with strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin, ritonavir, indinavir, nelfinavir, saquinavir, *etc.*). Because copanlisib is a substrate of P-gp and BCRP, inducers/inhibitors of these transporters have potential to affect copanlisib exposure.

Summary of Clinical Safety of Copanlisib and Special Warnings (Copanlisib Investigator's Brochure, 2018)

In clinical studies, the most serious adverse events (SAEs) reported in patients with NHL (indolent and aggressive) and solid tumors treated with copanlisib monotherapy included pneumonitis, lower respiratory tract infections (including pneumonia), and febrile neutropenia (Copanlisib Investigator's Brochure, 2018). In clinical studies, the most common adverse reactions (≥20%) were hyperglycemia, decreased general strength and energy (including fatigue and asthenia), hypertension, diarrhea, nausea, leukopenia and neutropenia.

<u>Infections</u>
Serious infections (including fatal infections) occurred in 19% of patients treated with copanlisib monotherapy (Copanlisib Investigator's Brochure, 2018). The most common infections were pneumonia, lung infection and lower respiratory tract infection. Patients should be monitored for symptoms of infection and copanlisib dosing should be interrupted for Grade ≥3 infections until resolution. *Pneumocystis jirovecii* pneumonia occurred in 0.6% of patients treated with copanlisib. Prophylaxis should be considered for patients at risk for this infection, and copanlisib should be interrupted for any grade of this infection.

<u>Non-Infectious Pneumonitis</u>
Non-infectious pneumonitis (all events were Grade ≤3) occurred in 5% of patients (Copanlisib Investigator's Brochure, 2018). Treatment with copanlisib should be permanently discontinued in patients experiencing non-infectious pneumonitis of Grade ≥3 and if Grade 2 recurs.

<u>Neutropenia and Febrile Neutropenia</u>
Grade 4 neutropenia occurred in 9.1% of patients, including 1.9% of patients having febrile neutropenia (Copanlisib Investigator's Brochure, 2018).

Transient Hypertension
Treatment with copanlisib may result in transient hypertension; blood pressure increases were seen after cycle 1 day1 infusion of copanlisib and started to decrease approximately 2 hours post-infusion. Serious hypertension (Grade ≥3) occurred in 0.9% of patients (Copanlisib Investigator's Brochure, 2018). Copanlisib should be permanently discontinued for uncontrolled hypersensitivity or the Grade 4 event.

Transient Hyperglycemia
Treatment with copanlisib may result in transient hyperglycemia, with a peak in blood glucose level peak observed at 5-8 hours post-infusion followed by subsequent decline to baseline (Copanlisib Investigator's Brochure, 2018). More serious hyperglycemia (Grade ≥3) occurred in 0.9% of patients. Optimal glucose levels should be achieved before each infusion of copanlisib. Copanlisib dosing should be delayed, reduced, or permanently discontinued depending on severity of the event.

Embryo-Fetal Toxicity
Based on the mechanism of action and non-clinical study finding in rats, copanlisib may cause embryo-fetal harm (Copanlisib Investigator's Brochure, 2018). Copanlisib should not be used during pregnancy. Highly effective contraception in addition to a barrier method should be used by males and females of child-bearing potential.

Pregnancy and Lactation
There are no data on the use of copanlisib in pregnant women (Copanlisib Investigator's Brochure, 2018). It is not known whether copanlisib is excreted in human milk. Nonclinical studies in lactating rats showed that ~2% of radioactively labeled copanlisib was excreted into milk. Therefore, copanlisib can potentially harm infants and breastfeeding must be discontinued while on copanlisib treatment.

Recommended Phase 2 Dose of Copanlisib as Monotherapy (Copanlisib Investigator's Brochure, 2018)

The maximum tolerated dose (MTD) of a single-agent copanlisib in non-diabetic patients with solid malignancies was 0.8 mg/kg 1-hour IV administered once weekly for 3 weeks (days 1, 8, and 15) on a 28-day cycle (Copanlisib Investigator's Brochure, 2018). No impact of either body weight, body surface area (BSA), or other body size-related factors was found on the clearance of copanlisib, which was the basis to switch to a fixed-dose regimen of copanlisib based on the population PK.

The recommended phase 2 dose (RP2D) of copanlisib monotherapy is 60 mg 1-hour IV given once weekly for 3 weeks (days 1, 8, and 15) on 4-week cycle. A dose reduction to 45 mg for toxicities is allowed. No dose adjustment is required in patients with mild or moderate renal impairment or patients with mild hepatic impairment.

The choice of copanlisib is supported by our preclinical data of olaparib/BKM120 and olaparib/alpelisib in the OC PDX models which indicate that pan-class I PI3K inhibition and alpha-specific PI3K inhibition are effective in sensitizing to PARPi therapy. The preclinical

data provided and in the literature (Juvekar, 2012, Rehman, 2012, Juvekar, 2016), as well as our clinical data (Matulonis, 2016, Konstantinopoulos, 2019) suggest that there is no difference between the pan-PI3Ki/PARPi (BKM120/olaparib) and the alpha-specific PI3Ki/PARPi (BYL719/olaparib) and that they both are efficacious. Accordingly, we anticipate that copanlisib, which is a pan class-I PI3K inhibitor with predominant activity against the alpha and delta isoforms, will be effective in sensitizing to the PARPi olaparib, similar to BYL719 and BKM120.

Agent / IC50 (nM)	**α isoform**	**β isoform**	**γ isoform**	**δ isoform**
BKM120 (buparlisib)	**52**	**166**	**116**	**262**
BYL719 (alpelisib)	**5**	1250	290	250
Copanlisib	**0.5**	**3.7**	**6.4**	**0.7**

Table 1. IC50s of BKM120, BYL719 and copanlisib for the α/β/γ/δ PI3K isoforms. Copanlisib is a pan-PI3K inhibitor with predominant activity against the alpha and delta isoforms.

In terms of safety, unlike BKM120 (buparlisib), copanlisib has not been associated with CNS toxicity. Specifically, neurotoxicity was not seen in clinical trials of single agent copanlisib in hematologic malignancies (Dreyling, 2017, Markham, 2017, Patnaik, 2016). This differs from our previous clinical experience with BKM120 and may be partly explained by the since-discovered CNS-penetrating abilities of BKM120 (de Gooijer, 2018), which have led to clinical trials of BKM120 in glioblastoma. Overall, copanlisib is well tolerated and has received FDA approval in follicular lymphoma (Markham, 2017).

2.6 Rationale for Copanlisib/Olaparib in patients with platinum resistant ovarian cancer that has progressed through prior PARPi

This is a randomized phase 2 trial comparing the combination of the PI3-Kinase inhibitor copanlisib and the PARP-inhibitor olaparib to standard non-platinum chemotherapy in patients with recurrent platinum resistant ovarian, fallopian tube, or primary peritoneal cancer who have progressed through prior PARP-inhibitor therapy.

Given the approval of PARPi as maintenance therapy after platinum-based chemotherapy both in the upfront and the recurrent setting regardless of BRCA mutation and HR status, an important clinical question that has evolved is what would be the ideal therapy for patients who progress on PARPi therapy. A number of these patients will stay on PARPi maintenance therapy for less than 6 months and would hence be characterized as platinum resistant OR will eventually become platinum resistant. Based on the preclinical and clinical data discussed above, we hypothesize that rechallenging these patients with PARPi therapy (olaparib) in combination with the PI3K inhibitor (copanlisib), will fare better than standard chemotherapy in this setting (i.e., in patients with platinum resistant ovarian cancers which have already progressed through PARPi therapy).

The rationale for this study is supported by preclinical in vivo data in PDX models, whereby both olaparib/BYL719 and olaparib/BKM120 showed activity in platinum resistant and PARPi resistant HGSOC PDX models (Figures 1 and 2) including a model (DF68) taken from a patient who had progressed through prior PARPi.

In our proof of mechanisms studies in vitro and in vivo, we have shown that PIK3i (BKM120 and BYL719) inhibit homologous recombination (HR), i.e., induce "BRCAness", and thus sensitize HR proficient tumors to PARPi olaparib.

The rationale behind evaluating olaparib/copanlisib in this cohort of OC patients is further supported by the findings of the olaparib/BKM120 and olaparib/BYL719 studies discussed above. In these studies, ORR of approximately 30% was observed in recurrent ovarian cancer regardless of platinum sensitivity status and regardless of BRCA mutation status, with an ORR of 27% for olaparib/BKM120 and 35% for olaparib/BYL719 in recurrent platinum resistant disease. Notably, among non-BRCA mutation carriers with platinum resistant disease, the ORR of olaparib/BYL719 was 33%, much higher than what expected from olaparib monotherapy, which is 4% in this population (Gelmon, 2011).

Given that platinum resistant ovarian cancers that have progressed through prior PARPi are enriched for HR proficiency (Konstantinopoulos, 2015), and based on our preclinical data, we hypothesize that copanlisib will inhibit HR, induce "BRCAness" and therefore sensitize these tumors to olaparib and thus the combination of olaparib and copanlisib will fare better than standard non-platinum chemotherapy in this setting.

The choice of copanlisib is supported by the preclinical data which indicate that pan-class I PI3K inhibition and alpha-specific PI3K inhibition are effective in sensitizing to PARPi therapy. The preclinical data provided and in the literature (Juvekar, 2012, Rehman, 2012, Juvekar, 2016), as well as our clinical data (Matulonis, 2016) suggest that there is no difference between the pan-PI3Ki/PARPi (BKM120/olaparib) and the alpha-specific PI3Ki/PARPi (BYL719/olaparib) and that they both are efficacious.

Accordingly, we expect that copanlisib, which is a pan class-I PI3K inhibitor with predominant activity against the alpha and delta isoforms, will be effective in sensitizing to the PARPi olaparib, similar to BYL719 and BKM120. Furthermore, copanlisib is well tolerated and has received FDA approval in follicular lymphoma (Markham, 2017) and, unlike BKM120 (buparlisib), copanlisib has not been associated with CNS toxicity (Dreyling, 2017, Markham, 2017, Patnaik, 2016).

2.7 Randomized Phase II Trial

This is a randomized phase 2 trial comparing the combination of copanlisib and olaparib to standard non-platinum chemotherapy in patients with recurrent platinum resistant ovarian, fallopian or primary peritoneal cancer which has progressed through prior PARPi therapy.

Patients will be randomized 1:1 to olaparib/copanlisib or standard chemotherapy in an open-label manner. The planned standard of care chemotherapy regimen will be declared by the investigator prior to randomization. Standard non-platinum regimens will include pegylated

liposomal doxorubicin (PLD or Doxil), weekly paclitaxel or topotecan (weekly regimen). Use of chemotherapy in the standard arm will not be allowed if these drugs have been used previously in the recurrent setting (e.g., if a patient has already received PLD (alone or in combination) in the recurrent setting, PLD cannot be used in the standard arm). Treatments will take place in an outpatient setting. Due to the differing schedules and routes of administration, patients will not be blinded. Two stratification factors will be included: i) *BRCA 1/2* status (Known or suspected deleterious germline OR somatic BRCA variant VERSUS non-deleterious/benign germline and somatic BRCA AND unknown somatic BRCA status) and ii) timing of prior PARPi therapy (PARPi as last line of therapy prior to initiation of this trial VERSUS other intervening therapy prior to initiation of this trial).

Tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI performed once every 8weeks (+/- 7 days) for the first year and every 12 weeks (+/- 7 days) after the first year, and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression is confirmed according to RECIST 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue on the protocol-outlined schedule until progression (or initiation of subsequent therapy). After 1 years of protocol therapy or follow-up (measured from approximately cycle 1, day 1), imaging studies will be conducted every 12 weeks.

Based on the results of the phase I trial of copanlisib/olaparib/durvalumab (NCI 10217; NCT03842228), dosing of experimental arm will be: 45 mg Copanlisib IV days 1, 8, 15 and 300 mg Olaparib PO BID of a 28-day cycle. An initial safety lead-in will be performed as described below.

Specifically, in the Phase I NCI 10217 dose escalation study, in dose level 1 (DL1, copanlisib 45mg IV, Days 1,8,15 + olaparib 200mg po BID) 3 patients (all evaluable) were enrolled and no DLT was observed. However, rash occurred in all 3 patients, so 3 additional patients (all evaluable) were enrolled in the same DL1 (copanlisib 45mg IV, Days 1,8,15 + olaparib 200mg po BID) with 25 mg Benadryl IV prior to every copanlisib infusion initiated at C1D1. One DLT (LFT elevation) was observed, and rash was observed in 2 of these 3 patients. Therefore, 3 additional patients (all evaluable) were enrolled in the same DL1 with the addition of 4 mg dexamethasone prior to every copanlisib infusion initiated at C1D1 to mitigate/prevent development of rash. No DLTs were observed and only one patient developed G1 rash. This prompted use of 25mg of diphenhydramine and 4 mg dexamethasone prior to every copanlisib infusion for all subsequent patients. Overall, 9 patients (all evaluable) were enrolled in DL1 (copanlisib 45mg IV, Days 1,8,15 + olaparib 200mg po BID) and only 1 DLT was observed (LFT elevation) prompting escalation to the next dose level (DL2).

DL2 (copanlisib 45mg IV, Days 1,8,15 + olaparib 300mg po BID) was also well tolerated without DLTs (0 DLTs out of three evaluable patients), prompting escalation to DL3 (copanlisib 60mg IV, Days 1,8,15 + olaparib 300mg po BID). Of the 6 patients enrolled in DL3, 2 patients were taken off study because of toxicities prior to restaging (one patient was an official DLT while the other was not an official DLT because he stopped olaparib on his

own and was therefore deemed unevaluable for DLT). Furthermore, a third patient in DL3 had G3 platelet decrease and withdrew consent after 2.5 weeks on trial to pursue other treatment. Therefore, based on the toxicity observed in DL3, the recommended phase 2 dose used in the current study is the DL2 regimen of copanlisib 45mg IV, Days 1,8,15 + olaparib 300mg po BID.

This trial addresses a population of patients with OC that is only expected to grow with the recent FDA approvals allowing wider use of PARP inhibitors in upfront and recurrent setting regardless of BRCA mutation and HR status. Patients with tumors which have progressed while on PARP inhibitor therapy and have become platinum resistant represent a great unmet need and face important therapeutic challenges: (1) subsequent chemotherapies do not address the restoration of homologous recombination the most prevalent mechanism of PARPi resistance; (2) there are no currently approved combination therapies that incorporate rechallenge with a PARP after progression through prior PARP, potentially prematurely truncating the therapeutic benefit of a PARP; and (3) there are very few trials that allow prior PARP exposure and even fewer allowing progression while on prior PARP inhibitor therapy.

Demonstration of clinical efficacy with copanlisib/olaparib in patients with platinum resistant tumors who have progressed through prior PARPi would have significant implications on future practice. This would confirm the biologic rationale and mechanism for restoring PARP inhibitor sensitivity and could inform on future therapeutic combinations.

2.8 Rationale for Copanlisib/Olaparib Starting Dose Regimen (02-JUN-2022)

In this hypothesis generating Phase 2 study, the rationale and additional considerations for the starting dosing regimen of copanlisib (45 mg on Day 1, 8 and 15 of a 28-day cycle) and olaparib (300 mg QD) include the following:

a) The starting dosing regimen of copanlisib (45 mg on Day 1, 8 and 15 of a 28-day cycle) and olaparib (300 mg QD) was based on the MTD identified in the dose escalation part of Study NCI 10217 (NCT03842228). Given that NRG-GY029 evaluates an extremely challenging patient population (patients with platinum resistant ovarian cancer who have progressed through prior PARP inhibitor (PARPi) therapy) with no effective salvage treatment options, we employ the maximum tolerated dose of copanlisib (45 mg on Days 1, 8 and 15 of a 28-day cycle) plus olaparib (300 mg po BID) as determined in the NCI 10217 study. This strategy will afford these patients the maximum tolerated doses of olaparib/copanlisib that were deemed safe.

b) In NCI 10217, the starting dosing regimen of copanlisib 45mg IV, Days 1,8,15 + olaparib 300 mg po BID was well tolerated without DLTs (0 DLTs out of three evaluable patients). Nonetheless, in NRG-GY029, the safety and tolerability of this dosing regimen of copanlisib/olaparib will be further evaluated in a safety run-in

whereby at least 10 patients will be assessed in this dose as described in our protocol (section 15.4.1).

c) If the copanlisib 45mg IV, Days 1,8,15 + olaparib 300mg po BID is not tolerated in the safety run-in, then an alternative dosing regimen of copanlisib (45mg on Days 1, 8 and 15 of a 28-day cycle) plus olaparib (300 mg po BID) will be evaluated for safety and tolerability, again in at least 10 patients.

d) The starting dosing regimen of copanlisib (45 mg on Day 1, 8 and 15 of a 28-day cycle) and olaparib (300 mg QD) was not only well tolerated but also showed evidence of anti-tumor activity among patients who had previously received a PARP-inhibitor. Specifically, one patient with ovarian cancer who had previously received niraparib exhibited shrinkage of her tumor by 17% compared to baseline as well as experienced a drop in her CA125 by more than 50% (from 167.6 to a nadir of 55.4). Of note, this patient stayed on study for 8 cycles, i.e., more than 6 months. This is highly relevant to the patient population of NRG-GY029 which includes patients who have progressed through prior PARPi therapy.

e) Given that all patients enrolled in NRG-GY029 will have progressed through prior PARPi therapy, our intention is to rechallenge these patients with the highest tolerable dose of PARPi therapy, in this case olaparib 300mg BID that was the MTD in NCI 10217.

f) The preclinical rationale behind use of combined PARP/PI3K blockade is based on the fact that inhibition of PI3K pathway leads to abrogation of homologous recombination repair (HRR) and sensitization to PARPi therapy. Based on PK and PD data from copanlisib monotherapy, the on-target inhibition of the PI3K pathway by copanlisib occurs in a dose-dependent manner. Specifically, treatment with copanlisib reduced the PD marker pAKT in surrogate tissue platelet-rich plasma (PRP), with a median decrease up to 73.75% at the 0.4 mg/kg dose level and up to 79.60% at the 0.8 mg/kg dose level compared with baseline. Furthermore, treatment with copanlisib was associated with transient modulation of blood glucose with corresponding changes in C-peptide and insulin in a dose-dependent manner (0.8 mg/kg > 0.4 mg/kg). In addition, exposure-PD biomarker relationship studies were evaluated in Study 16790 using individual Cmax and average plasma concentration (Cavg) estimates derived from the population PK model for the same weekly copanlisib infusion during which the maximal biomarker change from baseline was observed. A significant relationship between copanlisib exposure (Cmax or Cavg) and glucose, insulin, C-peptide, and SUVmax was observed. There was also a positive correlation between copanlisib exposure Cmax and tumor pAKT S473 inhibition ($p=0.05$). Based on all these, we selected the maximum tolerated dose of copanlisib (in this case 45mg on Days 1, 8 and 15) identified in 10217 in order to achieve the maximum possible inhibition of PI3K pathway to abrogate HR and resensitize to PARPi therapy.

As stated above, a safety lead-in is incorporated in NRG-GY029 (Section 15.4.1) with two dose levels evaluated: i) copanlisib (45 mg on Days 1, 8 and 15 of a 28-day cycle) plus olaparib (300 mg po BID) and ii) copanlisib (45 mg on Days 1 and 15 of a 28-day cycle) plus olaparib (300 mg po BID). If both dosing regimens are not tolerated in the incorporated safety lead-in, alternative copanlisib/olaparib dosing regimens may be pursued depending on toxicities, PK and PD data generated from NCI 10217 and other trials.**(28-DEC-2022)**

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

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

3.1 Eligibility Criteria

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

3.1.1 Patients with recurrent ovarian cancer. Ovarian cancer = fallopian tube cancer, ovarian cancer, primary peritoneal cancer

The following histology types are eligible*:

1) High grade serous
2) Endometrioid, grade 3
3) Any histology with BRCA1 and/or BRCA2 deleterious mutation (germline or somatic)

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

Confirmation of BRCA1 and BRCA2 germline status is required for all entered patients *(upload of report[s] required).*

Tumor/somatic genomic testing can be provided or entered as not done *(upload of report[s] required).*

HRD testing can be provided or entered as not done *(upload of report[s] required).*

Genetic/genomic testing results and HRD testing results, initially entered as not done, should be uploaded if they become available anytime during conduct of the study.

3.1.2 Participants must have progressed by imaging while receiving PARP inhibitor therapy (irrespective of whether PARP inhibitor therapy was given as maintenance therapy or as primary recurrence therapy); rising CA125 only is not considered as evidence of progression.

3.1.3 Platinum-resistant disease, defined as progression within < 6 months from completion of

platinum-based therapy, and inclusive of platinum refractory disease. The date should be calculated from the last administered dose of platinum therapy.

3.1.4 Unlimited lines of cytotoxic therapy allowed in the platinum-sensitive setting; ≤ 2 lines of cytotoxic therapy allowed in the platinum-resistant setting.

- Hormonal therapy (e.g., tamoxifen, aromatase inhibitors) will not count as a previous line of therapy.

3.1.5 Prior use of bevacizumab in the upfront or recurrent setting is required.

3.1.6 Participants must have evaluable disease – defined as RECIST 1.1 measurable disease OR non-measurable disease (defined as solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 definitions for target lesions OR ascites and/or pleural effusion that has been pathologically demonstrated to be disease-related in the setting of a CA125 > 2x ULN). .

3.1.7 Age ≥ 18

3.1.8 ECOG Performance Status of 0 or 1 or 2 (See Appendix II)

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

- Absolute Neutrophil Count (ANC) ≥ 1,500/mcl
- Hemoglobin ≥ 10 g/dL
- Platelets ≥ 100,000/mcL

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

- Creatine clearance (CrCL) >=51 mL/min (estimated using Cockcroft-Gault equation)

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

- Total serum bilirubin level ≤ 1.5 x ULN (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled)
- AST and ALT ≤ 3 x ULN

3.1.12 Lipase ≤1.5 x ULN within 14 days of registration

3.1.13 International normalized ration (INR) ≤1.5 x ULN (or an in-range INR, usually between 2 and 3, if a patient is on a stable dose of therapeutic warfarin) and a PTT ≤ 1.5 times the upper limit of normal within 14 days of registration

3.1.14 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better. (See Appendix III)

3.1.15 Patients who are therapeutically treated with an agent such as warfarin or heparin will be allowed to participate provided that their medication dose and INR/PTT is stable. Oral

anticoagulants are allowed provided there are no interactions as per Section 5.2.

3.1.16 The effects of copanlisib and olaparib on the developing human fetus are unknown. For this reason and because maternal toxicity, developmental toxicity and teratogenic effects have been observed in nonclinical studies and PI3K inhibitors agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, and for 1 month after the last dose of copanlisib and/or olaparib. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

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

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

3.1.19 Patients with evidence of chronic hepatitis B virus (HBV) infection must have an undetectable HBV viral load on suppressive therapy, if indicated.

Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.20 Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression and must be off steroids and stable at least one month.

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

3.2 Ineligibility Criteria

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

3.2.1 Prior therapy:

- No chemotherapy or radiotherapy within 4 weeks of registration.
- No hormonal therapy within 2 weeks of registration. Patients receiving raloxifene for bone health as per FDA indication may remain on raloxifene absent other drug interactions.
- No investigational agents within 4 weeks of registration.
- No prior PI3K-AKT-mTOR pathway inhibitor therapy.

3.2.2 History of allergic reactions attributed to compounds of similar chemical or biologic

composition to olaparib, copanlisib, or other agents used in this study.

3.2.3 Copanlisib and olaparib are 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 registration until the end of the study. (See Appendix V for a specific list of medications prohibited while on copanlisib treatment).

3.2.4 Systemic corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent is not permitted while on study. Patients may be using topical or inhaled corticosteroids.

3.2.5 Use of concomitant herbal medications/preparations (except for vitamins), alternative/complimentary medications, immunosuppressive therapy, or other prohibited medications per Section 5.2.

3.2.6 Patients with uncontrolled Type I or II diabetes mellitus; uncontrolled diabetes is defined as HbAlc >8.5%.

3.2.7 Patients with arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischemic attacks), deep vein thrombosis, or pulmonary embolism within 3 months before registration.

3.2.8 Gastrointestinal conditions that would preclude consumption (swallowing), retention, and/or absorption of oral medications.

3.2.9 Patients with drainage gastrostomy tube are not allowed.

3.2.10 Patients with dependency on IV hydration or TPN are not allowed.

3.2.11 Patients with uncontrolled intercurrent illness, including but not limited to:

- Persistent Grade ≥2 adverse events due to prior anti-cancer therapy with the exception of alopecia, hypothyroidism requiring medication, vitiligo, and the laboratory values defined in the inclusion criteria.
- Known psychiatric illness/social situations that would limit compliance with study requirements.
- History of or current autoimmune disease
- Non-healing wound, ulcer, or bone fracture
- Active, clinically serious infections >Grade 2 (CTCAE v5.0)

3.2.12 Women who are pregnant or unwilling to discontinue nursing.

3.2.13 Patients who have a history of non-infectious pneumonitis/ILD that required steroids, or current non-infectious pneumonitis/ILD.

NIH Participant Population Inclusion Policy

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

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

4.1 PRE-TREATMENT ASSESSMENTS (28-DEC-2022)

The following studies done for registration can be used for pretreatment assessment also: CA-125, INR/PTT, Radiographic Tumor Measurement, History and Physical, Concomitant Medications, Vital Signs, Height, Weight, Performance Status, Toxicity Assessment, HgbA1C, Lipase and Electrocardiogram.

Assessments	**Prior to Registration (calendar days)**	**Prior to Treatment (calendar days) (Cycle 1, Day 1)***
History and Physical	≤ 14 days	≤ 14 days
Concomitant Medications	≤ 14 days	≤ 14 days
Vital Signs (blood pressure, heart rate, temperature, and oxygen saturation)[g]	≤ 14 days	X
Height[a]	X	-
Weight	≤ 14 days	≤ 14 days
Performance Status	≤ 14 days	≤ 14 days
Toxicity Assessment	≤ 14 days	≤ 14 days
CBC/Differential/Platelets	≤ 14 days	≤ 14 days
Chemistries (BUN, creatinine, sodium, potassium, chloride, CO2, calcium, glucose, total bilirubin, total protein, albumin, alkaline phosphatase, AST, ALT)[h]	≤ 14 days	≤ 14 days
CA-125	≤ 28 days	≤ 28 days
INR/PTT[b]	≤ 28 days	≤ 28 days
HgbA1C [c]	≤ 28 days	≤ 28 days
Lipase	≤ 28 days	≤ 28 days
Electrocardiogram (ECG)	≤ 3 months	≤ 3 months
MUGA or echocardiogram[e]	≤ 28 days	≤ 28 days
Pregnancy test (for women of childbearing potential) Urine or serum testing is permitted[f]	≤ 14 days	≤ 14 days
Radiographic Tumor Measurement[d]	≤ 28 days	≤ 28 days

Prior to Registration Assessments should be used for Cycle 1, Day,1 as long as they are within the stated Cycle 1, Day 1 window.

[a] Height measurement is performed on adult participants during admission or at initial visit to an outpatient facility per clinical practice. As height measurement on adults is not routinely performed during follow up

visits, the height measurement previously recorded for adult participants may be used for calculating drug dosages or body surface area as applicable and can be used for baseline and follow up visits data capture.

[b] Patients who are taking warfarin may participate in this trial. 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.

[c] For patients with Type I or Type II diabetes.

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

[e] MUGA or echocardiogram to be performed only for patients planned to receive PLD (as per Section 5.1 the planned standard of care chemotherapy regimen must be declared by the investigator prior to randomization)

[f] Pregnancy test need only be done once for WOCBP within 14 days prior to registration and C1D1

[g] Patients randomized to Arm 2 will receive additional blood pressure monitoring before, during, and after copanlisib infusion on C1D1. See Section 6.2.5.

[h] Patients randomized to Arm 2 will receive additional glucose monitoring before, during, and after copanlisib infusion on C1D1. See Section 5.1.1.

4.2 ASSESSMENTS DURING TREATMENT

ARM 1 (Non-platinum single agent chemotherapy) (28-DEC-2022):

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

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

[2] **Tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI performed once every 8 weeks (+/- 7 days) from cycle 1 day 1,** for the first 12 months, then every 12 weeks (+/- 7 days) thereafter, and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression is confirmed according to RECIST 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 8 weeks (+/- 7 days) for the firt 12 months, then every 12 weeks (+/- 7 days) thereafter until progression (or initiation of subsequent therapy). Utilize **same** imaging modality of abdomen and pelvis +/- chest (for patients with evidence of measurable disease on baseline chest imaging; then subsequent radiographic tumor assessments must also include chest imaging). A tool is provided to calculate dates of re-imaging. Utilize same imaging modality of abdomen, pelvis and chest (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. PET CT

should not be used.

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

ARM 2 (Copanlisib and Olaparib)(28-DEC-2022)

Assessments	**Prior to Each Cycle, Day 1 (after Cycle 1, Day 1)**	**Every week for first 8 weeks of study therapy (in person, telemedicine, or phone)**	**Timed (Treatment Cycle Independent)**
History and Physical	≤ 3 days		
Concomitant Medications	≤ 3 days		
Toxicity Assessment	≤ 3 day	X	
Vital Signs, weight required	≤ 3 day		
Performance Status	≤ 3 days		
CBC/Differential/Platelets	≤ 3 days		
Chemistries[1]	≤ 3 days		
CA125	≤ 3 days		
Radiographic Tumor Measurement[2]			X
Review of olaparib pill diary to assess treatment compliance	X		

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

[2]**Tumor reassessment will be time-based, and not cycle-based, with CT scan or MRI performed once every 8 weeks (+/- 7 days) from cycle 1 Day 1,** for the first 12 months, then every 12 weeks (+/- 7 days) thereafter, and at any other time if clinically indicated based on symptoms or physical signs suggestive of progressive disease. Imaging assessments can be discontinued if disease progression is confirmed according to RECIST 1.1. However, if a patient discontinues study treatment for any reason other than progression, imaging studies should continue every 8 weeks (+/- 7 days)**,** for the first 12 months, then every 12 weeks (+/- 7 days) thereafter until progression (or initiation of subsequent therapy). Utilize **same** imaging modality of abdomen and pelvis +/- chest (for patients with evidence of measurable disease on baseline chest imaging; then subsequent radiographic tumor assessments must also include chest imaging). A tool is provided to calculate dates of re-imaging. Utilize same imaging modality of abdomen, pelvis, and chest (see footnote under Pre-Treatment Assessments) as for pre-cycle 1 baseline assessment. PET CT should not be used.

Patients randomized to Arm 2 will receive additional blood pressure monitoring (see Section 6.2.5) and glucose monitoring (see Section 5.1.1) before each copanlisib infusion after C1D1.

Please note: Glucose measurements on C1D1, and subsequent infusion days, may be done by laboratory analysis or in capillary blood. (28-DEC-2022)

4.3 ASSESSMENTS IN FOLLOW UP

Assessments	From end of treatment
Vital Status	1
Toxicity Assessment	2
Radiographic tumor measurement	3

1 Every 3 months for 2 years and then every 6 months for 3 years. Follow-up Forms are collected for the 5-year follow-up period or until study termination, whichever occurs first.
2 Patients who discontinue treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. For reporting of delayed toxicity, see Section 7.
3 In the case that protocol-directed therapy is discontinued for reasons other than disease progression, follow radiographic tumor measurement schedule as defined under Assessments During Treatment (until disease progression documented by RECIST 1.1 or until patient initiates a subsequent cancer therapy). Patients who discontinue treatment, electively (e.g. withdrawal of consent for treatment) or not, should remain on study until primary endpoint or initiation of other anti-neoplastic intervention. The study team should clarify with the patient if withdrawal of consent is for treatment or for treatment and follow up.

Definition of Disease Assessments

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

For this study, a rise in CA-125 alone is not sufficient to declare progression, and progression events should be determined by radiographic evidence of progression.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Each cohort will undergo 1:1 randomization to one of two treatment arms, with stratification as noted.

Protocol treatment should begin within 7 days of registration.

5.1 Treatment

Arm 1 (Standard of Care/Control Arm):

Non-platinum chemotherapy per investigator's discretion. Standard non-platinum regimens will include pegylated liposomal doxorubicin PLD, weekly paclitaxel or topotecan (weekly regimen).

Patients randomized to the non-platinum-based chemotherapy arm may be treated with one

of the three regimens specified in this section per investigator discretion (the planned regimen must be specified prior to randomization). The number of cycles of therapy should be administered as clinically appropriate.

- Regimen 1: Paclitaxel 80 mg/m^2 intravenously (IV) over approximately 60 minutes on day(s) 1, 8, and 15 every 28 days until disease progression or adverse events prohibit further therapy. **(28-DEC-2022)**

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

- Regimen 3: Topotecan 4 mg/m^2 IV over approximately 30 minutes on days 1, 8, and 15 every 28 days or 1.25 mg/m^2 IV over approximately 30 minutes on days 1 to 5 every 21 days until disease until disease progression or adverse events prohibit further therapy. **(28-DEC-2022)**

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

Use of chemotherapy agents in the standard arm will not be allowed if these drugs have been used previously in the recurrent setting (e.g., if a patient has already received PLD (alone or in combination) in the recurrent setting, PLD cannot be used in the standard arm).

The planned standard of care chemotherapy regimen must be declared by the investigator prior to randomization.

Arm 2 (Experimental Arm):
Combination therapy with copanlisib and olaparib.

Treatment will be administered on an outpatient basis. No investigational or commercial agents or therapies other than olaparib and copanlisib may be administered with the intent to treat the patient's malignancy.

Copanlisib is given as an intravenous (IV) infusion and olaparib is given as an oral (PO) pill.

Patients on Arm 2 will need to keep a medication diary. See Appendix IX.

See Appendix V for general treatment guidelines.

5.1.1 Copanlisib

Based on NCI 10217, copanlisib will be administered at a dose of 45 mg over 1 hour as an IV infusion weekly for 3 weeks (Days 1, 8, and 15) every 4 weeks (Days 1 ,8, and 15 of a 28-day cycle). A copanlisib dose reduction to 45 mg on Days 1 and 15 of a 28-day cycle will be allowed for toxicities (see Section 6.2).

Administer copanlisib as an IV infusion over one hour. 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.

Use of antiemetics should not be needed since each patient will receive 25 mg diphenhydramine and 4 mg dexamethasone to prevent copanlisib-induced rash. Should a patient require antiemetics after the first infusion, use of additional corticosteroids is not allowed. Prior to every copanlisib infusion, premedication will be administered that includes 25 mg Diphenhydramine IV (or other equivalent H1 receptor antagonist) and 4 mg dexamethasone (orally or intravenously). Copanlisib will be administered as an IV infusion over one hour. After administration, line will be flushed with 0.9 % sodium chloride to ensure complete dose is given. No IV glucose preparations should be administered on the days of infusion.

Dexamethasone will be used as premedication in this protocol to mitigate/prevent development of rash. Specifically, in NCI 10217, in the first 6 patients treated in DL1 (copanlisib 45mg IV Days 1, 8, 15 / olaparib 200 mg BID) without dexamethasone premedication, 5 of 6 patients developed G2 or G3 rash. When the 4 mg dexamethasone was added prior to each copanlisib infusion, the incidence of rash decreased (only 2 of 6 patients had G2 or G3 rash and in both patients, the rash did not reappear after resolution).

Importantly, the 4mg dose of dexamethasone prior to each copanlisib infusion did not exacerbate copanlisib-associated hyperglycemia; only 1 out of 12 patients premedicated with 4 mg dexamethasone developed hyperglycemia (this patient had G1 hyperglycemia and was treated in DL3 with the 60 mg dose of copanlisib which is above the DL2 (45 mg copanlisib) which will be used in this study).

NOTE: On days that both copanlisib and olaparib are given, olaparib should be given 30 minutes prior to copanlisib infusion.

Recommendations on meal timing on copanlisib infusion days
Because of an inhibitory effect on the PI3Kα-isoform, which is implicated in insulin metabolism, copanlisib infusions could be associated with temporarily increase in blood glucose. Consuming a meal in close proximity to copanlisib infusion may exacerbate a glucose level increase. On infusion days, a low carbohydrate diet is recommended. The timing and content of meal intake, and additional glucose testing (if clinically indicated), should be managed and monitored by the investigators based on glucose response patterns during prior treatment days.

NOTE: If patient needs to take a meal, then glucose testing should be taken prior to meal intake. All glucose measurements, oral glucose lowering medication and/or insulin administration, if applicable, pre-dose fasting/non-fasting status, and meal intake timing on infusion days 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 (prior to copanlisib infusion) should be:

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.

Glucose monitoring is required before and after the C1D1 copanlisib infusion and before each subsequent copanlisib infusion. The glucose testing is scheduled as follows:

On Cycle 1 Day 1: Glucose test is performed before starting copanlisib IV infusion at time 0 hour (pre-dose), at the end of the infusion (1 hour after starting infusion), 1 hour after completing the infusion, and 2 hours after completing the infusion (a window of ± 10 minutes is allowed except for pre-dose measurement).

All subsequent visits: Glucose test is performed before starting copanlisib IV infusion at time 0 hour. Additional measurements are to be performed at the clinic as clinically indicated at the investigator's discretion. Review blood glucose measurements/meal timing/insulin administration/oral glucose lowering medication, if applicable.

5.1.2 Olaparib

Patients will be administered olaparib BID every day (Days 1-28 of a 28-day cycle) at a starting dose of 300 mg PO 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.

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.

NOTE: On days that both copanlisib and olaparib are given, olaparib should be given 30 minutes prior to copanlisib infusion.

Refer to Section 6.3 for guidance on dose interruption or dose reduction of olaparib.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Copanlisib

Because there is a potential for interaction of copanlisib with other concomitantly administered drugs, the case report form 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.

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.

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

Systemic corticosteroid therapy at a daily dose higher than 15 mg prednisone or equivalent is not permitted while on study. As indicated in Section 5.1.1, dexamethasone 4 mg will be permitted as premedication to prevent development of skin rash. Patients may be using topical or inhaled corticosteroids. The use of corticosteroids as antiemetics prior to copanlisib administration will not be allowed.

5.2.2 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.

5.2.2.1 Dietary Restrictions

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.

5.2.2.2 Restricted Concomitant Medications (28-DEC-2022)

Strong or Moderate CYP3A Inhibitors

Known strong CYP3A inhibitors (e.g., itraconazole, telithromycin, clarithromycin, boosted protease inhibitors, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) should not be taken with olaparib. If a patient requires use of moderate CYP3A inhibitors (ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) then they must be monitored carefully for any change in efficacy of olaparib.

Strong or Moderate CYP3A Inducers

Strong (e.g., phenobarbital, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine, enzalutamide and St John's Wort) should not be taken with olaparib. If a patient requires use of moderate CYP3A inducers (e.g., bosentan, efavirenz, modafinil) of CYP3A then they must be monitored carefully for any change in efficacy of olaparib.

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

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.

5.2.2.3 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

5.3 Supportive/Ancillary Care

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

5.3.1 Herbal Supplements, Vitamins, Alternative Therapies

The concomitant use of herbal therapies is not permitted, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. Patients should stop using herbal medications at least 14 days prior to the first dose of study therapy. 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.

The use of general nutritional foundation supplements will be allowed including calcium with vitamin D and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, basic multivitamins, L-glutamine, or probiotics oral supplements will be permitted either at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins are not allowed.

5.3.2 Anti-emetics

Prophylactic antiemetics may be administered according to standard practice. The routine use of standard antiemetics, including 5-HT3 blockers, such as granisetron, ondansetron, or an equivalent agent, is allowed as needed. The use of corticosteroids as antiemetics is not allowed for participants receiving copanlisib.

5.3.3 Anti-diarrheals

Diarrhea is a common problem experienced by many patients and is a risk with olaparib, copanlisib, and chemotherapy agents. If it is not controlled quickly, it can lead to dehydration. Patients are recommended to have loperamide (Imodium) on hand at home before starting study therapy.

Participants should be advised to notify the treating investigator and their clinical team if:

- Fever of 100.3°F (38°C) or higher, with diarrhea.
- First onset of diarrhea after starting therapy
- If diarrhea persists after 24 hours, or more than 6 loose bowel movements are experienced, despite use of Imodium.

Anti-diarrheal therapies may be administered according to standard practice. An example of diarrhea management includes:

- For the first episode of diarrhea, take 4mg of loperamide. For subsequent episodes of diarrhea during the daytime, take 2mg of loperamide after each episode of diarrhea.
- Encourage aggressive oral hydration, such as water, electrolyte-replacement drinks (e.g.

Gatorade), clear soup or broth. Caffeinated beverages should be avoided.
- Advise a BRAT diet (bananas, rice, applesauce, toast) or similar bland, low-fiber foods.

5.3.4 Use of hematopoietic agents and transfusions

- Myeloid growth factors (including biosimilars) may be used per institutional Standards and/or NCCN and/or ASCO guidelines.
- Transfusions may be administered as clinically indicated for management of anemia and thrombocytopenia.

5.3.5 Bone strengthening agents

Patients may continue the use of bisphosphonates, or denosumab for bone disease.

5.4 Vaccines

Live virus and live bacterial vaccines should not be administered while the patient is receiving study medication and during the 30-day follow-up period. An increased risk of infection by the administration of live virus and bacterial vaccines has been observed with conventional chemotherapy drugs and the effects with olaparib and copanlisib are unknown.

5.5 Other Anti-Cancer Agents and Participation in Other Trials

No other anti-cancer therapy is permitted while on study, including other chemotherapy, immunotherapy, radiotherapy, biologic therapy, or other novel agents. Hormone/endocrine therapy is prohibited if used as an anti-cancer therapy. Hormone replacement therapy (HRT) is acceptable.

Concurrent participation in other therapeutic trials is prohibited. However, trials that do not add experimental agents are allowed (e.g., imaging trials, quality of life, etc.).

5.6 Duration of Therapy

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

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

Note:

- Patient has the right to refuse further treatment, but that does not necessitate withdrawing consent for participation in the study (e.g. follow-up) (See Section 8.2.2 study consent withdrawal)
- See Section 6 to determine if individual treatment components can be stopped independently.

- If all protocol treatment is discontinued, follow-up and data collection will continue as specified in the protocol.

6. TREATMENT MODIFICATIONS/MANAGEMENT

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

6.1 Arm 1 (Standard of Care/Control Arm)

Table 6.1.A: Guidelines for dose reductions

Drug	Initial dose level	First reduction	Second reduction
Paclitaxel[1]	80 mg/m^2	Decrease dose to 70 mg/m^2	Decrease dose to 60 mg/ m^2
Pegylated liposomal doxorubicin	40 mg/m^2	Decrease dose to 30 mg/m^2	Decrease dose to 20 mg/ m^2
Topotecan weekly	4 mg/m^2	Decrease dose to 3.5 mg/m^2	Decrease dose to 3 mg/m^2

[1]Up to 2 dose reductions (70 mg/m^2 and 60 mg/m^2) are acceptable for paclitaxel. Instead of a second dose reduction, 70 mg/m^2 can be maintained if subsequently one weekly dose is omitted within one cycle and paclitaxel is given 70mg/ m^2 days #1, #8, and #15. For selected patients, after discussion with Study Chair, a third dose reduction in paclitaxel to 60 mg/m^2 days #1, #8, and #15 can be considered.

Standard of care chemotherapy will be administered according to prescribing information or treatment guidance in general use by the site, including any required premedication and/or supportive care medications (e.g., antiemetics).

- Initial treatment modifications will consist of cycle delay and/or dose reduction as indicated below for each regimen.
- All Arms require ANC of 1500/mm^3 and platelets of 100,000/mm^3 for treatment initiation. All Arms require ANC of 1000/mm^3 and platelets of 100,000/mm^3 for the start of each subsequent cycle (Day #1).
- Investigators should follow local standard clinical practice regarding dose modifications for standard of care chemotherapy.

Note: If substitution of paclitaxel for Docetaxel or paclitaxel protein-bound particles for injectable suspension (Abraxane) is required for reasons other than hypersensitivity reaction (e.g., drug shortage), contact the study team for review and approval prior to making the substitution. **(28-DEC-2022)**

6.2 Arm 2: Copanlisib

Treatment modifications/management of toxicities potentially related to be both olaparib and copanlisib are discussed in Section 6.4.

Copanlisib will be administered at a dose of 45 mg over 1 hour as IV infusion weekly for 3 weeks (Days 1, 8, and 15) every 4 weeks (Days 1 ,8, and 15 of a 28-day cycle). Dose reduction may be indicated for management of toxicities.

Copanlisib Dose Reductions

Starting Dose	First Dose Reduction	Second Dose Reduction
45mg IV on Days 1,8, 15 every 4 weeks	45mg IV on Days 1, 15 every 4 weeks	Discontinue copanlisib

In the case of olaparib discontinuation (toxicity), patient may continue single agent copanlisib.

6.2.1 Gastrointestinal Toxicity

See Section 6.4 for management of nausea and vomiting.

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
*Copanlisib may be held for up to 14 days. Drug holds of greater than 14 days where the patient is experiencing ongoing clinical benefit may be considered after discussion with the study team/chair.	
**Patients requiring more than 1 dose reduction of copanlisib should discontinue copanlisib to continue olaparib alone .	
Recommended management: Loperamide antidiarrheal therapy (see Section 5.3.3) Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose stool until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal therapy is permitted and should be recorded when used.	

6.2.2 Hematologic Toxicity

See Section 5.3.4 for guidance on hematopoietic agents and transfusions.

See Section 6.4.4 for management of neutropenia and thrombocytopenia.

6.2.3 Rash

Rash	Management/Next Dose for Copanlisib
Grade ≤1 (<10% BSA with active skin toxicity*)	· **Maintain dose level.** · Initiate topical corticosteroids 3-4 x daily, preferred compounds to use are triamcinolone and betamethasone for up to 28 days, as long as skin toxicity is active. For participants with symptoms like burning, stinging and/or pruritus, add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.
Grade 2 (10-30% BSA with active skin toxicity*)	· **Maintain dose level.** · Initiate or intensify topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone for up to 28 days, as long as skin toxicity is active · Add systemic corticosteroids 20-40mg daily. · If rash improves to ≤ Grade 1 within 10 days, systemic corticosteroid may be discontinued. For participants with symptoms like burning, stinging and/or pruritus add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night.
Grade 3 (> 30% BSA with active skin toxicity*)	· **Omit copanlisib** dose until rash /skin toxicity has improved to ≤ Grade 1 or resolved, recommend documentation by photography and consider performing a skin biopsy. · Initiate topical corticosteroids 3-4x daily, preferred compounds to use are triamcinolone or betamethasone for at least 28 days. · Add systemic corticosteroids (methylprednisolone 20-40 mg or equivalent) daily. · If rash improves to ≤ Grade 1 within 10 days, systemic corticosteroid may be discontinued. · Re-start copanlisib dose once rash /skin toxicity is fading, but no longer active (Grade 1): - At reduced dose in case of first occurrence.

	- If rash/skin toxicity still active in up to 10% BSA after more than 14 days, continue oral corticosteroid for at least 48 hours upon re-challenge with copanlisib; if rash and/or pruritus do not reoccur within 48 hours after re-challenge with copanlisib, systemic corticosteroid may be discontinued. For participants with symptoms like burning, stinging and/or pruritus, add a non-sedating anti-histamine such as cetirizine once daily during daytime and a sedating anti-histamine such as diphenhydramine once daily at night. Antihistamine regimen should be continued for a minimum of 28 days after re-challenge with copanlisib.
Grade 4	· Permanently discontinue participant from copanlisib. Patient may continue olaparib alone. · Consult a dermatologist, ensure documentation by photography and obtain a skin biopsy. · Treatment may follow guidelines for Grade 3 above with the exception of rechallenge. · Additional measures may be taken as per local treatment guidance.
Any Grade of Stevens-Johnson-Syndrome / Toxic Epidermal Necrolysis/ Drug Reaction with Eosinophilia and Systemic Symptoms or other SJS/TEN/DRESS like severe skin reactions	· Permanently discontinue participant from copanlisib. Patient may continue olaparib alone. · Consult a dermatologist, ensure documentation by photography, and obtain a skin biopsy. · Follow local treatment guidelines for SJS/TEN/DRESS.
* “Active” skin toxicities: If there are no new lesions or new areas of involvement developing, and if lesion appearance is changing color from red to pale or light brown, it is likely the skin toxicity has begun to fade and is not to be considered “active” any longer. Treatment reduction can be considered for these areas. The appearance of skin toxicity may fade slowly, over 10 days or more but not requiring ongoing therapy.	

6.2.4 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. 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 copanlisib; patient may continue olaparib alone.

Management of Glucose Increase on the Day of Copanlisib Infusion

Criteria	Recommendation	Suggested Treatment
Asymptomatic glucose increase ≤250 mg	• Does not generally require treatment with glucose lowering medication.	None
Asymptomatic glucose increase >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. • If the repeated glucose value is persistent or rising, glucose lowering medication should be administered. • Consultation with endocrinologist is recommended.	• Hydration if appropriate. • Short acting insulin may be given as per institutional standard of care. • When planning next infusion consider prophylaxis with oral glucose lowering medication.

Symptomatic glucose increase >250 mg/dL	• Hydration status should be clinically assessed • Glucose lowering medication should be administered, and repeat glucose value should be obtained to ensure improvement. • Obtain consultation from an endocrinologist.	• Hydration if clinical assessment is consistent with intravascular volume depletion • Short acting insulin and other supportive care may be given as per institutional standard of care. • When planning next infusion consider prophylaxis with oral glucose lowering medication.

Management of Glucose Increase on Subsequent Days Following Copanlisib Infusion

Criteria	Recommendation	Suggested Treatment
Highest post infusion glucose >200 mg/dL noted on days following copanlisib infusion	• Oral glucose lowering medication recommended on subsequent days. • Consultation with endocrinologist is 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 use of sulfonylurea/metaglinides or insulin secretagogues to manage increased glucose levels post drug infusions is not recommended.

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.

6.2.4.1 Monitoring of diabetic patients

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

6.2.5 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.

Blood pressure measurement on treatment days
The patient should rest for 5-10 min before blood pressure (BP) is obtained. 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.

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

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

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). 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. See the below Table 6.2.5 for management of hypertension.

Dose Modification of Copanlisib for Arterial Hypertension

Table 6.2.5: Management of Hypertension

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.

Post-dose: Drug-related BP ≥160/100 mmHg (Grade 3) [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]
Malignant hypertension, hypertensive crisis (Grade 4)	Permanent discontinuation	–
[a]: The next dose level is 45 mg on Days 1 and 15 of a 28-day cycle (Section 6.2 for copanlisib dose reduction table) [b]: Not manageable despite optimal antihypertensive treatment. CTCAE = Common Terminology Criteria for Adverse Events; BP = blood pressure,		

6.2.6 Non-Infectious Pneumonitis

See Section 6.4.2 for management of non-infectious pneumonitis.

6.3 Arm 2: Olaparib

Treatment modifications/management of toxicities potentially related to be both olaparib and copanlisib are discussed in Section 6.4.

Except where otherwise specified, the table below provides olaparib dose reduction recommendations from the initial dose of 300 mg BID.

Olaparib dose reductions for study treatment

Initial Olaparib Dose	Following re-challenge post interruption: Dose reduction 1	Dose reduction 2
300 mg BID	200 mg BID	150 mg BID

Toxicities may be managed by dose interruption or dose reduction, as guided in the following sections. Olaparib may be held for up to 14 days. Drug holds of greater than 14 days where the patient is experiencing ongoing clinical benefit may be considered after discussion with the study Chair.

Once the dose is reduced, re-escalation is not permitted.

In the case of copanlisib discontinuation (toxicity), patient may continue single agent Olaparib.

6.3.1 Dose Reduction/Discontinuation for Organ Dysfunction

6.3.1.1 Hepatic Impairment

The effect of mild or moderate impairment (Child-Pugh classification A or B) on single dose of 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.

In case a patient shows an AST or ALT ≥3×ULN or total bilirubin ≥2×ULN, please refer to Appendix IV: Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin – Hy's Law for further instructions.

6.3.2 Management of Hematologic Toxicity

See Section 5.3.4 for guidance on hematopoietic agents and transfusions.

6.3.2.1 Management of Anemia

Common treatable causes of anemia (e.g., iron, vitamin B12, or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. Blood transfusions are allowed if determined to be necessary by the treating investigator.

Hemoglobin (Hb) (CTCAE Severity)	**Action to be taken**
Hb <10 but ≥8 g/dL (Grade 2)	**First Occurrence:** • Give appropriate supportive treatment and investigate causality. • Continue olaparib with supportive treatment (e.g., transfusion).. **Subsequent Occurrence:** • If Hb **<10** *but* **≥9 g/dL**, continue olaparib with supporting treatment (e.g., transfusion) • If Hb **<9** *but* **≥8 g/dL**, hold olaparib (for max of 2 weeks) until Hb **≥9** g/dL and upon recovery dose **reduction to the next lower dose level (Section 6.3 Olaparib dose reduction table)**
Hb <8 g/dL (Grade 3)	• Give appropriate supportive treatment (*e.g.* transfusion) and investigate causality. • Hold olaparib for a maximum of 2 weeks until improved to Hb **≥9**g/dL. • Upon recovery dose reduce **to the next lower dose level**

	(Section 6.3 Olaparib dose reduction table) • Hold olaparib for grade 3 anemia, transfuse and reduce dose v. introduce epo-stimulating agents (some patients benefit from these, not all)

6.3.2.2 Management of Neutropenia, and Thrombocytopenia
See Section 6.4.3.

6.3.3 Management of Non-Hematological Toxicity

6.3.3.1 Management of Non-Infectious Pneumonitis
See Section 6.4.2.

6.3.3.2 Management of Nausea and Vomiting
See Section 6.4.1.

6.3.3.3 Interruption for Intercurrent Non-Toxicity Related Events

Olaparib dose interruption for conditions other than toxicity resolution should be kept as short as possible. If a patient cannot restart olaparib within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussedwith 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).

6.3.3.4 Interruption for Procedures
Olaparib should be stopped at least 3 days prior to planned surgery or a procedure. After surgery/procedure, olaparib can be restarted when the wound has healed. No stoppage of study treatment is required for needle biopsy procedures.

6.3.3.5 Management of Fatigue

Fatigue	
Grade 1-2	Supportive care. Maintain olaparib dose.
Grade 3	Hold for up to 14 days until resolved to < Grade 2, then reduce olaparib to 200mg BID. If patients experience > Grade 2 fatigue at the 200mg BID dose, further reduce olaparib dose to 150mg BID.

6.4 Management of potentially Overlapping Toxicities

6.4.1 Management of Nausea/Vomiting

Nausea and Vomiting	Management/Next Dose
Grade 1-2	**First occurrence:** • Initiate appropriate anti-emetic treatment as required, 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) to abrogate nausea/vomiting. • If antiemetics are not sufficient to control nausea, then omit olaparib and resume at the same dose when nausea has subsided. **Second occurrence:** • If participant still complains of significant nausea despite antiemetics and previous olaparib interruption, omit olaparib again. • When nausea has subsided, resume olaparib and decrease at one dose level lower. • If olaparib has been dose reduced twice, then decrease copanlisib by one dose level**.
Grade 3	• Hold olaparib and copanlisib until resolved to < Grade 2. Then decrease olaparib one dose level. • If olaparib has been dose reduced twice, then decrease copanlisib by one dose level**. • Hold olaparib and copanlisib for ≥ Grade 3 vomiting or Grade 3 nausea only if the vomiting or nausea cannot be controlled with optimal antiemetic as per local standard of care*.
Grade 4	Off protocol therapy
The time a given drug is held should not exceed 14 days. *Grade 3 nausea/vomiting that does not resolve to grade 0-2 within 14 days despite maximum supportive care after treating patient at the lowest reduced dose level of olaparib and copanlisib should lead to discontinuation of protocol therapy. **Patients requiring more than 1 dose reduction should go off protocol therapy.	
Recommended management: antiemetics. The use of corticosteroids as antiemetics is not allowed for participants receiving copanlisib.	

6.4.2 Management of Non-infectious Pneumonitis

If new or worsening pulmonary symptoms (e.g., dyspnea) or radiographic pulmonary abnormalities develop, effort should be made to determine the etiology. If a clear diagnosis (e.g., allergic, infectious, aspiration) is not evident, olaparib/copanlisib dosing should be interrupted and further diagnostic workup obtained to exclude a drug-related pneumonitis. Per the judgment of the treating investigator, evaluation may include a high-resolution CT Chest, infectious studies, pulmonary function tests, and/or referral to a pulmonologist. 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

or olaparib; 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".

If symptoms resolve and no pulmonary abnormalities are observed on imaging, then study treatment can be restarted if deemed appropriate by the treating investigator.
In the event of suspected non-infectious pneumonitis, modify copanlisib and olaparib treatment as per table below.

Dose Adjustments for non-infectious pneumonitis

Suspected or confirmed NIP per CTCAE	**Action Taken**	**Re-treatment dose after recovery**
Grade 1	No change to copanlisib/olaparib dosing	NA
Grade 2	Hold copanlisib and olaparib until recovery to ≤ Grade 1 Treat NIP, consider seeking Pulmonology consultation.	Decrease copanlisib and olaparib dose by one dose level[a]
Grade 2 (second occurrence)	Discontinue protocol therapy	NA
Grade 3	Discontinue protocol therapy	NA
Grade 4	Discontinue protocol therapy	NA

NA=Not applicable; NIP=Non-infectious pneumonitis; CTCAE=Common Terminology Criteria for Adverse Events
[a]If olaparib or copanlisib have already been dose reduced to the lowest dose level, then discontinue protocol therapy.

6.4.3 Management of Neutropenia and Thrombocytopenia

Toxicity (CTCAE Severity)	**Study treatment dose adjustment**
Grade 1-2	Appropriate supportive treatment and causality investigation. Continue olaparib and copanlisib at the same dose.
Grade 3-4	• Appropriate supportive treatment and causality investigation. • Interrupt olaparib and copanlisib dosing for a maximum of 2 weeks, until recovered to Grade 1 or better and dose reduce olaparib. • If repeat Grade 3-4 occurrence, then dose reduce olaparib to the next lower dose level (Section 6.3 Olaparib dose reduction table). If olaparib has been dose reduced to the lowest level, then dose reduce copanlisib. If both drugs have been dose reduced to the lowest level, then

	discontinue protocol therapy. • For cases where patients develop prolonged hematological toxicity with ≥2 week interruption/delay in study treatment due to CTCAE grade 3 or worse, refer to Section 6.4.4.

Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) is not permitted for participants receiving olaparib. However, use of G-CSF/filgrastim may be used as per national guidelines (See Section 5.3.4). G-CSF should not be used within 24 hours of the last dose of study treatment.

Platelet transfusions, if indicated, should be administered if deemed necessary by the treating investigator and according to local institutional guidelines.

6.4.4 Management of Prolonged Hematological Toxicities While on Study Treatment

If a patient develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in olaparib due to CTCAE Grade 3 or worse anemia and/or development of blood transfusion dependence
- ≥2 week interruption/delay in olaparib due to CTCAE Grade 3 or worse neutropenia (ANC $<1\times10^9$/L)
- ≥2 week interruption/delay in olaparib 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. Olaparib should be discontinued if blood counts do not recover to CTCAE Grade 1 orbetter 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 a hematologist for further investigation. 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 and copanlisib treatment should be discontinued if a diagnosis of MDSand/or AML is confirmed.

6.4.5 Management of Non-Hematological Toxicity (not covered in the above sections)

Dose interruptions are allowed as required, for a maximum of 2 weeks on each occasion.If the interruption is longer than 2 weeks, the CTEP Medical Monitor must be informed.

Where toxicity reoccurs following re-challenge with olaparib and/or copanlisib, and where further dose interruptions are considered inadequate for management of toxicity, then the patient should be considered for dose reduction of the drugs (olaparib or copanlisib or both) causing the toxicity or must permanently discontinue the offending agents (olaparib or copanlisib or both).

For treatment-related non-hematologic AEs not covered in the above sections:

- Treatment must be interrupted if a grade 3 or 4 AE occurs which the investigator considers to be related to administration of study treatment. In that scenario, the offending agent should be dose reduced by one dose level (except for easily correctable, asymptomatic, G3 laboratory abnormalities). Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the Study Chair if evidence of clinical benefit.

- One drug may be held or dose modified or discontinued independently if the observed toxicity is attributed to only one of the drugs, while the patient continues to receive the second drug not associated with the observed toxicity. The time a given drug is held should not exceed 14 days.

- Grade 3 or 4 non-hematologic AE related to treatment that does not resolve to grade 0-2 within 14 days despite maximum supportive care after treating patient at the lowest reduced dose level of the offending agent should prompt discontinuation of the offending agent.

- Grade 3 or 4 non-hematologic AE related to treatment lasting > 14 days despite maximum supportive care and treatment being held should prompt discontinuation of the offending agent.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agents administered in NRG-GY029 are copanlisib and olaparib, which are being made available under an IND sponsored by CTEP. For patients receiving copanlisib and olaparib determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.5.2.1 of the protocol.

Commercial Agents

The commercial agent(s) in NRG-GY029 are paclitaxel, pegylated liposomal doxorubicin and topotecan. For patients receiving paclitaxel, pegylated liposomal doxorubicin, and topotecan, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.4 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (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 website: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.2 Definition of an Adverse Event (AE)

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

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

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

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

7.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for 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 702 patients.* Below is the CAEPR for Copanlisib 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.

Adverse Events with Possible Relationship to Copanlisib dihydrochloride (BAY 80-6946 dihydrochloride) (CTCAE 5.0 Term) [n= 702]			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)***
INFECTIONS AND INFESTATIONS			
Infection[2]			***Infection[2] (Gr 2)***
INVESTIGATIONS			
Neutrophil count decreased			***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
	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; Sinus tachycardia
GASTROINTESTINAL DISORDERS - Abdominal pain; Colitis; Constipation; Dry mouth; Dyspepsia; Esophagitis;

Flatulence; Gastritis; Gastroesophageal reflux disease; Oral dysesthesia; Oral pain; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Death NOS; Fever; General disorders and administration site conditions - Other (failure to thrive); Non-cardiac chest pain
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; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Electrocardiogram T wave abnormal; Investigations - Other (electrocardiogram U wave abnormal); Lipase increased; Lymphocyte count decreased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypertriglyceridemia; Hyperuricemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (blood insulin increased)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (psoriatic arthropathy); Myalgia
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
PSYCHIATRIC DISORDERS - Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (renal insufficiency)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea[3]; Hypoxia; Pleural effusion; Pulmonary hypertension; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (pulmonary congestion)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; 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.

7.3.2 Comprehensive Adverse Events and Potential Risks list (CAEPR)

for

Olaparib (AZD2281, NSC 747856)

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

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple

investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, July 1, 2021[1]

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

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%)**	
	Muscle cramp		
	Myalgia		
	Pain in extremity		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (angioedema)	
		Skin and subcutaneous tissue disorders - Other (erythema nodosum)	

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

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

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

CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus

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

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

7.4 Adverse Events for Commercial Study Agents

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

7.5 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site:
https://ctepcore.nci.nih.gov/ctepaers/security/login

For studies that utilize the RAVE-CTEP-AERS integration, expedited reports are initiated via RAVE: see Section 14.5.

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

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

7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERs-24 Hour Notification requires that a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the AE. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.

- Supporting source documentation is requested by CTEP as the IND sponsor for this study and by NRG as needed to complete adverse event review. Deidentified supporting source documentation should be uploaded to the Source Document Portal via the CTEP-AERS integration.

- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG Oncology safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements for Adverse Events

7.5.2.1 Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2] (For ARM 1)(28-DEC-2022)

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

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

Effective Date: May 5, 2011

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

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

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

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

Effective Date: May 5, 2011

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

N/A

7.5.3 Reporting to the Site IRB/REB

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

7.5.4 Secondary Malignancy:

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

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

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

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

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

7.6 Routine Reporting Requirements for Adverse Events

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

7.6.1 Pregnancy

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

8. REGISTRATION AND STUDY ENTRY PROCEDURES (28-DEC-2022)

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

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

and

- Associate Basic (AB) – individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

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

An active CTEP-IAM user account with a linked ID.me account (the latter required immediately for new CTEP-IAM accounts, and by July 1, 2023 for all users) is required to participate in NCI clinical trials supported by the Cancer Trials Support Unit (CTSU) and to access all CTEP and CTSU websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR Help Desk by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures

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

This study is supported by the NCI CTSU.

IRB Approval

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

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

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

- Have an Active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institutions(s) record;
- Include the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

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

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

Downloading Site Registration Documents

Download the site registration forms from the protocol specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted 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) using your CTEP-IAM username and password or linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- Click on Protocols in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select NRG, and protocol # NRG-GY029.
- 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 initiative, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents

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

To access the Regulatory Submission Portal log 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.

Checking Site's Registration Status

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

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

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. 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.

Delegation of Tasks Log (DTL)

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

8.2 Patient Enrollment

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

8.2.1 Oncology Patient Enrollment Network (OPEN)

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

Requirements for OPEN access:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users);
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;

- If a Delegation of Tasks Log (DTL) is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for a protocol prior to patient enrollment.

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

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

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

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

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

8.2.2 Patient-Initiated Consent Withdrawal from the Study

If a patient chooses to have no further interaction regarding the study (i.e., allow no future follow up data to be submitted to NRG Oncology), the study applicable form should be completed in Medidata Rave to report the patient's consent withdrawal.
NOTE: This should not be done if the patient has only chosen to stop protocol treatment and is willing to still be followed. (See Section 5.6).

9. DRUG INFORMATION

General Patient Care Implications
Patients must use highly effective contraception because the study treatment may be teratogenic. Highly effective contraception is defined as hormonal contraceptives (oral contraceptives, Nuvaring, Depo Provera), intrauterine device, true abstinence, two barrier methods of birth control including condoms with cervical cap or diaphragm, patient has received surgical sterilization.

9.1 Copanlisib (NSC# 784727, IND#)

9.1.1 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

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

9.1.3 Classification: Pan class I PI3K inhibitor

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

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

9.1.6 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.

9.1.7 Description: The powder is white to yellow solid substance.

9.1.8 How Supplied: Copanlisib is supplied by Bayer HealthCare AG and distributed by the Pharmaceutical Management Branch, CTEP, 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.

9.1.9 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 sterile 0.9% sodium chloride bag. Mix well by inverting.

9.1.10 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.

9.1.11 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.

9.1.12 Route of Administration: IV infusion

9.1.13 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.

9.1.14 Potential Drug Interactions: In vitro, copanlisib is metabolized primarily via CYP 3A4 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 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), MRP2, 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.

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

9.1.16 Patient Care Implications: Females of child-bearing potential and male patients must use adequate contraception while receiving copanlisib and for 1 month 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.

9.2 Olaparib (AZD2281) (NSC# 787856, IND#)

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

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

9.2.3 Classification: PARP inhibitor

9.2.4 CAS Registry Number: 763113-22-0

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

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

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

9.2.8 Description: crystalline solid

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

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

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

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

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

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

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

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

9.2.13 Potential Drug Interactions: *In vivo* data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of

strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

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

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

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

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

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

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

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

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

The investigator brochure for this drug will be supplied by *[insert source/link]*.

9.3 PMB Useful Links and Contacts

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

9.4 Agent Ordering

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

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

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

9.4.1 Investigator Brochure Availability

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

9.4.2 Agent Accountability

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

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

9.5 Commercial Agent—Paclitaxel (NSC# 673089)

9.5.1 Formulation:

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

9.5.2 Storage/Stability

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

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

9.5.3 Preparation:

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

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

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

All patients should be premedicated with corticosteroids, diphenhydramine, and H2 antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity

reactions. Patients who experience severe hypersensitivity reactions to paclitaxel may be re-challenged with the drug.

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

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

9.6 Commercial Agent: Pegylated Liposomal Doxorubicin (PLD) (NSC# 712227)

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

Refer to the PLD package insert for the most complete and current information on the following:

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

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

9.6.3 Preparation:
PLD doses up to 90 mg must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 mL of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in PLD. Diluted PLD should be refrigerated at 2°C–8°C (36°F–46°F) and administered within 24 hours.

- Do not mix with other drugs.
- Do not use with any diluent other than 5% Dextrose Injection.
- Do not use any bacteriostatic agent, such as benzyl alcohol.
- PLD is not a clear solution but a translucent, red liposomal dispersion.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.
- Do not use in-line filter.

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

The use of gloves is required.

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

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

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

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

9.6.6 Supplier:
Commercially available.

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

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

9.7 Commercial Agent: Topotecan (NSC# 609699)

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

9.7.2 Supplier/How Supplied:
Topotecan is commercially available and is supplied in a sterile form for intravenous use only.

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

solution of topotecan HCl equivalent to 4 mg of topotecan as the free-base at a concentration of 1 mg/mL.

9.7.3 Solution Preparation:
Topotecan for Injection (lyophilized powder) reconstitution:

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

Topotecan Injection (solution) reconstitution:

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

9.7.4 Storage/Stability:
Topotecan for Injection (lyophilized powder) storage and stability:

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

Topotecan Injection (solution) storage and stability:

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

9.7.5 Adverse effects:

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

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

10. PATHOLOGY/BIOSPECIMEN

Not Applicable

11. SPECIAL STUDIES (NON-TISSUE)

Not applicable

12. MODALITY REVIEWS

Not appliable

13. ASSESSMENT OF EFFECT

13.1 Antitumor Effect – Solid Tumors

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

For this study, a rise in CA-125 alone is not sufficient to declare progression, and progression events should be determined by radiographic evidence of progression.

13.1.1 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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

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

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if

the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

13.1.2 Methods for Evaluation of Measurable Disease

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

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans), but NOT lung.

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

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

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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

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

13.2 Response Criteria

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

13.2.1 Evaluation of Target Lesions

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

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

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

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

13.2.2 Evaluation of Non-Target Lesions

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

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

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

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

13.2.3 Evaluation of Best Overall Response

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

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

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

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

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

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

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

*See RECIST 1.1 manuscript for further details on what is evidence of a new lesion
** 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

13.2.4 Best Overall Confirmed Response

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

However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of results. Therefore, for NRG-GY029, confirmation of response is not required.

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

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

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.

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

Patients with a global deterioration of health status requiring discontinuation of treatment or

die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

13.3 Duration of Response

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

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since date of study entry, including the baseline measurements.

13.4 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression or death, whichever occurs first. Patients who are alive without documentation of disease progression will be censored on the date of their last tumor assessment.

13.5 Survival

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

14. DATA AND RECORDS

14.1 Data Management/Collection

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:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users); and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

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

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

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

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

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

14.2 NRG Data Management Forms

Refer to the CTSU member website for protocol Form Set.

14.3 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7.5 and Section 7.6 for information about expedited and routine reporting.

14.4 Central Monitoring (CM)

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP) application. This application is also available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with any of the Rave roles on a relevant site roster can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU SDP application under Browser > Document Repository in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

14.5 Rave-CTEP-AERS integration

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

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

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

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

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

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

an expedited report in CTEP-AERS.

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

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

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

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

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

14.6 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, form 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 in the DQP modules.

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

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

14.7 Global Reporting/Monitoring

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

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

15. STATISTICAL CONSIDERATIONS

15.1 Abstract

This is as a two-arm, multicenter, open-label, 1:1 randomized Phase 2 superiority trial to test the efficacy of the copanlisib/olaparib combination (Arm 2) relative to physicians' choice standard chemotherapy (Arm 1). The Phase 2 design includes one interim analysis for futility of Arm 2. The trial starts with a safety lead-in among the first patients randomized to Arm 2. The safety lead-in includes two dose levels and will determine the recommended Phase 2 dose (RP2D) for Arm 2.

15.2 Stratification and Randomization

Treatments will be allocated 1:1 within randomly permuted blocks. This procedure tends to allocate the treatment regimens to an equal number of enrollees within the 4 groups defined by combinations of the stratification factors. The randomized treatment assignment will be revealed to the patient and physician at the end of the registration process. The following stratification factors will be incorporated into the randomization plan:

- BRCA 1/2 status: Any germline or somatic BRCA variant known or suspected to be deleterious VERSUS a germline BRCA variant that is either non-deleterious or benign and a somatic BRCA variant that is either non-deleterious, benign or unknown

- Timing of prior PARPi therapy: PARPi as last line of therapy prior to initiation of the trial VERSUS other intervening therapy prior to initiation of the trial

15.3 Patient Cohorts for Analysis

Table POPS: Population Definitions

Population	Description
DLT Evaluable	The DLT Evaluable population includes patients randomized to Arm 2 and assessed for toxicity during the safety lead-in. Patients who stop protocol therapy for reasons other than toxicity, disease progression or death before the end of cycle 2 may be replaced, and will be excluded from the DLT Evaluable population. This population includes 2 possible subsets: those who are treated at the RP2D, and those who are not. DLT Evaluable patients who are not treated at the RP2D will be excluded from the Phase 2 analysis populations described below.
ITT[a]	The ITT population includes all randomized patients. Patients will be analyzed according to their randomized therapy assignment, regardless of compliance with that therapy. This population will be used for demographics and baseline characteristics summaries, participant disposition, and analyses of PFS and OS endpoints.
Safety[a]	The Safety population includes all randomized patients who receive any amount of protocol therapy. Treatment groups are determined using the actual treatment received regardless of the randomized treatment assignment. All adverse event analyses will be conducted using the safety population.
Measurable Disease[a]	The Measurable Disease population includes all randomized patients who 1. receive any amount of protocol therapy 2. have baseline measurable disease per RECIST 1.1 3. have at least one tumor assessment, disease progression, or death, whichever occurs first, within 12 months of starting protocol therapy. Patients will be analyzed according to their randomized treatment assignment, regardless of compliance with that therapy. This population will support all analyses related to ORR.

[a] Excludes DLT Evaluable patients who were not treated at the RP2D.

15.4 Primary Endpoint(s), Sample Size, and Analysis Plan

15.4.1 Safety Lead-In

The study will start with a safety lead-in, with the primary objective to assess the safety and tolerability of the Arm 2 combination. The following considerations characterize the safety

lead-in:

1. The NRG Phase 1 Subcommittee and Early Phase Oversight Committees, with support from the study team, will review toxicity data, determine dose level changes, and make a final recommendation about continuing the study after completion of the safety lead-in.
2. The primary endpoint is the proportion of DLT Evaluable patients with at least one dose limiting toxicity (DLT).
3. A DLT is defined as any treatment-related adverse event requiring permanent discontinuation of copanlisib within the first two treatment cycles.
4. Dose reductions for olaparib are permitted (as described in Section 6.3 Olaparib dose reduction table). Toxicity following olaparib dose-reduction and leading to a treatment delay of >30 days will be counted as a DLT. If more than two olaparib dose-reductions are needed, then this will be counted as a DLT.
5. A dose level may be considered overly toxic whenever the proportion of evaluable patients with at least one DLT is $\pi > 0.33$.
6. The evaluable patient set is the DLT Evaluable population, defined in Table POPS.
7. The dose levels available for the safety lead-in are shown in Table SLDoses.

Table SLDoses. Safety Lead-in Dose Levels:

Dose Level	Copanlisib	Olaparib
1	45mg D1, D8, D15 of a 28-day cycle	300mg BID
-1	45mg D1, D15 of a 28-day cycle	300mg BID

The following decision rules guide the safety lead-in:

1. The study treatments (olaparib+copanlisib vs chemotherapy) will be randomly allocated (1:1) to each individual enrolled during this component of the study.
2. Patients randomized to Arm 2 will start accruing to dose level DL1. Enrollment will proceed until at least n=10 patients receive any amount of the olaparib+copanlisib combination. Patients who do not meet the DLT Evaluable criteria (Table POPS) may be replaced.
3. At any time after n=3 DLT Evaluable patients have enrolled, if the DLT proportion among patients treated at DL1 is $\pi > 0.33$, or DL1 is otherwise considered intolerable, the Phase 1 Subcommittee and/or Early Phase Oversight Committee may suspend accrual to DL1, and open DL-1.
4. After the tenth patient in the DLT Evaluable cohort enrolls, accrual may be suspended for DLT assessment.
5. If accrual to DL-1 is opened, decision rules 1, 2, 3 and 4 will apply.
6. When an Arm 2 dose level is considered safe based on this assessment, the protocol will be amended to allow participation of NCTN sites and activation of the full phase II trial.

7. If DL-1 is not tolerated, alternative copanlisib/olaparib dosing regimens may be pursued depending on toxicities, PK and PD data generated from NCI 10217 and other trials. **(02-JUN-2022)**

15.4.2 Phase 2 Statistical Design

This is as a two-arm randomized phase II study. The primary endpoint is investigator-assessed progression-free survival (PFS), as defined in Section 13.4. The null and alternative hypotheses with regard to the relative PFS event rate for the experimental arm versus standard of care arm are as follows:

$$H_0: \Delta = \frac{\lambda_2}{\lambda_1} \geq 1.0 \text{ vs } H_1: \Delta = \frac{\lambda_2}{\lambda_1} < 1.0$$

where (λ_2, λ_1) are the PFS hazards in Arm 2 and Arm 1 respectively, and Δ is the corresponding hazard ratio. The design parameters are based on the following piecewise-hazard assumptions for the standard of care arm, obtained from control arm of the AURELIA trial (Pujade-Lauraine (2014) PMID: 24637997)

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

With a one-sided α=0.10, a total of 57 PFS events has power=0.90 to detect a hazard ratio of Δ=0.50. If the PFS times are exponentially distributed, and the median PFS is 3.4 months in the reference arm, a hazard ratio of Δ=0.50 corresponds to a median PFS of 6.8 months in the experimental arm. The relationship between the power and minimum detectable hazard ratio (HR) is shown in the table below. If the true HR is 0.55, the power decreases to 0.82.

HR	**Power**
0.50	0.90
0.55	0.82
0.60	0.73

15.4.3 Phase 2 Interim Futility Analyses

The design includes an interim futility analysis, using a Lan-Demets (O'Brien-Fleming) type futility boundary. The interim analysis is planned when a total of 29 PFS events (50% information) are observed. This is expected to occur approximately 11.4 months after starting accrual. If these assumptions hold and the HR estimate ($\Delta=\lambda_2/\lambda_1$) is >1.07, consideration will be given to stopping the study for futility of the experimental arm. Under the null hypothesis, the probability of stopping for futility is 0.43, and under the alternative

hypothesis, the probability is 0.02 (i.e., 0.02 of the $\beta = 0.10$ is spent at the interim analysis). The interim analysis results will be examined by the NRG Data Monitoring Committee. The decision to terminate accrual will include consideration of toxicities, treatment compliance, and progression-free survival and other endpoints, and results from external studies.

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

15.4.4 Accrual/Study Duration

With an accrual rate of 8 eligible patients per month and a 10% dropout rate, a sample size of 96 patients will accrue over about 15 months. A follow-up period of 2 months should provide the needed number of events. Total study duration is estimated to be 16 months. The final analysis will occur when at least 32 PFS events are observed in the standard of care arm (which is the expected number to occur with 57 events total and a hazard ratio of Δ=0.50).

If necessary, accrual may be suspended during the safety lead-in for DLT assessment, and for determination of the RP2D. No other accrual suspensions are planned.

15.4.5 Analysis Plan

The interim and primary analyses of PFS (defined in Section 13.4) will be based on a logrank test, stratified by the factors declared at randomization. These analyses will include all patients enrolled onto the study regardless of compliance to their assigned study regimen. Patients will be grouped by their randomized treatment for intention-to-treat analyses (ITT population, Section 15.3). For the purposes of the primary analyses, the documentation of disease progression will be determined by the treating physician.

The treatment hazard ratios and their 95% confidence intervals will be estimated using a multivariable proportional hazards model specified with main effects for the randomized treatment assignment (Arm 2 vs Arm 1) and covariate adjustment for the stratification factors declared at randomization.

15.5 Monitoring/Oversight Committee

NRG Oncology Data Monitoring Committee (DMC)

The NRG Oncology Data Monitoring Committee (DMC) meets twice a year to review the progress of all ongoing NRG Oncology randomized phase II or III trials. Approximately eight weeks prior to the scheduled meetings, the study database is locked for preparation of a study report. This study report includes summaries of accrual and adverse event data. Information related to the safety lead-in will be included in these DMC reports.

The DMC will review the study for protocol-specified interim analyses on an “as needed” basis. If the prerequisite number of events for an interim analysis has been attained, a report summarizing the interim analysis results is also prepared and presented to the DMC. The

decision to terminate accrual or to release study results includes consideration of toxicities, treatment compliance, and results from external studies.

NRG Phase 1 Subcommittee and Early Phase Oversight Committee
NRG Phase 1 Subcommittee and Early Phase Oversight Committee, with support from the study team, will review toxicity data, determine dose level changes, and make a final recommendation about continuing the study after completion of the safety lead-in. These findings will be presented to the DMC for final approval.

15.6 Secondary Endpoints and Analysis Plans

[Each secondary endpoint will be a subsection with paragraph(s) as needed for the following info: define the endpoint, list hypothesis (if applicable), describe analysis plan, and address cohort size if different from overall sample size]

15.6.1 (Objective 1.2.1) To assess the clinical efficacy of the combination of copanlisib/olaparib, as measured by objective response rate (ORR), per RECIST 1.1 measurement of target lesions.

The Measurable Disease population (Section 15.3) will support these analyses. The objective response rate (ORR) is defined as the binomial proportion of evaluable patients with a best overall response of CR or PR (by RECIST 1.1). Responses reported by the treating physician will be used for these analyses.

The ORR estimates by treatment arm will be supported by their 2-sided, 95% Wilson-Score confidence intervals (Wilson, 1927, Agresti, 1998). The relative odds of response in the experimental group (vs. the reference group) will be estimated using a multivariable logistic regression model specified with main effects for the treatment group and covariate adjustments for the stratification factors reported at baseline.

15.6.2 (Objective 1.2.2) To assess the clinical efficacy of the combination of copanlisib/olaparib, as measured by overall survival (OS), compared to standard chemotherapy in the setting of platinum resistant ovarian cancer that has progressed through prior PARP inhibitor therapy

The OS treatment hypothesis test will be based on a logrank test, stratified by the factors specified at randomization. These analyses will be supported by the ITT population (Section 15.3).

The treatment hazard ratios and their 95% confidence intervals will be estimated using a multivariable proportional hazards model specified with main effects for the randomized treatment assignment (Arm 2 vs Arm 1) and covariate adjustment for the stratification factors used in the randomization.

15.6.3 (Objective 1.2.3) To determine the nature, frequency, and degree of toxicity as assessed by CTCAE v.5.0 for each treatment arm

The Safety Population (Section 15.3) will support these analyses. The nature, frequency, and degree of toxicity will be tabulated at the System Organ Class and AE-specific term

levels using CTCAE v5.0. Each patient will be represented according to the maximum grade observed for each term. Tabulations will show the number and percentage of patients by maximum grade, within the treatment group received, regardless of the randomized treatment assignment. No specific hypothesis test is pre-specified.

15.7 Exploratory Endpoints

There are none.

15.8 Gender/Ethnicity/Race Distribution

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	0	0	0	1
Asian	5	0	0	0	5
Native Hawaiian or Other Pacific Islander	1	0	0	0	1
Black or African American	5	0	3	0	8
White	68	0	2	0	70
More Than One Race	0	0	0	0	0
Total	80	0	5	0	85

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

16. REFERENCES

Agresti, A. and B. A. Coull. Approximate is better than "exact" for interval estimation of binomial proportions. The American Statistician 1998; 52 (2), 119-126.

Ali, K., D.R. Soond, R. Pineiro*, et al.* (2014). Inactivation of PI(3)K p110delta breaks regulatory T-cell-mediated immune tolerance to cancer. *Nature*. 510:407-411.

de Gooijer MC, Zhang P, Buil LCM, et al. Buparlisib is a brain penetrable pan-PI3K inhibitor. *Sci Rep.* 2018;8(1):10784.

Dreyling M, Morschhauser F, Bouabdallah K, et al. Phase II study of copanlisib, a PI3K inhibitor, in relapsed or refractory, indolent or aggressive lymphoma. *Ann Oncol.* 2017;28(9):2169-2178.

Gelmon KA, Tischkowitz M, Mackay H, et al. Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: a phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol.* 2011;12(9):852-861.

Gockeritz, E., S. Kerwien, M. Baumann*, et al.* (2015). Efficacy of phosphatidylinositol-3 kinase inhibitors with diverse isoform selectivity profiles for inhibiting the survival of chronic lymphocytic leukemia cells. *Int J Cancer*. 137:2234-2242.

Ibrahim YH, Garcia-Garcia C, Serra V, et al. PI3K inhibition impairs BRCA1/2 expression and sensitizes BRCA-proficient triple-negative breast cancer to PARP inhibition. *Cancer Discov.* 2012;2(11):1036-1047.

Investigator's Brochure (2018). Copanlisib (BAY 80-6946). Bayer AG. *Edition 11.0* (August 10, 2018).

Juvekar A, Burga LN, Hu H, et al. Combining a PI3K inhibitor with a PARP inhibitor provides an effective therapy for BRCA1-related breast cancer. *Cancer Discov.* 2012;2(11):1048-1063.

Juvekar A, Hu H, Yadegarynia S, et al. Phosphoinositide 3-kinase inhibitors induce DNA damage through nucleoside depletion. *Proc Natl Acad Sci U S A.* 2016;113(30):E4338-4347.

Konstantinopoulos PA, Barry WT, Birrer M, et al. Olaparib and alpha-specific PI3K inhibitor alpelisib for patients with epithelial ovarian cancer: a dose-escalation and dose-expansion phase 1b trial. *Lancet Oncol.* 2019;20(4):570-580.

Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov.* 2015;5(11):1137-1154.

Liu JF, Palakurthi S, Zeng Q, et al. Establishment of Patient-Derived Tumor Xenograft Models of Epithelial Ovarian Cancer for Preclinical Evaluation of Novel Therapeutics. *Clin Cancer Res.* 2016;23(5):1263-1273.

Liu, N., B.R. Rowley, C.O. Bull*, et al.* (2013). BAY 80-6946 is a highly selective intravenous PI3K inhibitor with potent p110alpha and p110delta activities in tumor cell lines and xenograft models. *Mol Cancer Ther*. 12:2319-2330.

Markham A. Copanlisib: First Global Approval. *Drugs.* 2017;77(18):2057-2062.

Matulonis UA, Wulf GM, Barry WT, et al. Phase I dose escalation study of the PI3kinase pathway inhibitor BKM120 and the oral poly (ADP ribose) polymerase (PARP) inhibitor olaparib for the treatment of high-grade serous ovarian and breast cancer. *Ann Oncol.* 2016;28(3):512-518.

Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol.* 2019;20(5):636-648.

Okkenhaug, K., and J.A. Burger. (2016). PI3K signaling in normal B cells and chronic lymphocytic leukemia (CLL). *Curr Top Microbiol Immunol*. 393:123-142.

Patnaik A, Appleman LJ, Tolcher AW, et al. First-in-human phase I study of copanlisib (BAY 80-6946), an intravenous pan-class I phosphatidylinositol 3-kinase inhibitor, in patients with advanced solid tumors and non-Hodgkin's lymphomas. *Ann Oncol.* 2016;27(10):1928-1940.

Rehman FL, Lord CJ, Ashworth A. The promise of combining inhibition of PI3K and PARP as cancer therapy. *Cancer Discov.* 2012;2(11):982-984.

Westin, J.R. (2014). Status of PI3K/Akt/mTOR pathway inhibitors in lymphoma. *Clin Lymphoma Myeloma Leuk*. 14:335-342.

Wilson, E. B. Probable inference, the law of succession, and statistical inference. Journal of the American Statistical Association 1927; 22 (158), 209-212.

APPENDIX I – FIGO OVARIAN CANCER STAGING 2014

STAGE I: Tumor confined to ovaries

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

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

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

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

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

STAGE IV: Distant metastasis excluding peritoneal metastasis

- IVA Pleural effusion with positive cytology

APPENDIX II – PERFORMANCE STATUS

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX III – NYHA CLASSIFICATION

Congestive Heart Failure – New York Heart Association Classification

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

Class	Objective Assessment
A	No objective evidence of cardiovascular disease. No symptoms and no limitation in ordinary physical activity.
B	Objective evidence of minimal cardiovascular disease. Mild symptoms and slight limitation during ordinary activity. Comfortable at rest.
C	Objective evidence of moderately severe cardiovascular disease. Marked limitation in activity due to symptoms, even during less-than-ordinary activity. Comfortable only at rest.
D	Objective evidence of severe cardiovascular disease. Severe limitations. Experiences symptoms even while at rest.

APPENDIX IV- 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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 Study Chair consulted.

APPENDIX V – LIST OF PROHIBITED MEDICATIONS WHILE ON COPANLISIB AND OLAPARIB TREATMENT

This list is not comprehensive. Refer to the protocol document concerning the co-administration of strong CYP3A inhibitors.

Category	Drug name
Strong 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), ginkgo biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications 14 days prior to first dose of study drug

APPENDIX VI – GENERAL THERAPY GUIDELINES

- For cycle lengths greater than or equal to 21 days, a patient will be permitted to have a new cycle of chemotherapy delayed up to 7 days (without being considered a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

- It will be acceptable for individual chemotherapy doses to be delivered within a "24-hour window before and after the protocol-defined date" for "Day 1" treatment of cycle lengths greater than or equal to 21 days. If the treatment due date is a Friday, and the patient cannot be treated on that Friday, then the window for treatment would include the Thursday (1 day earlier than due) through the Monday (day 3 past due).

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

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

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

APPENDIX VII – CTEP COLLABORATIVE AGREEMENTS LANGUAGE

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

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator

(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm).

Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

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

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

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

   E-mail: ncicteppubs@mail.nih.gov

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

APPENDIX VIII– PATIENT CLINICAL TRIAL WALLET CARD FOR COPANLISIB AND OLAPARIB

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): Copanlisib and Olaparib

Version JAN/2019

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX IX – OLAPARIB DRUG DIARY

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

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

OLAPARIB
Take __(number) ____mg and __(number) ____ mg tablets twice a day 12 hours apart.

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

Patient's Signature: _____ Date: _____

Physician/Nurse's Signature _____ Date _____